EFFECTIVE, EFFICIENT AND PERSONALIZED ORTHODONTICS: PATIENT-CENTERED APPROACHES AND INNOVATIONS

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DEDICATION

Researcher. Clinician. Educator. World lecturer. All these terms describe Dr. Jim McNamara.

Born in San Francisco, Jim's college education began with a Bachelor of Arts degree (Speech) in 1964 from the University of California, Berkley. Four years later, he followed with Bachelor of Science and D.D.S. degrees along with an Orthodontic Specialty certificate from the University of California, San Francisco (Curriculum II). Afterward, Jim accepted a post-doctoral fellowship in the Department of Anatomy at the University of Michigan.

Moving to Ann Arbor in 1968 proved to be life changing for Jim, both personally and professionally. It was there he met and married the love of his life, the former Charlene Beach. Together they raised their two children, Laurie and David. Meanwhile, Jim earned his Master's and Ph.D. degrees in anatomy and began a lengthy career with the university, its Center for Human Growth and Development and, of course, its Department of Orthodontics.

Along the way, Jim accumulated a remarkable list of the highest awards in orthodontics, beginning with the Milo Hellman Research Award in 1973. In addition, he received the Jacob A. Salzmann Award (1994); the B.F. Dewel Biomedical Research Award (1997), given by the American Association of Orthodontists Foundation; the James E. Brophy Distinguished Service Award (2001), given by the American Association of Orthodontists; and the Albert H. Ketcham Award (2008), given by the American Board of Orthodontics. In 2015, the American Association of Orthodontists Foundation established the James A. McNamara Orthodontic Faculty Fellowship Award in his honor.

Jim's funded research interests have included a wide array of topics, beginning with electromyography and the study of the muscles of mastication in rhesus monkeys, the functional adaptation of the temporomandibular joint, the effects of several functional appliances including most notably the Fränkel and Herbst, early orthodontic and orthopedic treatment, and cervical vertebral maturation, along with many other topics. He has published more than 300 articles in scientific journals and authored 77 books, monographs and book chapters. Jim has given over 400 lectures throughout six of the seven continents of the world, having somehow not been invited to speak in Antarctica, an oversight which we are sure will be rectified someday.

In addition to his own research, Jim has served as an educator and mentor to countless orthodontic residents, having chaired 62 Master's Thesis committees and been a member of 65 more. In addition, many of those who came to Michigan to visit and work became colleagues and friends; he has always been eager to help others. All these activities have been in addition to running his own private practice of orthodontics in Ann Arbor, which he now shares with his daughter.

Over the 50 years Jim has been at the University of Michigan, he has served as a post-doctorate fellow, research associate, a professor in both the Departments of Anatomy and Orthodontics and the Center of Human Growth and Development, Interim Chair of the Department of Orthodontics and Pediatric Dentistry, the Curator of the Michigan Growth Study, the Thomas M. and Doris Graber Endowed Professor of Dentistry and now the Graber Endowed Professor Emeritus.

The most recognizable person at the Moyers Symposium is Jim. He made a presentation at the very first Symposium in 1974; the first

published monograph by the Center of what is now the 55-volume Craniofacial Growth Series was his Ph.D. thesis. Since those early days he has served on the planning committee and management team for every symposium (45) and served as author, editor or co-editor for more than 90% of the 55 monographs published thus far. That the Moyers symposium has continued and flourished even after the passing of Robert E. Moyers in 1996 is a testament to the efforts of Jim McNamara.

One of the seminal moments that eventually would affect orthodontic residents throughout the United States and Canada occurred in 1989 when Jim founded the Graduate Orthodontic Residents Program (GORP). Starting as an offhand suggestion at gathering of Michigan residents, GORP has become a highlight of orthodontic residency. It is unique as the first annual program to bring together residents in a dental or medical specialty program and it continues to attract nearly 500 residents each year.

On March 3, 2018, a reception was held at the Moyers Symposium honoring Jim's 50 years at the University of Michigan. I (CR) had the honor as presiding as the Master of Ceremonies while several of Jim's close friends and colleagues said a few words. At one point, I couldn't help thinking about Sir Christopher Wren, the great English architect and designer of St. Paul's Cathedral in London, among many other magnificent buildings. He was buried within St. Paul's where the inscription over the spot reads, "If you want to see his monument, look around you."

The same can be said for Jim. No matter where any of us travel throughout the world, all we need to do is look around for a smiling face. Chances are, the orthodontist who created that smile was influenced in some way by Jim McNamara. What a wonderful legacy, indeed. Just look around you.

Few have accomplished as much over a career and we applaud Dr. Jim McNamara for his 50 years of service to the University, department, program and the specialty of orthodontics. Speaking for all the lives he has affected, we thank you. Salute!

Christopher A. Roberts
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PREFACE

Advances in technology are responsible for the paradigm shift from an evidence-based approach to healthcare intervention, which focuses on average estimates of disease to precision medicine where treatment is targeted to each patient's unique characteristics. Recent developments in methods for gene sequencing and analysis have made it possible to understand the genomic basis for risk, susceptibility and the probability of successful outcomes. Biomarkers from quantifiable analytes, incorporation of 3D imaging techniques, contemporary soft- and hard-tissue analysis, computer-aided treatments and customized devices can be used for patient-centered orthodontic treatment to improve efficiency and effectiveness. In the near future, with the integration of innovation in technology, biomedical and clinical research and large datasets, it may be possible to deliver precision orthodontics that takes into account each patient's genomic, phenotypic and environmental characteristics for a personalized approach to diagnosis, analysis and treatment.

The topic of precision orthodontics, patient-centered approaches and innovations was addressed during the *45th Annual Moyers Symposium* and the *43rd Annual International Conference on Craniofacial Research (Pre-symposium)* held at The University of Michigan from Friday through Sunday, March 2-4, 2018. This meeting was co-sponsored by the Department of Orthodontics and Pediatric Dentistry, School of Dentistry and the Center for Human Growth and Development. The proceeding of this annual meeting is memorialized in the 55th volume of the Craniofacial Growth Series and contains reports, original research and review articles from internationally renowned experts, scientists and clinicians.

As in previous years, the *Symposium* honored the late Dr. Robert Moyers, Professor Emeritus of Dentistry and Fellow Emeritus and Founding Director of the Center for Human Growth and Development at The University of Michigan. This meeting also honored Dr. James A. McNamara Jr., Graber Endowed Professor Emeritus and his 50-year career at The University of Michigan. Family, friends, colleagues and attendees of the *Symposium* celebrated Jim's many contributions to the university, department, program and the profession at a reception held at "The Big House."

We thank Michelle Jones of the Office of Continuing Dental Education for coordinating and managing both the *Pre-symposium* and the

Symposium. We also appreciate Kris De Koster's invaluable help in editing and facilitating the publication of this book.

The support of Dr. Nan Hatch, the Chair of the Department of Orthodontics and Pediatric Dentistry and Dr. Brenda Volling, the Director of the Center for Human Growth and Development are recognized for this meeting and publication. Starting this year, through the efforts of Dr. Hatch, the entire Craniofacial Growth Series has been made available online so that all previous, present and future volumes can be accessed by anyone (http://moyerssymposium.org/); the reader may access this list *via* the Craniofacial Growth Series tab in the upper right corner of the home page.

Finally, we thank the speakers and participants of the *Symposium* and the *Pre-symposium.* Their attendance and support throughout the 45 years of history of the meeting are appreciated.

Hera Kim-Berman
The University of Michigan
Ann Arbor, Michigan
January 2019

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PRECISION MEDICINE FROM AN ORTHODONTIC PERSPECTIVE

David S. Carlson

ABSTRACT

Significant advances in the fields of genomics and bioinformatics over the past two decades have led to the initiation of precision medicine as a new paradigm for healthcare. Development of methods for gene sequencing and analysis of minor genetic variations (e.g., single nucleotide polymorphisms) that are shared by individuals in affected populations have made it possible to understand the possible genomic basis for the risk and susceptibility of a number of intractable diseases and disorders in individual patients. Precision medicine also has provided a basis for understanding the possible reasons for individual variation in response to treatment of diseases and disorders. With such awareness, clinicians may be able to customize treatment for existing or developing diseases and/or disorders for each individual patient.

In general, dentistry has not been on the forefront of the advancement of research leading to precision medicine and has lagged with respect to transfer of the approach of precision medicine to clinical treatment. However, the significance of precision medicine in the area of dental diseases and disorders cannot be denied. The origin and effective treatment of dentofacial deformities in the general orthodontic population has a predominantly ontogenetic basis. Adopting the approach of precision medicine through analysis of minor genomic variations and how this may affect treatment ranging from guided tooth eruption, orthodontic tooth movement and modification of the growth of the jaws (i.e., development of precision orthodontics) may lead to significant advances in orthodontic treatment in the future.

KEY WORDS: precision medicine, genomics, dentofacial deformities

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PRECISION MEDICINE INITIATIVE

Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes—and to give all of us

> *access to the personalized information we need to keep ourselves and our families healthier.*
>
> President Barack Obama, State of the Union Address[1]

President Obama's announcement of the Precision Medicine Initiative, which was accompanied by a commitment of more than an additional $200 million to the National Institutes of Health (NIH) budget, represents the culmination of breakthrough research from basic and clinical sciences supported primarily through the NIH and National Cancer Institute. Immediately after the President's announcement, the principal architects of the initiative—Francis Collins, Director of the NIH, and Harold Varmus, then Director of the National Cancer Institute—jointly defined *A New Initiative on Precision Medicine* in the New England Journal of Medicine.[2] As a result of this initiative, precision medicine officially began as a new, different and distinct approach for the diagnosis, prevention and treatment of human diseases and disorders.

This chapter provides an overview of precision medicine from the perspective of orthodontics. Consistent with the precision medicine paradigm, the principal tenets of this chapter are that: 1) minor, normal variations in the genome play a significant role in the appearance of subtle variations in dentofacial growth and form; and 2) recognition of variations at the genomic level likely has significant implications for outcomes related to treatment of dentofacial deformities and even minor dental discrepancies. The overall goal of this chapter is to promote the view that greater understanding of the human genome and the complementary epigenome as it relates to craniofacial development and growth will promote significant advances in the individual treatment of developing dentofacial deformities.

INTRODUCTION

Sequencing of the human genome was completed as part of the Human Genome Project at the beginning of the 21st century (2003). Even prior to that time, by the late 1990s, as the academic field of genetics evolved into genomics, there was growing awareness among leaders in the biomedical community of the enormous potential that working knowledge of the human genome could provide for diagnosis, treatment and prevention of many otherwise intractable human diseas-

es and disorders. By the end of the first decade of the 21st century, progressive advances in basic and clinical research in genomics resulted in the approach of what was called "personalized medicine," which now goes under the moniker of "precision medicine" as an entirely new paradigm for healthcare.

The diseases and disorders most likely to benefit from sequencing of the human genome and development of precision medicine were not those attributable primarily to profound genetic mutations since information about major genetic anomalies generally was accessible through other approaches. Rather, knowledge of the human genome would be of greatest benefit for understanding both inherited and acquired diseases and disorders that result from more subtle variations in the genome. Such variation could affect the risk and susceptibility of many diseases and disorders, as well as variations in response to specific treatment approaches in individuals and groups. Examples of such diseases and disorders include various forms of cancer; certain infectious diseases (e.g., hepatitis C); neurological disorders (e.g., Alzheimer's and Parkinson's diseases); mental disorders (e.g., schizophrenia and bipolar disorder); and endocrine and metabolic disorders (e.g., diabetes and hypocholesteremia).

Dentistry has not been associated significantly with diseases and disorders such as those listed above that have differential mortality as a primary consequence. This is true especially for orthodontics, where the principal emphasis is on children and young adults who generally are considered "normal," but have relatively minor dentofacial deformities (e.g., discrepancies in the size and position of the jaws and misalignment of the dentition). As a result, the broad field of dentistry has tended to lag behind medicine in the development and implementation of new genomic approaches, as well as the transfer of those approaches to clinical practice.

Nevertheless, dental scientists and educators have contributed significantly to research in genome-based approaches to healthcare. For obvious reasons, the greatest attention in dentistry has been placed on preventable diseases (e.g., oral cancer and periodontal disease), as well as craniofacial anomalies, with particular emphasis on cleft palate. However, there is good evidence from basic and clinical research that normal genome variations in concert with epigenomic factors could give

rise to significant variations in development and growth that result in dentofacial deformities, ranging from discrepancies in maxillomandibular size and position, and even to tooth alignment. The logical extension of that idea presents the intriguing possibility that variation in the outcome of treatment to correct a developing dentofacial deformity also may be influenced by normal genomic variations.

What is Precision Medicine?

Precision medicine is a new paradigm in healthcare that came about principally as a result of the confluence of major technical and conceptual advances in genomics, pharmacogenomics, computational science and bioinformatics. The precision medicine paradigm represents a novel approach based on advances in molecular biology that uses individual personal genomic information as a primary basis for comparison within extremely large, stratified population-based genomic and clinical datasets. With information from such analyses, precision medicine is able to provide an individualized approach to healthcare by determining susceptibility to and diagnosis of diseases and disorders, as well as to provide the most effective information regarding individualized clinical treatment, thereby, enhancing the likelihood of treatment success. A fundamental principle of precision medicine is that variations in the genome, even minor variants or polymorphisms in the genome of each individual, may have an effect on the onset of a disease or disorder and its course, as well as the effectiveness and toxicity of drugs and other therapies used for treatment.[a] Clinical decisions, practices and interventions are tailored to the individual patient based on assessment of their risk of a disease or disorder and predicted response to treatment as revealed primarily from variations in their genome.

The fundamental goal of precision medicine is to provide treatment that is customized to each individual or like group through specific targeting of a disease or disorder. In order to accomplish this, the approach of precision medicine requires extremely large population-based datasets generated through large-scale genome-wide association stud-

[a] At least 60% of the approximately 20,000 genes in the human genome have an estimated total of over two million minor variations in the form of single nucleotide polymorphisms (SNPs) that could result in minor variations in gene expression and in susceptibility to epigenetic factors in “normal” individuals.

ies (GWAS) and electronic medical records to define the genomic basis of the disease or disorder, its course and its response to targeted treatment. Thus, a fundamental requirement of the precision medicine approach is the ability to identify and stratify patients accurately within groups according to a specific disease or disorder, similarities in their genome and responsiveness to treatment.

How Does Precision Medicine Differ from Traditional Medicine?

There are two fundamental factors—diagnosis and treatment—that provide the foundation of healthcare for any physical condition. Diagnosis relies on recognition of the signs and symptoms of existing or potential diseases and disorders. Treatment is dependent on the availability of appropriate options for the alleviation or correction of the condition. Diagnosis is limited to what can be determined from the phenotype and family history presented by the individual patient. In traditional medicine, the phenotype generally is limited to physical appearance, including broad classifications for gender, age and ethnicity; clinical laboratory results; and behavior. In the case of possible genetic conditions, analysis of the phenotype also would include genomic assessment of the presence of significant genetic or chromosomal abnormalities. Treatment of a medical condition then would be based on a combination of physical intervention, including surgery, rehabilitation, drug therapy and palliative care.

Perforce, the approach of traditional medicine is limited to an emphasis on treatment of individuals with given diseases and disorders based on the anticipated response of the average patient within a broad, non-stratified population. As noted by Collins, "For most of medicine's history ... physicians have been forced to approach prevention and treatment of disease based on the expected response of an average patient because that was the best that could be done."[3]

The approach of treating to the expected outcome based on the average patient is most reasonable in the absence of complete phenotypic information that would allow for appropriate stratification of individuals affected with a specific medical condition according to variations in their genome. With the sequencing of the human genome, however, it became possible to search for underlying, intrinsic factors that might affect the treatment of specific diseases and disorders across genomes. As a result, with the advent of complete genome sequencing, computa-

tional methods and bioinformatics, it now is appropriate for the genomic makeup of the individual—the genotype—to be viewed as part of the phenotype that routinely is considered in health assessment, even for patients with no genetic abnormality.[4]

Precision Medicine Timeline

A principal component of precision medicine's development was the advancement of pharmacological research on patient variability in the effectiveness of drug therapy for a variety of intractable health issues. In fact, most of the obvious early successes of the precision medicine paradigm, beginning in 2014, can be found in the development and use of new drugs for major human diseases and disorders. In 2015 alone, the Federal Drug Agency (FDA) approved 17 drugs that were developed using the precision medicine approach to clinical research (Table 1).

Table 1. Drugs developed and approved to address major diseases and disorders using the approach of personalized/precision medicine. GENOME Magazine, Spring 2016.

DATE	DISEASE/DISORDER	PERSONALIZED DRUG
December 2014	Leukemia	Blincyte
	Hepatitis C	Vierkira Pak
	Ovarian cancer	Lynparza
February-March 2015	Breast cancer	Ibrance
	Synthesis disorders	Cholbam
July 2015	Cystic fibrosis	Orkambi
	Schizophrenia	Rexulti
	Lung cancer	Igressa
	Hepatitis C	Technivie
	Hepatitis C	Dalkinza
	Hypercholesterolemia	Praluent
August-October 2015	Hypercholesterolemia	Repatha
	Orotic cciduria	Xuriden
	Lung cancer	Keytruda
	Schizophrenia	Aristada
	Lung cancer	Opdivo
	Hypophosphaturia	Strensig

A Rose is a Rose: Why Do We Need a New Name?

Within the medical community, no less than six terms have been used to describe the clinical approach that relies principally on application of genomic information in the diagnosis, treatment and prevention of diseases and disorders.[5] "Targeted medicine" is a term used most commonly in pharmacotherapy and cancer treatment to emphasize the use of drugs that uniquely target a discrete physiological process and organ pharmacologically. "Deep phenotyping" refers to detailed standards for comprehensive phenotyping as part of electronic medical records. "Stratified medicine"—a term used more widely in the United Kingdom—emphasizes identification of subgroups, or strata of patients, with distinct mechanisms of disease and particular responses to treatments. Finally, "genomic medicine"—a term very close in meaning to precision medicine—is associated with the analysis of an individual's total genome (i.e., all of the available "omics"). Genomic medicine also is an academic field of study that emphasizes the process of medical decision making using genomic information.[6]

The term "personalized medicine" has historical precedence for the approach that incorporates consideration of genomic information in the assessment of diseases and disorders of individual patients. As a result, "personalized medicine" became engrained within the health sciences and continues to be used by many researchers and clinicians interchangeably and synonymously with "precision medicine." However, leaders from the NIH, the National Research Council and the Center for Disease Control (CDC) put forward the argument that subtle differences in the emphases represented by these two terms warrant preferential use of "precision medicine."

At its core, the term "personalized medicine" implies a strong individual patient-centered approach.[b] The goal of precision medicine also is successful treatment of the individual and thus, it too is patient centered. The fundamental difference between "personalized" and "precision" medicine is the additional requirement in precision medicine for delineation of distinct sub-groups of individuals based on molecular

[b] It is interesting and somewhat ironic that some clinicians have objected to the term "personalized medicine" to emphasize care that is focused on the individual patient as it implies that some medical care is *not* individualized and patient centered.

variation in order to assess the possibility of a genomic basis for risk, susceptibility and treatment efficacy of defined diseases and disorders in the individual patient.

The most compelling rationale for the transition away from use of the term "personalized medicine" stems from the position put forward by Collins and Varmus that "precision medicine" represents an entirely new and novel paradigm for all healthcare based on the need for a new taxonomy of human disease that is contingent on molecular biology.[2][c] With the new paradigm, scientific discoveries and medical advances based on studies of the genome certainly will continue to benefit individual patients. In addition, precision medicine also will have population-wide benefit. According to Muin Khoury, Director of the Office of Public Health Genomics of the Centers for Disease Control and Prevention:

> *…a simple shift from 'personalized medicine' to 'precision medicine' allows us to imagine a future … in which large-scale biologic, personal, environmental and social information can be analyzed with new computational tools to identify determinants of health and disease, and to develop both individualized and population-level interventions to treat and prevent human disease and improve health equity.[8]*

For the purposes of this chapter, the terms "precision" and "personalized" essentially are considered synonymous. "Precision" will be used whenever possible to refer to the new paradigm that focuses on advanced molecular, genomic information as part of the phenotype as a strategy for improving treatment of health conditions. However, "personalized" may be used depending on the term utilized in previous medical, dental and orthodontic literature references.

PRECISION ORTHODONTICS

The issue of ambiguity because of the interchangeable use of the terms "precision" and "personalized" in the field of medicine is mi-

[c] According to Kuhn in his classic book, *The Structure of Scientific Revolutions*, one of the hallmarks of a new paradigm is the development of new terms because the old terms truly do not embody the new concepts and thus create ambiguity.[7]

nor when compared to the historical use of those terms by for-profit companies in the field of dentistry and orthodontics for marketing strategy purposes. To illustrate this point, an informal Google search was conducted using keywords "personalized" and "precision" combined with "dental practice" or "orthodontic practice." "Practice" was added as a qualifier to "orthodontic" in an effort to exclude research papers as much as possible. It was astounding to find that the searches for a combination of "personalized," "precision" and "dental practice" keywords produced over one million hits and the number of results for personalized," "precision" and "orthodontic practice" was nearly 900,000.

Onset of Personalized Dentistry

Modern concepts of genomics were not appreciated widely among most clinical researchers within the field of orthodontics before initiation of the Human Genome Project in the late 1990s. At that time, position papers by a number of thought leaders in dental research and education began to appear with the purpose of drawing attention to the potential of understanding the human genome for future advances in dentistry (Table 2). Each of those papers expressed a number of shared characteristics in their consideration of the relevance of advances in modern genomics for future approaches to dental health and care. First, all of the papers expressed enthusiasm regarding the exceptional promise presented by understanding the Human Genome Project and the emerging approach of genomic medicine for advancing human health in general. Second, each of the reviews emphasized the need to develop personalized dentistry as a parallel to personalized medicine. However, they also stressed that dental schools must improve education in modern genetics in order to ensure that the new generations of dentists could take advantage of the significant advances that inevitably would emerge from detailed knowledge of the human genome. Finally, virtually all of the papers specifically addressed the promise of personalized dentistry for prevention and treatment of three prominent dental diseases and disorders: caries, periodontal disease and oral cancer. Although one would think that developmental deformities such as craniofacial anomalies and dental agenesis should have a significant role in personalized or precision dentistry, only a few general overview papers made more than a passing note of the potential for application of the

Table 2. Significant reviews addressing the rise of genomic medicine and the approach of personalized/precision medicine in the dental literature. Italicized font = title; regular font = topic.

YEAR	TOPIC/TITLE	AUTHOR(S)
1999	*Entering the era of molecular dentistry*	Slavkin[13]
	Growth modification: From molecules to mandibles	Carlson[9]
ORTHODONTIC GENOMICS ERA (2000-2009)		
2001	*The human genome, implications for oral health and diseases …and dental education*	Slavkin[14}
2002	*The genome projects: Implications for dental practice and education*	Wright and Hart[15]
	Biological rationale for early treatment of dentofacial deformities	Carlson[16]
2004	Genetics and the Human Genome Project …	Slavkin[11]
	Reforming dental health professions education … A white paper	DePaola and Slavkin[17]
	A call for increased dental education in genetics for dental health professionals	Collins and Tabak[18]
2005	*Theories of craniofacial growth in the post-genomic era*	Carlson[10]
2008	*Beyond the "omics": Translating science into improved health*	Garcia and Tabak[19]
	Genetics and its implications for practice and education	Johnson et al.[20]
	Personalized orthodontics, the future of dental practice	Hartsfield[12]
	Microarrays: Applications in dental research	Nazmul-Hossain et al.[21]
2009	Science is the fuel for technology and clinical practice	Snead and Slavkin[22]
POST-GENOMIC/EPIGENOMIC PERIOD (2010-2014)		
2010	Molecular diagnosis in orthodontics …	Harzer et al.[23]
2012	*Genome technologies and personalized dental medicine*	Eng et al.[24]
	Personalized medicine: Will dentistry ride the wave or watch from the beach?	Kornman and Duff[25]
	How will personalized medicine affect orthodontics?	Zanardi et al.[26]
	Personalized oral health care: Providing '-omic' answers …	Glick[27]
2013	*Genetics and non-syndromal facial growth*	Hartsfield et al.[28]
	Translational genetics and craniofacial health	D'Souza et al.[29]
	Expanding the foundation for personalized medicine …	Garcia et al.[30]
	Personalized medicine enters dentistry … What might this mean for clinical practice?	Giannobile et al.[31]

2014	*…A genomic-epigenomic basis for dentofacial orthopedic treatment*	Carlson[4]
	From phenotype to genotype…	Slavkin[32]
	Revising the scope of practice for oral health professionals: Enter genomics	Slavkin[33]
PRECISION ORTHODONTICS PERIOD (2015-)		
2015	*Epigenetics: A new frontier in dentistry*	Williams et al.[34]
	Personalized and precision orthodontic therapy	Iwasaki et al.[35]
	Evolving concepts of heredity and genetics in orthodontics	Carlson[36]
2017	*… Precision orthodontics: An evolving paradigm shift …*	Jheon et al.[37]
	Genetic disorders of dental development: Tales from the bony crypt	Frazier-Bowers and Vora[38]
	Precision dentistry in early childhood…	Divaris[39]
	Heredity, genetics and orthodontics: How much has this research really helped?	Hartsfield et al., 2017[40]
2018	*Oral cancer: Genetics and the role of precision medicine*	Li et al. [41]

precision medicine approach for diagnosis, prevention and treatment of dentofacial deformities.[9-12] This is especially disconcerting as it is obvious and should be well known that virtually all developmental deformities affecting the dentofacial region have an underlying genomic basis and thus, would seem to be suited ideally to the approach of precision medicine.

Emergence of Precision Orthodontics

A series of papers spanning the past 30 years has traced the development of concepts and theories regarding the biological basis for treatment of dentofacial deformities, including why and how the principles of precision medicine might be applied appropriately to orthodontics. The initial paper in that series noted that orthodontic research and practice in the mid-to-late 20th century were in the midst of a "scientific revolution" between two historically competing paradigms: the genomic paradigm and the functional paradigm.[42] Contained within each of those paradigms was a series of "theories" regarding the specific craniofacial tissues and mechanisms responsible for craniofacial growth. The genomic paradigm and its subsidiary theories asserted that unknown, but immutable, inherited genetic factors in bone and/or cartilage associated with sutures, synchondroses and the mandibular condyles determine the growth and form of the craniofacial complex. The function-

al paradigm maintained that the growth of bone, sutures and cartilages in the craniofacial complex is adaptable.[d] Thus, it was possible to modify the growth and form of the dentofacial complex within certain limits by extrinsic factors (e.g., functional, biomechanical forces as well as variations in molecular growth factors). It also was noted that attempts to separate genetic ("intrinsic") and environmental ("extrinsic") factors affecting craniofacial growth clearly have been based on a false dichotomy related to historically naive concepts of heredity and genetics, and of emerging understanding of epigenetics. Craniofacial growth and form are the result of the interplay of the underlying genomics and factors in the environment, or the epigenome, which includes treatment. However, the underlying principles of genetics as they might affect growth of the craniofacial complex remained unclear in the 1980s and in any event, could not be changed in the individual. Therefore, it was proposed that translation of craniofacial research into orthodontic treatment could be most productive if focused on the epigenetic factors, including orthodontic treatment itself, that influence expression of the underlying genome in order to bring about the most successful treatment of dentofacial deformities.

Significant progress toward a resolution of the dichotomy between the genomic and functional paradigms was made as a result of groundbreaking research during the genomic era of genetics and medicine, beginning especially in the 1980s. Based on awareness of developments in medicine and as a benchmark for initiation of the orthodontic genomic period at the end of the century, it was predicted that "within the next several decades, orthodontists will be using molecular kits to diagnose growth-related problems [for] treatment of specific growth discrepancies."[9] Further, the method of personalized-genomic medicine will be used to determine whether individual patients possess key molecular mediators that should be considered "in conjunction with conventional orthodontic-orthopedic approaches to modify facial growth and prevent or correct a developing dentofacial deformity."[16] Orthodontists will develop the ability to assess the presence or absence of genetic polymorphisms of key molecular mediators of growth in in-

[d] The *functional paradigm* should not be confused with early articulations of the *functional matrix hypothesis* of Moss.

dividual patients and thus support "…treatment of individual patients at the appropriate times and in appropriate measure to produce a biologically meaningful effect and a predictable and clinically efficacious result."[10]

Hartsfield, who was perhaps the first actually to use the term "personalized orthodontics" from an academic, pedagogical perspective, significantly expanded on those ideas.[12] He stressed that orthodontic researchers need to initiate use of modern genomic methods, including large GWAs linked with randomized clinical trials (RCTs) with appropriately stratified samples based on genomic profile that form the fundamental core of modern precision medicine in clinical orthodontic research. He concluded that "only then will we begin to truly understand how nature (genetic factors) and nurture (environmental factors, including treatment) together affect our treatment of our patients."

The historical dialectic between the genomic and functional paradigms in orthodontics came full circle with proposition of a synthesis of the principles of genomics with epigenomics at the beginning of the post-genomic/epigenomic period in orthodontics.[4] A subsequent review of the literature then traced the evolution of scientific discoveries and concepts in the study of heredity and genetics, beginning with Aristotle and Hippocrates, and culminating with Collins and Varmus.[2,36] Review of developments in the field of genetics-genomics made the rationale for the transition from traditional medicine to the approach now termed "precision medicine" readily apparent. Moreover, by juxtaposing developments in the scientific field of genetics and in genomic medicine with research and clinical developments in orthodontics, the review also underscored that orthodontics now is in an excellent position to begin to make similar major advances in understanding and treatment of dental diseases and disorders with initiation of a precision orthodontic period.

With the onset of the genomic era of orthodontics around the beginning of the 21st century, the role of genomic variation in the development and growth of the craniofacial complex had become a major topic for basic and clinical research (Table 3). Evidence of that trend is reflected in the increased number of scientific papers that focus on genomics and the application of precision medicine published in the orthodontic literature through the post-genomic/epigenomic period of orthodontics.[36]

Table 3. Primary clinical research papers focusing on the approach of genomics and in the scientific orthodontic literature leding up to the precision orthodontic period. Italicized font = title; regular font = topic.

YEAR	TOPIC/TITLE	AUTHOR(S)
ORTHODONTIC GENOMICS ERA (2000-2009)		
2000	Human tooth agenesis	Vastardis[43]
2001	GH receptor variant and mandibular growth	Yamaguchi et al.[44]
	Seratonin transport gene polymorphism and TMJ	Herken et al.[45]
2003	Apical root resorption in orthodontic patients	Al-Qawasmi et al.[46]
2006	*Phenotypic characterization of Class III patients*	Bui et al.[47]
	Tooth movement and IL-1 gene polymorphisms	Iwasaki et al.[48]
2008	*Gene therapy to enhance condylar growth…*	Dai and Rabie[49]
2009	Genetic linkage and a Class III dentofacial phenotype	Frazier-Bowers et al.[50]
	Familial non-syndromic primary failure of eruption	Frazier-Bowers et al.[51]
	IL-1 gene polymorphisms and speed of tooth movement	Iwasaki et al.[52]
	Mechanism and control of tooth eruption: Overview and clinical implications	Proffit and Frazier-Bowers[53]
	Polymorphism and mandibular growth	Sasaki et al.[54]
	GH receptor and mandibular growth	Tomoyasu et al.[55]
	IL-1beta polymorphism and apical root resorption	Bastos Lages et al.[56]
	IGF and skeletal maturity	Masoud et al.[57]
2010	Tooth eruption and PTH1R	Frazier-Bowers et al.[58]
	Genes, genetics, and Class III malocclusion	Xue et al.[59]
POST-GENOMIC/EPIGENOMIC PERIOD (2010-2014)		
2011	Polymorphisms in skeletal Class I crowding	Ting et al.[60]
2012	CYP19A1 genotype and pubertal sagittal jaw growth	He et al.[61]
	Myosin 1H and mandibular prognathism	Tassopoulou-Fishell et al.[62]
	IGF and skeletal maturity	Masoud et al.[63]
2013	Genetics of eruption disorders	Rhoads et al.[64]
	KAT6B and HDAC4 and skeletal malocclusion	Huh et al.[65]
2014	COL2A1, IGF-1 with mandibular prognathism	Xue et al.[66]
	ACTN3 R577X and Class II and deepbite malocclusions	Zebrick et al.[67]
	ENPP1 and ESR1 and treatment of dentofacial deformities	Nicot et al.[68]
	GWA for mandibular prognathism	Ikuno et al.[69]

PRECISION ORTHODONTICS PERIOD (2015-present)		
2015	Candidate genes for variation in malocclusion	da Fontoura et al.[70]
	Genetic risk factors for apical root resorption	Sharab et al.[71]
	Genetic variants and mandibular prognathism	Perillo et al.[72]
2016	GWAS of normal human facial morphology	Shaffer et al.[73]
2017	GWAS of facial morphology with FREM1 and PARK2	Lee et al.[74]
2018	GWA mapping of genetic effects on facial shape	Claes et al.[75]

The post-genomic/epigenomic period of orthodontics represented a continuation of the orthodontic genomics era, but with two notable advancements. First, researchers began to consider the use of genomic information to improve diagnosis and treatment of dental disorders and dentofacial deformities in orthodontic patients. Second, orthodontic research moved toward greater emphasis on the genomic factors underlying clinical problems seen more regularly in orthodontic practices (e.g., malocclusion, tooth movement and dental crowding), rather than focusing primarily on craniofacial anomalies that are known to have profound genetic basis. For example, a significant number of orthodontic researchers began to address the role of gene variants as they affect dentofacial growth and problems in the dentition associated with eruption and orthodontic tooth movement. Clinical researchers also began to use analysis of gene variants in an effort to improve diagnosis and treatment of dental disorders and dentofacial deformities in orthodontic patients.

With advances in molecular analysis of genes from both animals and humans, orthodontic researchers have addressed the specific effects of gene variants for growth factors and cytokines as they might affect dental development tooth movement. Of particular note is the number of recent papers that deal primarily with gene variants associated with Class II and Class III malocclusion. As an example of the scope of that research, a principal components analysis by da Fontoura and coworkers found single nucleotide polymorphisms for skeletal variation in malocclusion in twelve genes known to be associated with craniofacial growth.[70] Recent studies also have extended research on the genomics of craniofacial form from skeletal and dental tissues to soft tissues and facial appearance. Based on large-scale GWAS, Shaffer and associates have identified over 20 SNPs from 19 genes that are associated

with external facial morphology (e.g., nose width and height, distance between the eyes and chin protuberance).[73-75]

AXIOMS FOR PRECISION ORTHODONTICS

A series of sequentially organized axioms recently were put forward as a heuristic device to summarize a proposed synthesis between historical and current concepts in orthodontics with modern principles of genomics and epigenomics with respect to the treatment of dentofacial deformities.[4] Those axioms, somewhat modified, similarly provide an effective way to summarize the application of modern genomics to orthodontics and to promote development of precision orthodontics specifically.

Axiom 1: Dentofacial Phenotypes are a Product of the Interaction Between the Genome and the Epigenome

Review of the history of orthodontics demonstrates that for more than the past 100 years, there has been passionate debate about the relative importance of intrinsic and immutable genetic factors (nature) and extrinsic, environment factors (nurture) in the growth of the craniofacial complex. At the present time, however, there are virtually no modern researchers and few orthodontic clinicians who would challenge the assertion that both genetics, as understood today, and extrinsic-environmental factors relating in particular to individual behavior and orthodontic treatment play significant roles in the development, growth and form of the dentofacial complex.

Axiom 2: The Individual Genome Should be Considered as Part of the Phenotype

The dentofacial phenotype generally includes facial appearance, as well as clinical assessment of radiographic cephalograms, dental models and maturational status. Clinical evaluation typically also would include at least informal assessment of the patient's parents and siblings; however, modern advances in genomics have afforded both a reason to look deeper into the genome of selected individual patients, as well as means accomplish that.

Details about the nature and significance of gene variants undoubtedly will continue to emerge increasingly over the next several years. However, it now is understood that normal gene variants, espe-

cially polymorphisms that affect the amount and timing of expression of proteins that regulate growth, provide an underlying basis for variations in growth and form that occur normally throughout ontogeny and in association with adaptive responses to changes in extrinsic factors, including treatment in particular. Moreover, continuing advancements and increasingly more affordable methods for gene sequencing make it feasible to assess each patient's genome to search for key gene variants. Thus, each patient's phenotypic traits eventually will include not only morphological features, but also the presence, absence and assessment of the relative capacity for expression of growth factors based on their individual genome.

Axiom 3: The Capability of Patients to Respond to Treatment is Part of the Phenotype

Gene products do not regulate craniofacial development and growth in the sense that they determine variations in form. Rather, they affect the receptivity and responsiveness of growing structures to intrinsic, genomic factors and extrinsic stimuli. The presence of variants of regulatory proteins that mediate expression of growth factors at specific times of development is critical to understand variability in craniofacial growth and form. Variations in the presence and differential expression of these same gene products at various stages of development and post-natal growth undoubtedly are critical with respect to the capability of patients to respond in a predictable fashion to certain types of dentofacial orthopedic treatment. Therefore, selection of treatment options to correct a developing dentofacial deformity should take into account genomic variations (e.g., SNPs) that affect the ability of the patient to respond.

CONCLUSION: QUO VADIS ORTHODONTICS?

Personalized medicine uses advances in molecular biology to enhance the likelihood of successful treatment of a disease or disorder by targeting clinical treatment more precisely based on the unique genomics of the patient. That approach has the fundamental goals of disease risk and susceptibility prediction, as well as patient response to various options for treatment. Those goals are exactly the same as those for which clinicians should strive in order to facilitate enhanced diagnosis and treatment of dentofacial deformities.

From its inception, leaders in both orthodontic research and clinical treatment have recognized the need to understand heredity as it relates to normal and abnormal development of face, jaws and teeth. However, the principles of genomics generally did not become applicable in a meaningful way to issues and concerns in orthodontics until late in the 20th century. With advances in genetics leading to the rise of the field of genomics over the past 20 years, conditions now are ideal for the field of orthodontics to make a major transition into a modern precision orthodontics period. The ongoing evolution of the concepts and methods of genetics as applied to the field of orthodontics will lead to greater understanding of the genomic and epigenomic factors that affect the normal and abnormal growth of the dentofacial complex. Such developments inevitably will lead to further incorporation of the concepts and principles that now are part of precision medicine to establish precision orthodontics as a principal clinical approach. Adoption of precision orthodontics will not lead to changes in the overall process of orthodontic treatment of all patients necessarily; orthodontic biomechanics and appliances undoubtedly will continue to be the main approach for treatment of malocclusions and dentofacial deformities. The primary change will take place in the diagnosis and selection of the most appropriate treatment options in consideration of the most effective way to treat malocclusions and dentofacial deformities, from dental irregularities to major jaw discrepancies, on an individual, case-by-case basis.

DEDICATION

This chapter is dedicated to Dr. James A. McNamara, Jr., in recognition of his 50 years at The University of Michigan. Jim and I essentially were inseparable academically and with respect to our research programs throughout the entire time we were jointly on the faculties of the Department of Anatomy & Cell Biology, the Center for Human Growth and Development, and the Department of Orthodontics and Pediatric Dentistry at The University of Michigan (1974-1994). During that time, Jim was a mentor, a colleague and a close personal friend whose generosity was a major factor in the development of my career in craniofacial research and orthodontic education. I always will be extremely grateful to Jim for his incredible generosity and support.

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TOWARD EVIDENCE-BASED PRECISION ORTHODONTICS

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ABSTRACT

Precision orthodontics is an innovative approach in which treatments and interventions are targeted to each patient's unique genomic, phenotypic and environmental characteristics. It is a systems approach that integrates six dimensions into its definition: personalized, precise, predictive, preventive, patient-centered and pragmatic. Two main forces drive this approach: the technological advances in the field of orthodontics and the big data movement. Acquiring and providing data that exceeds traditionally available resources, big data is promising for the future of orthodontics.

Challenges must be overcome, however, especially with regard to the distinction between the precision orthodontics approach and the current traditional evidence-based orthodontics (EBO) approach. Contrary to precision orthodontics, the EBO approach is supported by high-quality literature and scientific evidence, rather than by innovative ideas or expert opinions. The EBO approach also focuses on average estimates of disease and does not take into account the variability between individuals, or the distribution and etiology of this variability. With this in mind, multiple methods are indicated to move toward a combined evidence-based precision orthodontics approach that benefits from the strengths of both approaches and overcomes each other's limitations (e.g., utilizing big data analytics, implementing the need for educating investigators on proper research methodology and accurate reporting of clinical trials, and advocating studies on genomics and other "-omic" areas).

KEY WORDS: precision medicine, evidence-based healthcare, dataset, orthodontics, informatics

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TRADITIONAL MEDICINE

For many years, traditional medicine has analyzed a limited sample of patients' signs and symptoms, with the analysis occurring over a short duration of time and treated patients with a narrow-minded, "one-size-fits-all" approach. Treatment is rendered without

consideration of the variability in the individual patient's biological, behavioral and genomic differences, which leads to many patients consistently being under- or over-treated and often results in avoidable symptomatic side effects.

PRECISION MEDICINE

Precision medicine is defined as targeting treatment to a patient's unique and variable genomic, phenotypic, or environmental characteristics, in order to tailor the clinical intervention to each individual and maximize the therapeutic benefit of a particular intervention or drug.[1] It is an innovative approach to providing healthcare with a broad range of implications in modern medicine. This "precision"—or specific delineation of genetic, physical, behavioral and other factors that result in disease—may provide more accurate diagnoses, minimize adverse side effects, provide better treatment selection, produce novel drug discoveries and result in more favorable treatment outcomes. Such approaches to medicine can help halt the progression of disease or even may prevent its development in the first place.

Key Elements of Precision Medicine

Precision medicine contrasts with the traditional approach in two aspects: the graded surveillance on the classification of risk for a disease; and the intervention to suppress pathophysiologic processes while still latent. Precision medicine's deep profiling of an individual allows for the understanding of the determinants of the disease, an individual's particular response to a therapy and for a more optimal treatment outcome. Cholerton and colleagues portray this concept in the article, *Clarity for the Complexity of Dementia,* where traditional medicine and the precision medicine approach are juxtaposed.[2] The authors describe the three key facets of precision medicine that differ from the traditional approach: stratification by risk; early detection of pathological processes; and the development of interventions that are specific to an individual's genetic driver of disease.

PRECISION ORTHODONTICS

The application of the precision medicine concept in dentistry is not new; much of its popularity has been gained in recent years,

however, with several authors contributing to advancements in the field of precision orthodontics.[3-6] Jheon and Oberoi have depicted the various technological advancements that currently are in use, those to be seen in the near future and in orthodontic treatment planning.[3] A study published in 2017 uncovered the need for collaborative efforts and future direction on the technological platforms required for precision orthodontics.[4] Computer-aided design and manufacturing (CAD/CAM) has been introduced for the manufacturing of individualized Hyrax intra-oral functional appliances as a specific application of precision dentistry applied to orthodontic therapy.[5] Frazier-Bowers and colleagues found that mutations in the parathyroid hormone receptor 1 (PTH1R) were correlated with primary failure of eruption.[6] Such an example of genetic sequencing illustrates how an orthodontist can devise a treatment plan that can avoid the unnecessary use of orthodontic extrusion and continuous archwire mechanics.

Yet, if we look at evidence relevant to "precision orthodontics" over the last decade, we can see a minimal increase in the number of studies published on the topic (150 papers in February 2008 *versus* 398 in February 2018), indicating that the precision orthodontics approach still is in its infancy (Fig. 1). During the same time period, there has been a plethora of research published on "precision medicine" (4,571 papers in February 2008 to 29,428 published papers in February 2018; using a keyword search in PubMed on February 2, 2018).

An appraisal of the identified literature on precision orthodontics indicates variability in nomenclature, which seems to depend on the author's perspective of the concept. Some studies have referred to precision orthodontics as "personalized" orthodontics. The term "personalized" may imply that the treatment or intervention is tailored to each individual, however, this may or may not be the case. The National Research Council (NRC) had similar concerns regarding the use of the term "precision" medicine *versus* "personalized" medicine. In their 2011 report, the NRC presented a rationale as to why the term "personalized" was retired and replaced with "precision."[7] More recent studies in orthodontics use terms such as "precision" orthodontics or "precision and personalized" orthodontics, while some others use "targeted" orthodontics. The variability in nomenclature and definitions is confusing and calls for action by researchers to elucidate and define this new innovative concept in the field.

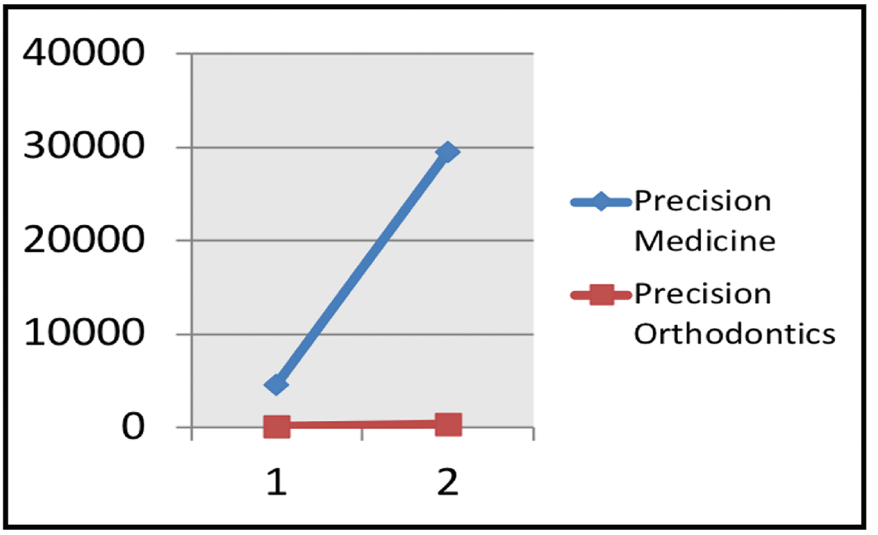

Figure 1. Evidence relevant to precision orthodontics and precision medicine. The Y-axis represents the number of studies published; the X-axis represents the area of study. Red = change in N of studies published on precision orthodontics between February 2008 (1) and 2018 (2); blue = change in N of studies published in precision medicine between February 2008 (1) and 2018 (2). PubMed search on February 2, 2018**.**

A Systems Approach to Precision Orthodontics

Expanding on Hood and colleagues' definition of precision medicine, the authors of this chapter argue that precision orthodontics is a systems approach that integrates six dimensions into its definition: personalized, precise, predictive, preventive, patient-centered and pragmatic (Fig. 2).[8-9]

- *Personalized:* Individualized treatment that is tailored to each patient.
- *Precise:* An approach that incorporates the biological, genetic, environmental and behavioral variation of each individual in treatment decisions.
- *Predictive:* An approach that incorporates personalized enrichment strategies in order to predict which populations are more robust with higher therapeutic responses to treatment. From a sampled cohort of participants that are representative of the

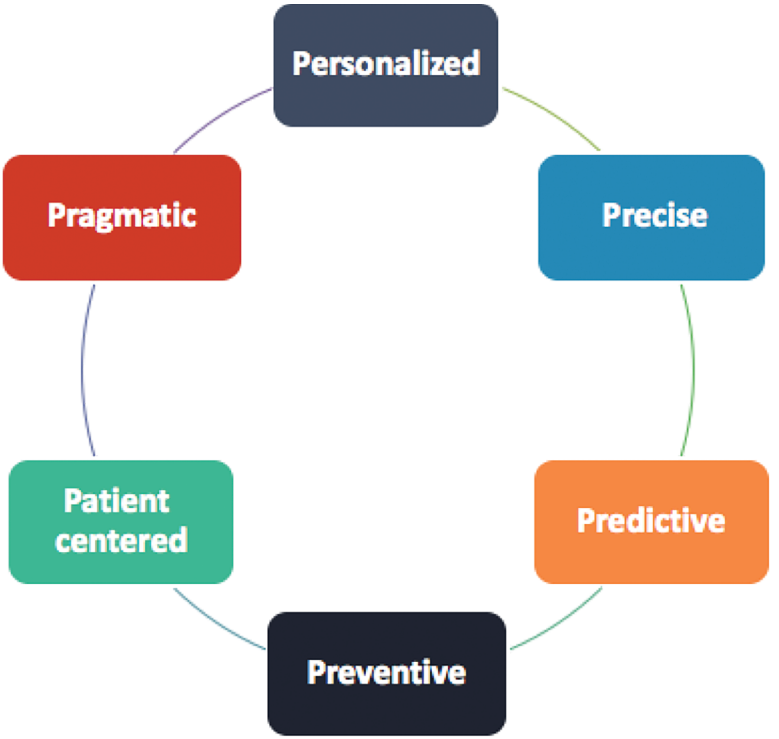

Figure 2. Systems approach to precision orthodontics. Modified from Hood and colleagues.[8,9]

population with disease, developing predictive rather than prognostic enrichment strategies can decrease the heterogeneity of a sample. This would allow for the categorization of subjects by risk and eventually for the selection of treatments that are optimal for each group.

- *Preventive:* This approach shifts the focus from reactive to proactive and from disease to wellness. Early detection of disease is a parallel concept, as it involves detecting the disease when it is easier and less expensive to treat, as opposed to the traditional model of treating a disease when it is symptomatic. This allows for the screening and identification of disease states in a population sample much earlier

and for the discovery of novel drug targets in disease.

- *Patient centered:* These strategies will take the patient's values and preferences into consideration while encouraging a shared decision-making mindset.
- *Pragmatic:* An approach that allows for a focus on assimilating data from a large cohort of volunteers in order to facilitate the integration of clinical data across all healthcare systems into a single large dataset. This is done for the purpose of extracting and assembling large amounts of information, while also decreasing regulations on the United States Food and Drug Administration (USFDA), National Institute of Health (NIH) and similar programs to promote efficient and innovative research. This approach also would reduce the time and cost of therapeutic interventions, as well as minimize the failure rates in clinical trials. When samples are stratified based on risk, treatments are tailored to each risk group separately. Therefore, failure rates of interventions tested in clinical trials potentially could be minimized.

Forces Accelerating Precision Orthodontics

Precision orthodontics is a healthcare model that uses multiple methods to gather information accurately on an individual and provide optimal treatment that is tailored to the individual's unique profile. Two main forces contribute significantly to its expansion and progression: technological advances in the field of orthodontics and the big data movement.

Technological Advances

Along with the recent increase in the number of adult patients seeking orthodontic treatment, there is a need for more timely and efficient care which drive technological advances. Technological advances in the field of imaging, genetics and epigenetics include cone-

beam computed tomography (CBCT) and other 3D imaging modalities, accelerated orthodontic therapies and bioengineered orthodontic appliances.

CBCT imaging provides valuable diagnostic and treatment planning implications for: impacted teeth; cleft lip and palate; skeletal discrepancies requiring surgical intervention; root morphology and angulation; alveolar bone conditions; maxillary transverse dimensions and expansion; airway morphology; temporomandibular joint morphology; pathology contributing to malocclusion; and temporary anchorage devices (TADs).[10,11] There also is a trend toward improving treatment outcomes, incorporating CBCT images into orthodontic 3D modeling and finite element analysis. This 3D modeling approach can be used to predict stresses and force distributions on the dental arches, teeth and surrounding periodontium (e.g., during space closure using TADs).[12,13] With the advent of future research, it may be easier to predict how the patient's dentofacial/craniofacial anatomy will respond to various orthodontic and orthopedic treatments, and to generate patient-specific approaches to model precision orthodontics.[10]

Another technological advance in modern orthodontics includes the use of intra-oral scanners for digital impressions. Digital impressions can result in less patient chair time, with a potential improvement in fit and accuracy of designed appliances. Periodontally accelerated tooth movement procedures (e.g., piezocision and micro-osteoperforation) are yet another technological advance. These accelerated therapies stem from the regional acceleratory phenomenon, which iatrogenically traumatizes bone in order to stimulate osteoclast and osteoblast proliferation to induce tooth movement. Vibrational devices that utilize pulsating, low-magnetic forces to the dentition to accelerate movement through bone remodeling also have been added to the orthodontic armamentarium.[14] Moreover, the use of low-level laser therapy (LLLT) is a topic of research that has been prevalent over the last decade. A previous study reported the effectiveness of LLLT in orthodontic tooth movement and in reducing acute pain, with a capacity to limit orthodontic relapse.[15] A recent systematic review concluded, however, that insufficient evidence is available to recommend the clinical use of LLLT in accelerating orthodontic movement, preventing tooth pain and preventing relapse.[16]

Three-dimensional (3D) printing in combination with biomedicine also has come into the fray for patient-specific orthodontic treatment modality. Such orthodontic technology will allow patient anatomy to be compared to biobanks and normative database libraries to calculate deficiencies in physical phenotypic, as well as genotypic differences, which may modulate and affect treatment times. With the advent of precision orthodontics, manipulating biology becomes an ever-present clinical norm that plays a role in advancing the field of genomic research, big data and individualized orthodontic treatment.

The orthodontic genomics era began in the 21st century, marking the start of the understanding between orthodontics and heredity. From 2010 to 2015, orthodontic research on the effect of normal polymorphisms for genes on craniofacial growth and orthodontic treatment increased significantly in orthodontic journals. The continuous evolution of genetic concepts will lead to a greater emphasis on genomic factors that affect the dentofacial complex and will propel precision orthodontics as the principal clinical approach. Precision orthodontics, as well as genomic and epigenomic research, can help strengthen the diagnosis to improve treatment planning using the most effective method to treat dentofacial deformities.[17]

Big Data Movement

Big data is the next objective that will help shape the future of precision orthodontics. As other fields continue to grow, precision orthodontics will rely on and require a foundation of integration between technological, biomedical, clinical research and data to deliver the optimal patient-tailored orthodontic treatment. Big data, commonly known as massive data, is the analysis of large datasets with the use of artificial intelligence (AI) algorithms to study the trends and correlations that already exist between data variables. Big data has contributed significantly to the thriving of the precision approach. While there is no standard definition at which data would be considered big data, Thomas Davenport suggested the following definition: “data that is too big to fit on a single server, too unstructured to fit into a row-and-column database, or too continuously flowing to fit into a static data warehouse.”[18] Although the name “big” data emphasizes the size of the data, it is not the most important feature. In fact, the core characteristic of big data is the unstructured nature of the data rather than the

size.[18] According to Gantz and Reinsel, the world utilized more than 28 zettabytes (> 2.8 trillion gigabytes), but only 0.5% of this data was analyzed.[19] The researchers expect a growth in the utilization up to 40 trillion gigabytes by 2020.[18,19]

Paradigm Shift with Big Data

Table 1 presents a shift in paradigm when using large datasets compared with conventional small datasets. With big data, there is a paradigm shift from studying causations in controlled trials to the study of correlations instead. Although correlations may have limitations (e.g., a lack of certainty and clear temporality), they can be found faster and cheaper than causation. In addition, correlations can pave the way to future controlled studies that determine causations. The types of outcomes studied using retrospective big datasets contrast with the current approach of controlled trials that identifies definitive outcomes. Big data focuses on studying proxies/surrogate outcomes (e.g., utilizing the development of white spot lesions as a definitive outcome in comparison to the use of bacterial counts and plaque index as a surrogate outcome to the occurrence of white spot lesions). With big data, we also move from analyzing small organized and generally well-structured datasets to the analytics of large semi-structured—or in many cases, unstructured datasets. With the use of big data, we have the advantage of studying all of the sample in a dataset. As a result, sampling may not be as important as it is in small datasets that only focus on small samples within the set. Thus, advantages of big data include better analytics from which to gather information and, therefore, to derive stronger and more evidence-based conclusions.

Big Data in Orthodontics

The future of orthodontics, as stated by Proffit, "has no choice but to become a data-driven specialty."[20] Anecdotes, case reports and uncontrolled experiments have tended to become the basis for clinical judgment, which often is postured as art more so than science and, therefore, not amenable to scientific analysis. Data-driven orthodontics may involve the retrospective study of large datasets and the application of predictive analytics with the help of data processing analytics software. Combining clinical, imaging and molecular datasets are key factors in precision orthodontics. The best orthodontic treatment approach

Table 1. Shifts in paradigm to big data.

SMALL DATA	BIG DATA
A shift from …	**to …**
Causation	Correlation
Definitive outcomes	Proxies/surrogate outcomes
Structured datasets (row-and-column format)	Unstructured, disorganized datasets
Analyzing a portion of the data on a topic	N = all by analyzing all data available on the topic
Regular models	Integrated models
Static data	Constant flow of data
Hypothesis driven	Machine learning

often is debatable and privy to varying opinions, with little solid data to demonstrate the best possible result. That data can and must be obtained for orthodontics to maintain the goals of credible orthodontic therapy. Thus, the importance of data for the advancement of the field cannot be overstated.

Big Data Sources

Big data could be obtained from different sources: electronic health records (EHRs) and clinical management systems; data registries including registries on mortality and morbidity and social indicators (e.g., National Health and Nutrition Examination Survey); clinical trial databases (e.g., clinicaltrials.gov); open data initiatives; administrative databases (e.g., insurance claims); lifelogging (e.g., activity self-monitoring applications); social media; and media clouds. Additionally, the NIH's *All of Us* research program had set the stage for future large big data analytics.

EHRs provide a rich source of clinical data that have been used by researchers to examine biological and environmental contributions to a wide array of conditions and health outcomes. Traditionally, many

healthcare centers capture and store an extremely large amount of patient information. The utilization of data stored in EHRs has been used in various healthcare applications (e.g., discovering comorbidities, predicting health risks and survival rates, and building a support system for the development of clinical trials and large-scale genomic discoveries). Crawford and coworkers managed to merge EHR data and different platforms of genotypic datasets utilizing the eMERGE network in combination with phenotypes from EHRs.[21] These researchers and many others have propelled the way for next genome sequencing and various contributions to genomics. In the future, such whole genome sequencing and other -omics data on DNA will be combined with large clinical EHR data to improve risk calculation and estimates. Such advances in big data analytics allowing for the prediction of healthcare emergencies and outbreaks are extremely important in order to develop the future of precision dentistry/medicine applications in biomedical, translational and clinical informatics.

The National Dental Practice-Based Research Network (NDPBRN) has been a large component of big data in dentistry as a whole.[22] Funded by the National Institute of Dental and Craniofacial Research, the NDPBRN creates networks of dental practices that coordinate prospective research projects. With this, well-designed clinical studies and efforts of utilizing large-scale clinical data and research surely will increase in prevalence.

The Manufacturer and User Facility Device Experience (MAUDE) database is another example of a publicly available registry or database from the United States Department of Health and Human Services.[23] MAUDE is a web-based search engine that houses information on all medical device adverse effects reported to the U.S. Food and Drug Association (USFDA) and has been used as a source for studies interested in the analysis of orthodontic devices (e.g., Invisalign aligners).[24]

NIH's "All of Us" Research Program

In 2015, President Obama launched the Precision Medicine Initiative (PMI) to lead the fight toward finding cures to diseases like cancer or diabetes and to give access to personalized information to keep U.S. families healthier. The NIH's *All of Us* research program is a key element of the PMI and big data constituent that is paving the way to precision orthodontics in the future. The goal of the PMI is to enable a

new era of medicine in which healthcare providers, patients and researchers will be able to work together to develop individualized care.

The *All of Us* research program aims to enroll at least one million participants throughout the country to provide insight into the individual differences in physiology, the risk of disease and response to therapy. Data collection from participants involves the collection and linkage of large sets of healthcare and patient data to a securely encrypted core dataset, which is queried through an analysis platform for research. Much of these data can be collected from smart data sensors and software applications that can be utilized for self-reported data on patient lifestyle and environment, providing researchers a clear view of these factors.

Throughout this program, an array of wireless sensor technologies enables the collection of individual physiologic and environmental data that were not available previously. Smartphone technology has made strides in that it is able to measure a person's motion, sound and activity level in order to provide valuable diagnostic information. Other options are wearable sensors including, but not limited to, wristbands and watches that currently can measure activity, sleep duration, heart rate and respiration. Additional sensor technologies include those placed within a participant's residence or automobile that passively can monitor environmental parameters like temperature and air quality along with a variety of biometrics.

The future of precision orthodontics will come to fruition: as comprehensive 3D databases are consolidated; as a patients' genetic background can be integrated into treatment modalities; and as further studies on the effects of biomodulation on tooth movement and skeletal growth can be elucidated.

Acquiring and providing data that exceeds traditionally available resources, big data is very promising for the future of orthodontics. Challenges must be overcome, however, before it may transition into the era of precision orthodontics.

Challenges Faced by Precision Orthodontics

Incorporating precision orthodontics into the field can present many barriers and challenges. Given that patients and clinicians alike will

be utilizing the data, the accuracy of the data is critical, considering the variability and volume of data used in the precision era. This may be challenging especially due to the complexity of the human genome and whole-genome sequencing assays, large inaccuracies in administrative data stemming from billing codes and large amounts of unstructured data in medical records and large data lakes.

Among the most challenging of the technical barriers is the analysis of the multi-dimensional data that will be curated, focusing on perpetual data sharing and updating, especially with the expected explosion in genomics research. The implementation of EHRs in current hospitals allows the collection of a wide range of clinical data at an extremely low cost. The accessibility and interoperability of EHRs—including the ability to exchange data across healthcare systems and for patients to access their own individual data—is an important present-day challenge that must be overcome as well. Thus, the privacy and confidentiality of the data, its ownership and governance, as well as its security and ethical considerations, are a few examples of many factors that require significant consideration when utilizing big data.

Additionally, there are many possibilities that can create false positives through multiple comparisons or by the exploration of data with no plausible biological model. The use of even bigger sample sizes and datasets, while an advantage for clinical studies, may be harmful as it can result in the production of unrepresentative samples. Care should be taken to control sampling bias when using insurance claims databases that contain data of a portion of a population that may not be representative of the whole. Additionally, as big data becomes more involved in consumer markets of mobile technology, EHR and wearable sensors, a skew in the representation of the population may happen with data being excluded or limited by variables such as socio-economic status, age and race.

Other notable barriers include socio-political challenges (e.g., the adequate representation of different stakeholder groups with an interest in the precision healthcare approach); use of better biomarkers to assist with disease detection and help guide treatment, particularly for common conditions without a strong genetic predisposition; establishment of sound evidence for interventions that are based on preci-

sion phenotyping and -omic analyses that can improve outcomes; and redefinition of the format of clinical trials and the level of evidence required by regulatory agencies for proof of benefit of an intervention.

Drawing conclusions from observational data also can become a common occurrence in large clinical record databases and may contain biases regarding assigned treatments and forming conclusions. Randomized controlled trials (RCTs) provide the highest level of evidence in the evidence pyramid, which is the gold standard for data interpretation in current evidence-based practice. Care should be taken to consider these research methodology implications when forming clinical judgment and conclusions from big databases. Therefore, it is essential that we differentiate between the precision orthodontics approach and the traditional current EBO approach. The two are not synonymous and the strengths and limitation of each of these approaches should be acknowledged and managed.

EVIDENCE-BASED ORTHODONTICS APPROACH

In the early 1900s, evidence-based medicine (EBM) focused on the use of published literature to optimize care. Recently, it has progressed to evaluating accumulated evidence and incorporating patient values critically while developing clinical practice guidelines. Similarly, evidence-based dentistry is defined according to the American Dental Association as “an approach to oral healthcare that requires the judicious integration of systematic assessments of clinically relevant scientific evidence, relating to the patient’s oral and medical condition and history, with the dentist’s clinical expertise and the patient’s treatment needs and preferences.”[25]

Application of the evidence-based approach into orthodontics relies on the evidence used to develop treatments that can achieve the best orthodontic results for patients. This approach is supported by high-quality literature and scientific evidence, in contrast to inconsistent or low-quality evidence for clinical care. It is important to assess information that is presented and utilize all the means available to do so. Published articles are accessible easily on the internet by utilizing engines like PubMed, Cochrane Collaboration, or other collaborative online databases that can provide quick, high-quality scientific evidence. The strongest currently available pre-appraised and appraised evidence

is that obtained from systematic reviews of multiple RCTs and RCTs, respectively.

Hierarchies of Methods, Evidence or Evidence Base

Guyatt and Busse suggested that the philosophy of EBM revolves around two fundamental principles: 1) "evidence alone is never sufficient to make a clinical decision;" and 2) "EBM posits a hierarchy of evidence to guide clinical decision making."[26]

Hierarchies are methods used to rank the evidence for clinical decision making. It is important to remind the reader that hierarchies can aid only in decision making and should not be used as the sole method for assessment of evidence. Although several researchers have argued that hierarchies are not needed to practice EBM, others have rejected this argument and indicated that clinical practice has improved due to the utilization of hierarchies.[27] Whether treatment outcomes have improved with the use of hierarchies as compared to not applying them remains unclear.

The development of hierarchies preceded EBM. To our knowledge, the first hierarchy was designed in 1979 by the Canadian Task Force on Periodic Health Examination and further modified by Sackett into the evidence pyramid.[28]

More than 80 evidence hierarchies currently are in use. Hierarchies vary in their assessment properties.[29] Some assess the level of evidence categorized from lowest to highest. Levels from the bottom to the top include *in vitro* or lab tests, animal studies, opinions, case reports, case series, case-control studies, cohort studies, RCTs and systematic reviews with or without meta-analysis, both representing the highest form of available evidence. Other hierarchies assess the quality of evidence, whether the study was planned and conducted well and has a low risk of bias. Other assessment properties include the scope of evidence (e.g., pre-appraised *versus* appraised and epidemiological *versus* non-epidemiological) and the strength of recommendation.

Hierarchies also vary in their focus. Most of them appraise the methodology within a study, some evaluate the evidence from an individual study, while the rest assess the evidence-base as a whole on a topic using the results of multiple studies, regardless of the quality of the individual studies included.[30] Yet, they generally are referred to as

hierarchies of “evidence” rather than hierarchies of “methodologies.” [29]

Limitations of Current Hierarchies

Although evidence-based practice is designed to provide the most effective recommendations for treating patients, evidence hierarchies frequently can be unhelpful. Many of the hierarchies that are available through the multiple organizations and evidence-based centers ignore pre-appraised evidence from their classification (e.g., those obtained through systematic reviews, meta-analyses, or critical summaries.) One example is the GRADE approach by the Cochrane Collaboration, which only categorizes RCTs and observational studies.[31] Additionally, many hierarchies underrate evidence categories related to expert opinion, ideas and biological plausibility. These categories are important when discussing the precision orthodontics approach that involves treating stratified groups of patients with severe conditions.[31] This includes patients requiring innovative management approaches that do not fit the current average estimates.

In orthodontics, not all study designs are applicable or feasible to the population and treatment modalities present. Treatments often are appliance driven, gradual and cumulative, with no clear-cut etiologic disease-pathogenic agent. Orthodontic cases of malocclusion, sleep apnea and orofacial myofunctional disorders are multi-factorial and may be too complex to fit the RCT study design model. In response, multiple pragmatic models have been proposed, one of which includes an evidence pyramid designed by Proffit, “the hierarchy of quality in the evidence for clinical outcomes in orthodontics.”[28,32] This helps to assess the validity of poorly conducted systematic reviews and give greater significance to good retrospective or non-random prospective studies.

High-quality evidence must have relevance to the population being treated, as well as provide a clinically significant effect. This can undermine and disprove results from RCTs or studies with high-quality "evidence" or methodology.

In addition, clinical trials are designed to determine the average effects of a treatment on a population and may not represent the varying differences among individuals. Additionally, although RCTs have high internal validity, their external validity (generalizability) is low given that

they are conducted in controlled environments by expert researchers on a small subset of a population. This contrasts with the daily clinical practice since many of the patients in clinical practice may not meet the inclusion/exclusion criteria set forth in these clinical trials.

TOWARD EVIDENCE-BASED PRECISION ORTHODONTICS (EBPO)

While appreciating the importance of precision orthodontics and evidence-based orthodontic approaches, each presents with unique strengths and limitations, despite the orthodontic specialty requiring both to progress. None of these approaches can exist independently of the other. Therefore, it is time to shift the paradigm toward a combined evidence-based precision orthodontics (EBPO) in order to leverage the strengths of both approaches and overcome the challenges that come with each. The question remains how the shift toward EBPO can happen; the following provide some recommendations.

Big Data Analytics

Big data analytics using complex computer models provide the first step toward reconciling the precision and evidence-based orthodontic approaches. Importance must be placed on a smart or AI analytic software that can update and consolidate large amounts of health information.

Developing harmonized pan-orthodontic datasets with standardized data entry and digitization will enhance inter-institutional collaboration. This is significant as it will provide sources for large samples that may not be available using small clinical trials. It is equally as important to improve access to these datasets and minimize burdens on researchers who are interested in studying them.

A step-up hierarchy method *via* linking multiple datasets is another method that can improve the quality of evidence coming from retrospective datasets. This can occur in the form of linking small trials with n of < 5 to databases and systems in order to study complex questions or by linking multiple large cross-sectional datasets. Additionally, adjusting for temporal relationships, the patient's background, values and context also must be considered. This could enhance or "step up" the level of evidence from a cross-sectional level to a higher level (i.e., cohort), hence the name, the step-up approach (Fig. 3).

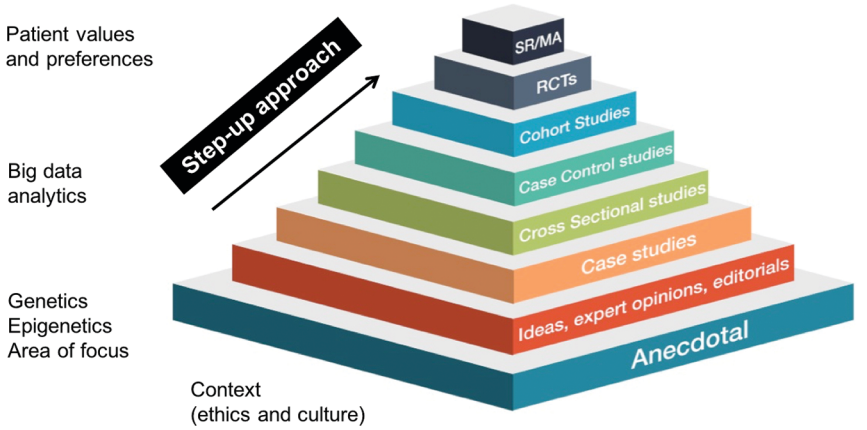

Figure 3. A step-up hierarchy approach. SR/MA = systematic reviews/meta-analysis.

Blogs and Forums as Important Sources of Information That Allow Clinicians and Patients Alike to Share Experiences and Treatment Outcomes

An international orthodontic registry for ongoing studies and collective, multi-centered efforts to pool healthcare data addresses the issues of generating clinical research data. The NDPBRN seeks to serve this purpose and allows clinicians to participate in research studies in oral healthcare and expand the professions' evidence-based network. Societies such as the American Association of Orthodontists (AAO) have been active in pursuing the collaboration of high-quality orthodontic research. To facilitate the development of a national network of orthodontic offices to participate in practice-based research (AAO-PBRN), they have established a practice-based research network task force that recruits and creates research questions that are important to clinicians. The NDPBRN can be involved further by posing research proposals to academic institutions to help carry out these studies. As there are fewer than 100 orthodontic offices registered to participate in the NDPBRN, more practitioners are needed to advance and improve the quality of orthodontic research.

Sharing patient EHR data through programs such as the NIH's *All of Us* research program will become much more feasible in the future as well. The NIH's Sync4Science (S4S) project will be creating a technology that allows users to share and transfer their own EHR data safely and

securely to be utilized for research and as an important source of information for clinicians.

Even more important is the need to standardize intra-oral scanning and 3D imaging, as well as to promote a standardized file platform to allow free exchange of big data among clinicians and researchers. This automated approach of assessing orthodontic needs through databases or 3D libraries of images will expand the future directions on effective diagnostic and treatment planning.

Educating Investigators on Proper Research Methodology and Accurate Reporting of Clinical Trials

The results of RCTs provide the highest quality of evidence and are the gold standard for considering intervention effects. Randomization reduces bias by randomly selecting interventions and treatment groups, in which differences in treatment groups are held to chance. However, true randomization in clinical trials is not always evident and may contribute to bias results. There seems to be pervasive evidence in the biomedical and dental literature that randomization and RCT quality are not optimal and that often-published titles and studies labeled as RCTs are not, in fact, true RCTs. The study by Koletsi and colleagues in 2012 concluded that "from 112 clinical trials in orthodontic literature described as RCTs, only 29.5% included a clear description of appropriate random number generation and allocation concealment in the text of the article."[33] Additionally, 46% of studies were classified as unclear and 24.1% were classified as not RCTs.[33] Therefore, funding agencies should begin implementing the need for educating investigators on proper research methodology and accurate reporting of clinical trials. As clinical practice and treatment depend on RCTs and systematic reviews, it can be important for investigators to verify specific guidelines (e.g., the CONSORT statement).[34] Research pertaining to educating the orthodontic specialty in clinical trial methodology should be considered. Non-standardized research contributes to health research waste, where research outcomes are not reported.

Studies such as an n-of-1 RCT often may be conducted to facilitate a more optimized and improved care to an individual patient. Personalized RCTs are another method to consider when big data could be used to obtain predictions.[35,36] Samples then may be selected based on these predictions to include in trials, or in order to use as a full sam-

ple frame for further study. Biomarkers also could be applied to clinical trials prior to randomization or applied in retrospective case-control studies to overcome limitations of cost and long follow-up periods in prospective studies.[37]

Advocating Studies on Genomics and Other "-Omic" Areas

Current clinical orthodontic records focus on patient's phenotypes, including age, sex, developmental status, radiographic cephalometrics, panoramic imaging and dental preliminary impression casts or scans. With the use of precision orthodontics in future practices, however, orthodontists may focus on taking samples of saliva or other body fluids (e.g., blood) for genetic analysis of variants that may affect the orthodontic treatment outcome positively, negatively or both. Individual genomes, key growth factors and signaling molecules specific to gene variants will become part of the screening that an orthodontist will assess during standard diagnosis and treatment planning. Thus, orthodontics will shift from a wholly phenotypic standpoint to a greater consideration for a patient's genotype.

Redesigning the Educational Curricula to Reflect the Shift in Paradigm

It is time to expand our curriculum to include precision approaches in addition to the traditional evidence-based methods. Advocates of the evidence-based and precision movements have a responsibility to adjust the pre-and post-doctoral curriculums to include content in these areas.

CONCLUSIONS

Precision orthodontics is a selective and evolving strategy for disease prevention and treatment that is governed and tailored to the individual's unique variabilities in genetic, environmental and experiential factors. With precision orthodontics' improved and more efficient clinical data gathering and research, drug discovery may be facilitated and clinical trial outcomes and design may be improved. Based on the array of data input into AI or smart learning systems, data analysis and reporting of predicted risk and treatments, identifying high-risk groups can lead to the development of novel interventions and drug therapies. Precision orthodontics, however, cannot exist without the evidence-based orthodontics approach that systematically evaluates the evi-

dence, while taking into account the clinician's experience and the patient's preferences. Multiple methods are indicated to move toward a combined evidence-based precision orthodontics approach.

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MECHANICS AND GINGIVAL CREVICULAR FLUID BIOMARKERS ASSOCIATED WITH SPEED OF HUMAN TOOTH MOVEMENT

Laura R. Iwasaki and Jeffrey C. Nickel

ABSTRACT

Speed of tooth movement was investigated; 1) to test for effects of applied stress and growth status; 2) to compare results with and without invasive methods; and 3) for associations with gingival crevicular fluid (GCF) biomarkers. Forty-six consenting subjects with orthodontic treatment plans involving first premolar extractions participated in a randomized split-mouth study that used segmental mechanics with definitive posterior anchorage and vertical-loop maxillary canine retraction appliances. Height and cephalometric changes determined growing (G) and non-growing (NG) subjects. Subjects were appointed for nine to eleven visits over 84 days for dental impressions to measure three-dimensional (3D) tooth movement, GCF sampling and to ensure retraction forces were applied continuously. Calibrated nitinol coil springs were custom selected to apply two different stresses of 4, 13, 26, 52, or 78 kPa to maxillary canines in each subject. Statistical analyses ($\alpha = 0.050$) included analysis of variance, effect size (partial η^2) and Tukey's Honest Significant Difference and two-group t-tests. Results were compared to reports in the literature regarding invasive methods to accelerate tooth movement. Additionally, GCF biomarkers associated with tooth movement were investigated. Stress magnitude and growth status significantly affected the speed of tooth translation. Optimal applied stresses were 26-52 kPa and overall speeds were 1.5-fold faster in G compared to NG subjects. These methods resulted in comparable or better rates than reported when invasive techniques were applied. Relative ratios of cytokines measured in GCF could account for over 50% of the variability in speed of tooth movement when stage of development, health status and applied stresses were controlled.

KEY WORDS: biomarkers, gingival crevicular fluid (GCF), human, orthodontic mechanics, tooth movement

OPTIMAL SPEED OF HUMAN TOOTH MOVEMENT

Evidence for Factors That Matter[1]

Magnitude and direction of applied forces are controllable variables during orthodontic treatment. Important questions remain, however, about how the magnitudes of applied forces can affect the speed of human tooth movement and what are optimal magnitudes for the fastest, non-harmful tooth movement.[2,3] Well-controlled, long-term clinical studies that address these important questions are rare. In particular, known sample population differences (e.g., the tendency for faster tooth movement in younger, growing [G] individuals compared to older, relatively non-growing [NG] individuals) need to be characterized.[4,5] Plus, the applied mechanics and outcomes should be expressed in ways that are translatable to various clinical conditions (i.e., by considering both the magnitude of force, area of tooth surface loaded by this force [*aka* stress] and amount of tooth movement over time [*aka* speed]). Previous research designed to address these important questions using a model of human maxillary canine retraction while controlling for stage of development and applied stress has suggested that there are optimal stress (and force) magnitudes.[5-9] Nevertheless, a limitation of this previous research was that the speed of tooth translation was measured orthogonally (i.e., distal tooth translation was considered the major direction of movement). This was an acceptable first approximation, but the resultant distolateral translation more aptly and completely depicts the total amount of clinical tooth movement because of the form of the dental arch. Hence, this section provides the results of an improved analysis of the effect of applied stress magnitude on the speed of maxillary canine translation in a larger sample than previously reported. The null hypotheses tested were that the speed of tooth translation was not affected by: 1) stress magnitude; and 2) growth status.

The protocols were approved by the Institutional Review Boards of the University of Nebraska Medical Center and University of Missouri-Kansas City, in accordance with the Helsinki Declaration. The protocols for recruitment of subjects and collection of data were described previously.[6,7] In brief, patients at two clinical sites with good oral hygiene and accepted orthodontic treatment plans involving extraction of

both maxillary first premolars and without other medical or dental problems were invited to participate.

After consenting, subjects received oral hygiene instructions, chlorhexidine gluconate (Sunstar Americas Inc., Chicago, IL) for twice-daily oral rinsing, instructions to avoid taking any other medications and custom maxillary posterior anchorage appliances (Fig. 1). Subjects then had both maxillary first premolars extracted; at least two weeks later, maxillary canine retraction was begun *via* a stainless steel wire (0.016" x 0.022" cross-section) vertical-loop auxiliary and nitinol coil spring. The auxiliary wire was customized initially to engage passively the canine bracket slot at one end and the auxiliary tube in the first molar band at the other end with the loop just distal to the canine bracket (Fig. 1*B*). This wire was tied in with both stainless steel wire and elastomeric ligatures at the canine bracket and free to slide through the molar band tube. The height of the loop matched the estimated center of resistance of the maxillary canine which was 0.24x the root length (LR) apical from the cemento-enamel junction (CEJ).[10] A periapical radiograph of each maxillary canine with a coronal reference wire was used to determine the LR corrected for magnification. A nitinol coil spring calibrated at oral temperature was selected to deliver a prescribed force magnitude for the distance activated between hooks, one distal to the auxiliary wire loop and the other on the first molar band on the same side (Fig. 1*B*). Engagement of the coil spring on Day 0 caused the legs of the loop to open and thus, delivered the desired force and moment for maxillary canine translation. A stress of either 4, 13, 26, 52, or 78 kPa was assigned randomly to one maxillary canine and a different stress was assigned to the other side. As described previously, the desired force (F) to attain the assigned stress (σ) was customized based on each canine's estimated distal root surface area (A) and $F = \sigma A$, where $A \approx$ triangular area defined by the interfocal distance of the elliptical cross section of the root at the CEJ and LR.[8]

Subjects were appointed for study visits on Days 0, 1, 3, 14 and every two weeks until Day 84. Some subjects also were appointed for visits on Day 7 and 35. At each study visit, a modified gingival index (MGI) score was recorded and a maxillary impression was made using a custom tray and polyvinylsiloxane impression material.[11] These impressions were used to make dental plaster models resulting in approxi-

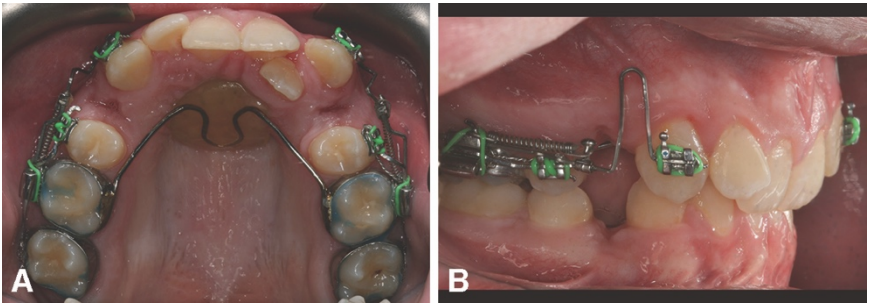

Figure 1. Occlusal (*A*) and vestibular (*B*) views of posterior anchorage and maxillary canine retraction appliances. The passive anchorage appliances connected posterior teeth and consisted of a Nance appliance, stainless steel passive buccal (≥ 0.016 x 0.022" cross-section) wire segments in bracket/band slots plus figure-eight stainless steel wire ligation (0.010" diameter) overlaid with elastomeric ties. Maxillary canines were retracted *via* a vertical-loop auxiliary retraction wire activated by a calibrated nickel titanium (NiTi) spring selected to deliver a prescribed force and stress.

mately ten models per subject. These models and a set of three crylic templates customized for each subject, which carried reference markers and fit the subject's maxillary canines and posterior teeth uniquely, were used with a three-axis microscope (Measurescope MM-22, Nikon Inc., Melville, NY) to measure canine movement over time with 6 degrees of freedom.[6]

Subjects were categorized as actively growing (G) or not growing (NG) based on height and cephalometric superimpositions compared at the beginning and end of orthodontic treatment. Linear and angular tooth movements were plotted for each maxillary canine *versus* time (days) to assess if these were progressive or fluctuating. The resultant distolateral movement, which was prescribed by the orthodontic appliance, was expected to be progressive and if so, the speed (mm/day) for each maxillary canine was calculated using data from Day 0 and ≥ Day 7. This precluded the relatively large movements at Days 1 and 3 due to compression of the periodontal ligament right after the loads were applied.[6,7]

Descriptive statistics including means and standard deviations (SD) were calculated. Two-way analysis of variance (ANOVA) was used to identify if stress and growth status significantly affected the speed of tooth movement. One-way ANOVA was used to determine differences

in speed between stresses for G and NG groups. Partial η^2 measured the effect sizes of the independent variables on speed, where a partial $\eta^2 > 0.14$ indicated a large effect size.[12] To keep the Type I error rate nominal and investigate if significant differences in speed existed between the five stress levels, pair-wise comparisons were made using Tukey's Honest Significant Difference *post-hoc* tests. For a given stress, t-tests were applied to investigate differences in speed of tooth movement between G and NG groups. The assumption of equal variances was assessed by Levene's test. All statistical analyses used $p < 0.050$ to indicate significance and were performed with commercial software (SPSS version 23, IBM SPSS Inc., Chicago, IL).

Forty-eight subjects gave informed consent, but two failed to participate due to scheduling conflicts. Thus, 46 subjects completed the study, 31 of these followed the schedule within at least three days. All subjects made at least eight study visits with 94% of subjects completing nine to eleven visits. The shortest and longest study times were 76 and 107 days, respectively. Each posterior template uniquely engaged the occlusal third of the posterior teeth for the entire set of dental models for each subject, indicating that the anchorage teeth were stable during the study. No root resorption was observed through a qualitative comparison of radiographs from the beginning and end of the study or completion of orthodontic treatment. Subjects maintained good oral hygiene, as evident by average MGI scores for each subject that were less than 1 (where 0 and 1 were defined by "absence of inflammation" and "mild inflammation," respectively). The numbers and mean ages ± SD of G and NG groups were 36 (19 females, 17 males) and 13.5 ± 1.7 years and 10 (eight females, two males) and 19.2 ± 5.3 years, respectively.

Extrusion, labial crown torque and distal crown tip fluctuated over time and were relatively small, showing average amounts ± SD at/near the end of the study (Day 84 ± 8) of 0.15 ± 1.45 mm, -1.29 ± 5.66° and 2.39 ± 4.50°, respectively (Table 1). Distopalatal rotations at/near the end of the study were relatively small for 4, 13, 26 and 52 kPa, which averaged 3.86 ± 6.83°; however, distopalatal rotations for teeth moved by 78 kPa were markedly larger at Day 84 ± 8 and averaged 18.03 ± 9.50° (Table 1). For all stress levels, distolateral movements were progressive and linearly related over time (Fig. 2), where the average amount ± SD at/near the end of the study was 4.55 ± 1.95 mm and average R^2 for movement *versus* time was 0.905 ± 0.132. Slopes

Table 1. Average amounts ± SD of tooth movement at/near the end of the study (Day 84 ± 8) for teeth moved by five stresses (kPa).

Stress (kPa)	Tooth movement (average ± SD)				
	Distolateral (mm)	Extrusion (mm)	Distal crown tip (°)	Labial crown torque (°)	Distopalatal rotation (°)
4	2.82 ± 1.20	0.31 ± 1.46	2.36 ± 4.92	0.40 ± 3.22	2.65 ± 5.22
13	3.96 ± 1.70	1.93 ± 1.74	1.61 ± 5.32	-0.99 ± 4.97	3.19 ± 8.82
26	5.38 ± 0.99	-0.08 ± 1.51	2.38 ± 2.14	-1.14 ± 4.16	2.78 ± 3.43
52	5.47 ± 1.39	-0.09 ± 1.10	3.31 ± 4.41	-1.66 ± 7.96	6.40 ± 7.66
78	5.96 ± 1.80	0.58 ± 1.43	2.84 ± 5.08	3.00 ± 6.66	18.03 ± 9.50

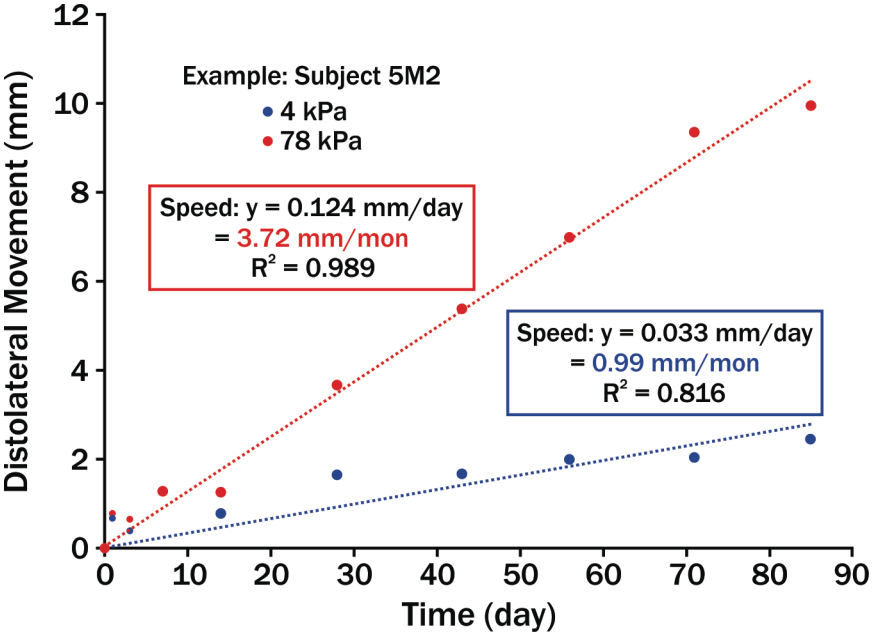

Figure 2. Distolateral tooth movement (mm) *versus* time (day) for right and left maxillary canines moved by 4 and 78 kPa, respectively, in a G male subject. These linear relationships for Day 0 and ≥ Day 7 are characterized by slopes (y = speed in mm/day) and R^2-values.

from the distolateral movement *versus* time plots determined speeds, where mean ± SD values for 4, 13, 26, 52 and 78 kPa were 0.034 ± 0.015, 0.047 ± 0.019, 0.066 ± 0.025, 0.068 ± 0.016 and 0.079 ± 0.030 mm/day, respectively (Fig. 3). These data fit a logarithmic curve with R^2 = 0.962 and the effect of stress on speed had partial η^2 = 0.376. Speeds were significantly higher for teeth moved by 26, 52 and 78 kPa (all $p < 0.0001$) than 4 kPa and for teeth moved by 52 kPa ($p = 0.022$) and 78 kPa ($p < 0.0001$) than 13 kPa.

Mean speed of distolateral tooth movement for G subjects was 0.062 ± 0.026 mm/day and was significantly higher ($p = 0.001$) than for NG subjects where speed was 0.041 ± 0.019 mm/day (Table 2). For each applied stress, mean speeds were higher for teeth in G than NG subjects and significantly so for 13, 26 and 78 kPa (Table 2).

Because growth status was a significant factor, a separate analysis of the 72 teeth moved in G subjects showed that the effect of stress on speed had partial η2 = 0.495. For teeth in G subjects, speeds were

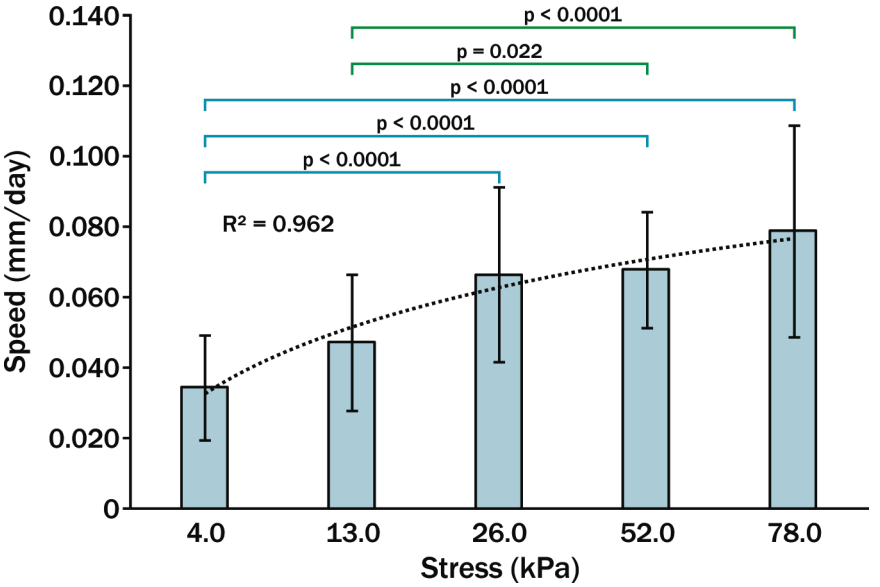

Figure 3. Mean speeds of distolateral tooth translation (mm/day) for five magnitudes of applied stress (kPa) for sample of 92 maxillary canines. Vertical bars indicate ± SD about the means. Dotted line indicates logarithmic relationship with R^2 = 0.962. Brackets denote significant differences with specific p-values as indicated.

Table 2. Mean speeds (mm/day and mm/month) of distolateral tooth movement for five applied stresses (kPa) in growing (G) and non-growing (NG) groups. [a,b,c,d] = significant differences ($p < 0.0001$) within G subjects using Tukey Honest Significant Difference post-hoc tests. p* = results of t-tests between G and NG groups within each stress level where significant results are shown in bold font.

Stress (kPa)	Teeth moved in G subjects		Teeth moved in NG subjects		p*
	Speed ± standard deviation (mm/day) [mm/month]	Number	Speed ± standard deviation (mm/day) [mm/month]	Number	
4	0.035 ± 0.014[a,b,c] [1.05]	16	0.030 ± 0.021 [0.96]	4	0.535
13	0.052 ± 0.017[d] [1.56]	16	0.025 ± 0.009 [0.75]	4	**0.006**
26	0.075 ± 0.020[a,d] [2.25]	12	0.040 ± 0.020 [1.20]	4	**0.007**
52	0.071 ± 0.016[b] [2.13]	16	0.055 ± 0.014 [1.65]	4	0.089
78	0.087 ± 0.029[c,d] [2.61]	12	0.053 ± 0.018 [1.59]	4	**0.046**
All combined	0.062 ± 0.026 [1.83]	72	0.041 ± 0.019 [1.23]	20	**0.001**

significantly higher (all $p < 0.0001$) for teeth moved by 26, 52 and 78 kPa than 4 kPa and for teeth moved by 26 kPa and 78 kPa than 13 kPa (Table 2). Speeds were nearly significantly different for teeth moved by 52 and 13 kPa ($p = 0.062$).

Herein is reported newly analyzed data from 92 maxillary canines in 46 subjects translated distolaterally using determinate, quantified mechanics with definitive posterior anchorage. Methods and some aspects of tooth movement data were reported previously.[6-8,13,14] The current results showed that the effects of stresses of 4, 13, 26, 52 and 78 kPa (on average 18, 60, 120, 240 and 360 cN of applied force, respectively) on speed of distolateral tooth translation were related logarithmically ($R^2 = 0.962$) and stress accounted for 37.6% of the variability in speed independent of sample size (partial $\eta^2 = 0.376$). These results show that the first null hypothesis was rejected and teeth moved by 26, 52 and 78 kPa (approximately 110 to 360 cN) moved faster than teeth moved by ≤ 13 kPa (≤ 60 cN). Although teeth moved by the highest

stress tested (78 kPa) on average showed faster speeds, these teeth also showed marked distopalatal rotation, outstripping the constraint conditions of the ligation compared to teeth moved by the other stresses. Furthermore, these results support the hypothesis that the rate of tooth movement increases with applied stress up to a relatively optimum magnitude and further increases do not show benefits or potentially undesirable side effects (e.g., more distopalatal rotation).[2]

In addition to applied stress, the stage of development of subjects also was an important factor, where speed of tooth movement was 1.5-fold and significantly faster in G compared to NG subjects. Hence, the second null hypothesis was rejected.

Limitations of the methods used previously have been described and include: unbalanced sample numbers in G and NG groups; assumptions that the distal end of the vertical-loop auxiliary wire was free to slide through the maxillary first molar band tube; and that static mechanical principles were applicable due the relatively slow speeds of tooth movement involved.[6] Applied strain rather than applied stress may be a more appropriate biological signaling mechanism in orthodontic tooth movement. However, strain is a more challenging mechanical prescription to estimate and apply *in vivo* compared to stress. Future studies are indicated using this tested human model of tooth movement with clinically translatable techniques for comparison to current results and to investigate biomarkers and adjunctive methods to improve orthodontic therapies.

Comparison of Results With/without Invasive Methods to Accelerate Tooth Movement

Increased speed of orthodontic tooth movement using adjunctive methods is of clinical interest (Table 3). For example, effects of corticotomies, piezocison and tissue micro-perforations compared to control canine retraction using sliding mechanics in split-mouth studies have been reported for 13 and 20 subjects, respectively.[15-17] These studies showed that after one month, speeds of tooth movement for corticotomies and micro-perforations *versus* controls were 1.89 *versus* 0.75 mm/month and 1.1 *versus* 0.5 mm/month, respectively.[15,17] The corticotomy *versus* control canine retraction study demonstrated that speeds were enhanced by the surgical intervention for the first two months, but by the third and fourth months experimental and control

Table 3. Results from maxillary canine retraction studies with and without stimuli intended to accelerate tooth movement.[1,15-17] n = number of maxillary canines; F = applied force; speed = rate of maxillary canine movement.

Study [reference #]	n	Age (years)	F(cN)	Speed (mm/month)		Stimulus	Time-point (month)
				Stimulus	No stimulus		
Aboul-Ela et al., 2011[15]	13	Mean: 19	150	1.89	0.75	Corticotomy	1st
				0.89	0.85	Corticotomy	4th
Alikhani et al., 2013[17]	20	20-33	100	1.10 ± 0.15	0.50 ± 0.15	Micro-perforation	1st
Abbas et al., 2016[16]	20	Mean: 21	150	1.56	0.84	Corticotomy	3rd
		Mean: 20		1.34		Piezocision	3rd
Iwasaki et al., 2017[1]	20	Mean: 14	18	Not applicable	1.03 ± 0.44	None	3rd
	20	Mean: 15	60		1.41 ± 0.58		
	16	Mean: 16	120		1.99 ± 0.74		
	20	Mean: 14	240		2.03 ± 0.49		
	16	Mean: 14	360		2.36 ± 0.90		

speeds were similar (e.g., 0.89 and 0.85 mm/month, respectively [Table 3]).[15] In the current study, using controlled tooth movements and stresses of 26-52 kPa resulted in average speeds of tooth movement of ≥ 2.13 mm/month in G subjects and ≥ 1.20 mm/month in NG subjects (Table 2) over three months. These results argue for use of quantified stresses—and thus, forces and sizes of teeth—for both effective and efficient tooth translation at comparable or better rates than has been demonstrated to date using relatively invasive techniques to increase rates temporarily.

BIOMARKERS FOR SPEED OF TOOTH MOVEMENT

Why Study Gingival Crevicular Fluid (GCF) During Tooth Movement?

Even when factors that affect the speed of orthodontic tooth movement are well controlled, quantified and equivalent, the variability in speed amongst teeth is high. That is, for the 92 maxillary canines described in the previous section, some teeth were translated distolaterally 21x faster than others. When stage of development and applied stress were the same, the results showed that for teeth moved by 4 kPa, the variability in speed of tooth movement was up to 5.0:1.0 in G subjects

and 8.1:1.0 in NG subjects. Further accounting for this variability would make rates of tooth movement more predictable for individual patients and improve treatment planning.

Applied orthodontic forces cause local inflammation in the paradental tissues and a series of events including increased capillary permeability and ultimately, paradental tissue changes that result in tooth movement. Fluid collected from the gingival crevice that is healthy and unstimulated is a transudate of interstitial fluid, whereas in inflammatory conditions, the fluid is an exudate that reflects levels of serum metabolites.[18] Hence, as many have already noted, gingival crevicular fluid (GCF) could be a source of quantifiable analytes, that if associated with rate of orthodontic tooth movement, could be useful biomarkers. GCF is distinct from saliva and likely has higher diagnostic potential because of its relative proximity to the sites of paradental tissues changes during orthodontic tooth movement compared to saliva.[19-27]

GCF, like saliva, is collectable relatively non-invasively and inexpensively. Much already has been written about GCF in terms of discovery, mechanisms of production, methods of collection and analyses, and detectable analytes that are elevated or reduced during orthodontic tooth movement.[17,18,20-23,25,28-33] Because the volumes of GCF from healthy tissues are small, the amounts of potential biomarkers also are very small, usually in the microgram range at most.[25] This has necessitated sufficiently sensitive and selective methods of quantifying important analytes to distinguish these from abundant proteins (e.g., albumin, immunoglobulin and keratin). In addition, the challenges of detection *versus* shielding associated with three-dimensional (3D) conformation and post-translational attachment of functional groups (e.g., phosphates and carbohydrates) must be addressed. Historically commonly used immunoassays and enzyme-linked immunosorbent assays (ELISA) are quantitative sufficiently, but restricted to about one analyte per GCF sample and are relatively expensive in terms of time and labor. More recently, advances in microchip and ionization technologies have made it possible *via* multiplex micro-arrays and mass spectroscopy, respectively, to measure multiple analytes accurately in small samples.[25] Considerations regarding all of these techniques have been covered in detail elsewhere.[25,33]

What Currently is Known About GCF Biomarkers and Speed of Tooth Movement?

The ability to measure more than 100 regulatory proteins in GCF has been established and challenges remain in determining which GCF analytes are important markers of the regulation of orthodontic tooth movement, what is the association between these markers and the rates of tooth movement, and how often should key markers be measured to make accurate predictions?[34] The latter is an important consideration because of the cyclic and coordinated secretion of proteins over time as part of homeostasis. In addition, evidence from available studies that have analyzed GCF from teeth before and after application of an orthodontic force, generally show peaks in amounts of substances one to two days after loading of the teeth and return to baseline levels after about one week.[17,35-37] However, many previous studies have not measured potential key analytes frequently over weeks or months while controlling important variables (e.g., anchorage and mechanics) to achieve bodily tooth movement. Furthermore, many previous studies included in this author's research have not measured both the applied orthodontic loads and the amount of tooth movement over time so that associations with key analytes can be elucidated.[20]

As described in the first section of this chapter, under conditions of controlled anchorage and mechanics, where continuous and equivalent applied stresses were used for retraction of maxillary canines and the outcomes were measured frequently over several months, predictable distolateral translation of maxillary canines at steady rates was demonstrated.[1] Under these conditions, GCF samples were collected *via* established methods from each subject at each study visit using sterile paper strips (Periopaper; Proflow Inc., Amityville, NY).[38] The experimental sites were on the distal (and in some cases, also the mesial) of the maxillary canines bilaterally plus a control site on the distal or mesial of a mandibular canine, where the mandibular arch was without orthodontic appliances. Specifically, two paper strips were used per site, each gently inserted into the gingival crevice for 30 seconds, with one minute in between. The two strips then were sealed in labelled polypropylene containers (ClickSeal tubes; National Scientific Supply Co., San Marcos, CA) and stored at −70°C until ready for analysis. Subsequently,

for the first 33 subjects in these tooth movement studies, GCF samples from nine or ten time points over approximately 84 days for each experimental and control site were analyzed for the pro-inflammatory cytokine interleukin-1β (IL-1β), its naturally-occurring competitive receptor antagonist (IL-1RA) and total protein using commercially available ELISA kits.[7,9,13,38] GCF sample volumes measured immediately after collection generally were small and in the range of 0.8 μL for the two strips combined. Because of these small volumes, amounts of IL-1β and IL-1RA from each site were normalized relative to the total amount of protein per site.[38]

When IL-1β and IL-1RA were assessed over time in experimental *versus* control GCF sites (Fig. 4*A* and 4*B*, respectively), similar to previous studies, amounts peaked initially and then returned to baseline levels. Under conditions of bodily tooth movement (rather than tipping), however, these peaks generally occurred within seven days of the orthodontic forces being applied and then returned to Day 0 levels (before tooth loading at experimental sites) by about 14 days (Fig. 4) to 28 days and subsequently showed fluctuations over time.[38] The fluctuations possibly were periodic (Fig. 4). However, these data demonstrate that measurements need to be more frequent than every 14 days in order to determine this and to discount aliasing.

The ebb and flow of biomarkers during controlled tooth movement should be expected because of the inflammatory response caused by applied orthodontic forces and subsequent local cascade of related molecular and cellular events. These events and many of the molecules involved are known to act synergistically or antagonistically in a coordinated fashion to restore and maintain homeostatic balance. Nevertheless, most studies investigating analytes in GCF during tooth movement to date have measured individual analytes at a given time point or time points by averaging results from pooled sites sampled in different subjects. The inter-tooth variability in rate of tooth movement during controlled tooth translation argues against pooling results from different teeth, especially from teeth in subjects at different stages of development. Furthermore, other studies have shown differences in GCF between adolescents and adults in terms of volumes and amounts of cytokines.[37,39]

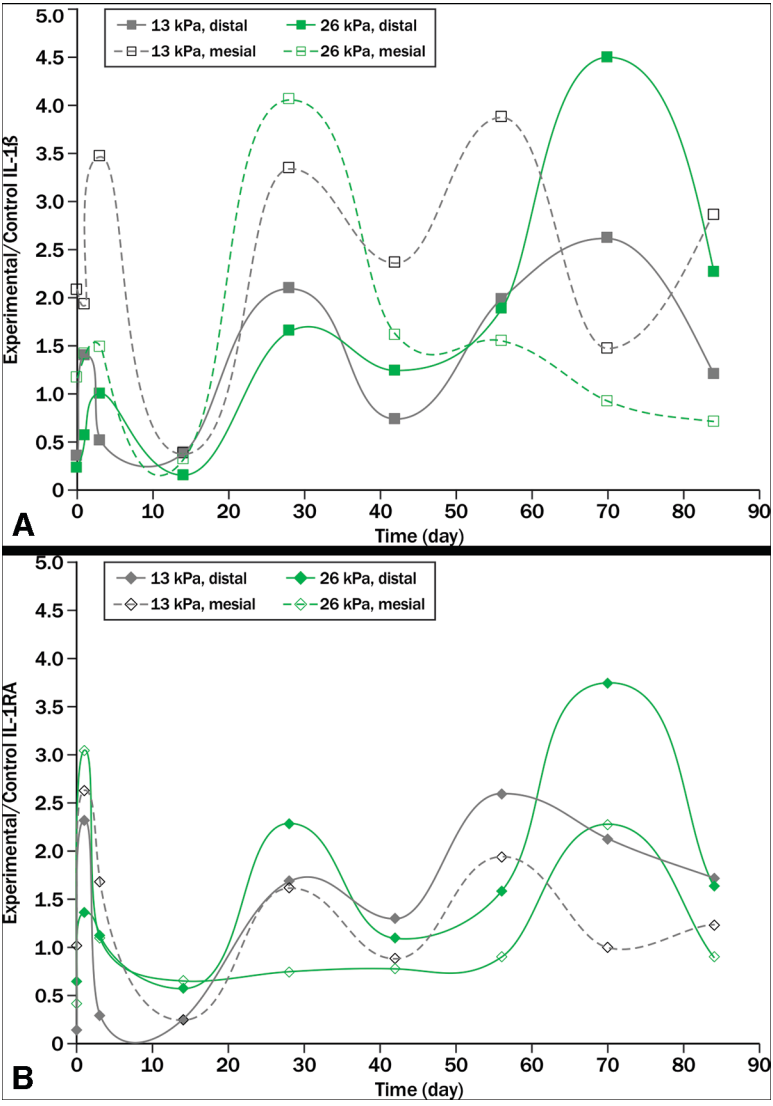

Figure 4. Experimental/control amounts of interleukin-1β (IL-1β; *A*) and IL-1 receptor antagonist (IL-1RA; *B*) in GCF over time (days) of tooth translation. These examples are from one NG female subject where the right and left maxillary canines (experimental teeth) were moved by 13 and 26 kPa, respectively, and sampled from distal and mesial sites. The control site was a mandibular canine without orthodontic appliances in the same subject. Amounts of IL-1β and IL-1RA were expressed relative to the total amount of protein measured in each GCF sample.

Despite the demonstrated complexity of the biological processes associated with alveolar bone turnover and tooth movement, so far, only rare examples in the current literature have considered combinations of analytes. For example, GCF amounts of receptor activator of nuclear factor kappa-B ligand (RANKL, a cell membrane protein expressed on osteoblasts/pre-osteoblasts) *versus* osteoprotegerin (OPG, a soluble decoy receptor secreted by osteoblasts/pre-osteoblasts), both of which bind to RANK (a cell membrane protein expressed on osteoclasts/osteoclast precursors) and promote or inhibit osteoclastogenesis have been assessed. Results measured at baseline and three time points for up to seven days showed significantly higher RANKL/OPG and faster tooth movement in adolescent compared to adult subjects.[37] Another example is IL-1β *versus* IL-1RA at experimental *versus* control sites (*aka* Activity Index = [Experimental IL-1β/IL-1RA]/[Control IL-1β/IL-1RA]), which shows promise in explaining the variability in speed of movement between teeth when the stage of development and mechanics are controlled.[9,13,38] That is, when a pro-inflammatory cytokine and its antagonist at experimental *versus* control sites were compared at approximately nine time points during about three months, the average Activity Index explained 55% and 53% of the variability in speed shown by teeth moved by 26 kPa and 52 kPa, respectively, in actively G subjects (Fig. 5).

What is Needed in the Future?

To date, the evidence shows that many potential biomarkers in GCF during tooth movement can be measured non-invasively and accurately. Next, to establish which analytes are key biomarkers, GCF measurements must be made longitudinally with sufficient frequency and the orthodontic tooth movement must be characterized well with important variables quantified and controlled, such as: applied stress magnitude, direction and timing; stage of development and health status (e.g., medications); and physical conditions (e.g., diabetes, obesity, osteoporosis). Then, for further improvements, multiple GCF analytes important to tooth movement must be quantified and more sophisticated statistical modeling must be applied in the future.

With current and forthcoming technological improvements, frequent and inexpensive measurements of GCF in individuals' natural environments during tooth movement should be possible. For instance, GCF

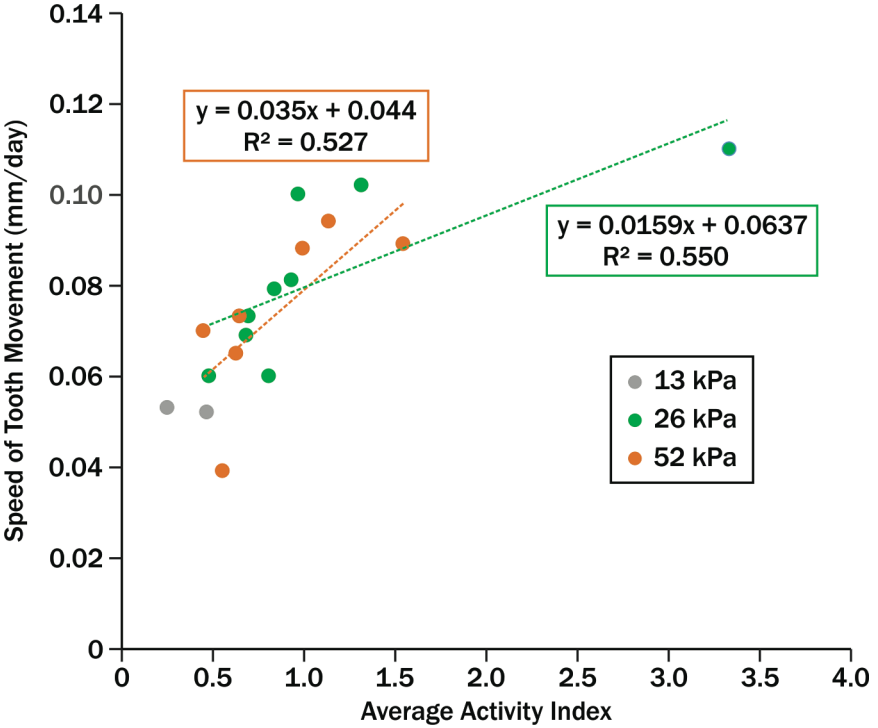

Figure 5. Speed of tooth movement *versus* average Activity Index ([Experimental IL-1β/IL-1RA]/[Control IL-1β/IL-1RA]) for actively G subjects whose maxillary canines were retracted by applied stresses of 13 kPa (n = 2), 26 kPa (n = 10) or 52 kPa (n = 8).

samples from one control and two experimental sites per subject at ten time points were analyzed recently using magnetic bead-based assays to quantify twelve analytes (IL-1β, IL-1RA, IL-6, interferon-γ, leptin, monocyte chemoattractant protein-1, matrix metalloproteinase (MMP)-3, MMP-9, OPG, osteopontin, regulated on activation normal T expressed and secreted, tumor necrosis factor-α).[40] The costs of these analyses were only 25% more than previously used ELISAs to quantify two analytes (IL-1β and IL-1RA) from the same number of samples per subject. In addition, new approaches are being developed to facilitate inexpensive and convenient testing of biological samples collected in individuals' natural environments.[41] These are important advances because the study of human conditions requires ecological validity, where

measurements accurately represent typical circumstances in natural, rather than laboratory settings.[42]

CONCLUSIONS

1. Stress magnitude significantly affected the speed of human tooth translation and accounted for 37.6% of the variability in speed. Optimal applied stresses were between 26 and 52 kPa.
2. For the same stress magnitude at 13, 26 and 78 kPa, tooth translation was affected significantly by growth status. Overall speed of tooth movement was 1.5-fold faster in G compared to NG subjects.
3. When the applied orthodontic mechanics were controlled and quantified, effective and efficient long-term tooth translation was achieved at comparable or better rates than reported in the literature when relatively invasive techniques were applied that increased rates only temporarily.
4. The average Activity Index measured in GCF accounted for over 50% of the variability in speed of tooth movement when stage of development, health status and applied mechanical stresses were controlled.
5. Potential biomarkers associated with rate of orthodontic tooth movement can be measured non-invasively and accurately. To improve on existing evidence, biomarkers also must be measured frequently over the long term under ecologically valid conditions during well controlled and quantified tooth movement.

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EXOSOMES: THERAPEUTIC AND DIAGNOSTIC TOOLS WITH PROMISING CLINICAL APPLICATIONS IN ORTHODONTICS

Wellington J. Rody Jr. and L. Shannon Holliday

ABSTRACT

Exosomes are nanometer-sized vesicles rich in biomarker molecules (e.g., RNAs and proteins). Evidence shows that osteoclasts secrete exosomes and this opens a window of opportunity for novel diagnostic and therapeutic applications in orthodontics. In addition, the ability to engineer exosomes and, thus, control their ability to bind specific targets, holds tremendous potential in the treatment of a host of oral diseases. In this chapter, we review the published literature about exosomes, present preliminary data showing that exosomes may be found in human gingival crevicular fluid (GCF) and discuss the practicality of using exosomes and/or their cargo as a clinical tool.

KEY WORDS: exosome, osteoclast, gingival crevicular fluid (GCF), biomarker, orthodontics

INTRODUCTION

Exosomes are minute vesicles (30 to 100 nanometers [nm] in size) secreted by most cell types that can be found in body fluids (Fig. 1). Recent research has shown that most of the molecules found in exosomes potentially are useful for diagnostic and therapeutic purposes. However, the clinical use of exosomes has been limited by their small size and the extensive sample preparation required for their isolation and measurement. The widespread use of exosomes in the medical field incited the curiosity of dental researchers and many articles exploring the potential use of exosomes in dentistry have been published in the past five years. Clinical applications that have been reported, to date, include dental pulp regeneration, oral cancer diagnosis, detection of external root resorption and tracking of tooth movement.[1-5] Since bone resorp-

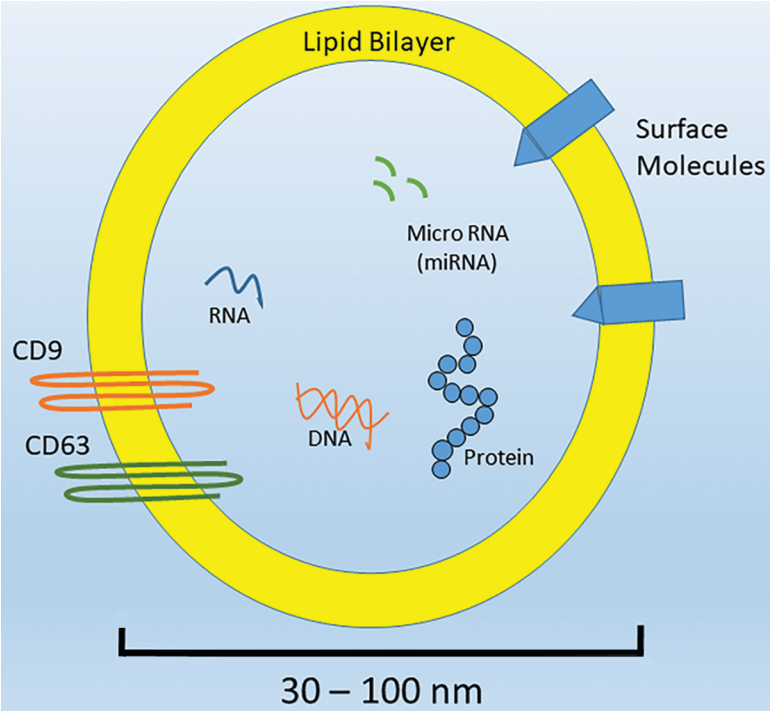

Figure 1. Simplified structure of an exosome. The content is protected well by a lipid bilayer membrane. While the molecular cargo of exosomes will vary according to the cell of origin, most exosomes carry common proteins on their surface (e.g., CD9 and CD63), which, in turn, allow the development of techniques that can capture them in body fluids or cell culture media.

tion is a key event in orthodontic treatment, it is highly likely that future clinical use in orthodontics demands a better understanding of osteoclast-derived exosome biology. Thus, the main goal in this chapter is to summarize the current knowledge on exosomes and discuss novel clinical applications with a focus in the orthodontic field.

OSTEOCLAST EXOSOMES AND POTENTIAL REGULATORY FUNCTIONS

Although exosomes first were demonstrated in 1983, it was not until 2016 that the initial studies examining exosomes released from osteoclasts appeared.[6-10] There were two primary factors for this delay.

First, for many years after the initial detection of exosomes, they were considered a means to dispose of unwanted proteins.[11] Even after it was shown in 1996 that exosomes could present antigen—making them signaling components of the immune system—interest in exosomes remained tepid.[12] The exosome field exploded in 2007 with the report of functional RNAs being transported from cell to cell in exosomes.[13] From this result, the hypothesis emerged that exosomes likely are both vital and powerful signaling agents. Bone, which requires fine communication between osteoclasts and osteoblasts/osteocytes to achieve the formation and remodeling, is a likely tissue in which regulatory exosome function is vital.[14] Nevertheless, the study of osteoclast exosomes was delayed for nearly a decade.

The second major reason for the delay was practical as osteoclast-derived exosomes are difficult to study. Osteoclasts are challenging to grow in cell culture and pre-differentiated osteoclasts cannot be obtained in sufficient quantities for most types of complex biochemical analysis. For many purposes, the best cell culture model is mouse-derived osteoclasts, where precursors are isolated from marrow and then stimulated to differentiate into osteoclasts with recombinant receptor activator of nuclear factor kappa-ß ligand (RANKL) and colony stimulating factor 1 (CSF-1).[15] To grow sufficient osteoclasts from this culture system to harvest even small numbers of exosomes, a relatively large numbers of mice must be sacrificed.[16] Isolation of exosomes required establishing new micro-scale procedures. To reduce the usage of mice during initial testing, author LSH's lab utilized RAW 264.7 cells—a mouse macrophage-like cell line which can be induced to differentiate into osteoclast-like cells—to pioneer techniques prior to exosome isolations from primary cells.[17] Unfortunately, the RAW 264.7 cells have certain crucial deficiencies as a model for osteoclasts and ultimately, primary osteoclasts are required for sound studies.

Three articles examining exosomes released from osteoclasts appeared concurrently in 2016.[8-10] Working in mouse models, all showed that osteoclast exosomes have paracrine regulatory activity. These reports presented data suggesting that semaphorin 4B or ephrinA2 were membrane proteins on the exosomes that interacted with receptors on osteoblasts to recruit the exosomes.[9,10] Although semaphorin 4D and ephrinA2 are known best as regulators of neural growth, both also have been implicated in bone growth.[18,19] Semaphorin 4D was shown to

inhibit bone formation in 2011; subsequently, efforts to block expression of semaphorin 4D or to interfere with its interaction with its receptor, Plexin-B1, for therapeutic purposes have been ongoing.[19-21] The presence of semaphorin 4D on exosomes released from osteoclasts could stimulate its receptor and potentially serve to dock semaphorin 4D containing vesicles onto osteoblasts so that they can fuse and deliver the luminal cargo, including miRNAs. Semaphorin 4D also has been shown to promote the ability of cancer cells to invade bone.[22] Like semaphorin 4D, some evidence exists suggesting that ephrinA2 from osteoclasts is involved in modulating bone remodeling.[18,23] EphrinA2 could stimulate both its surface receptor and mediate targeting and fusion of exosomes.

Two of the reports published in 2016 focused on the transfer of microRNA-214 (miR-214) from osteoclast to osteoblasts in exosomes and the resulting regulatory activity.[9,10] Numerous articles suggested that miR-214 has the ability to prevent osteoblastic differentiation. Wang and colleagues first identified activating transcription factor 4 (ATF4), a transcription factor that promotes the expression of osteoblast-specific genes, as a possible target for miR-214.[24] This mechanism has been identified by others in a number of additional articles, including the osteoclast exosome study of Li and colleagues that suggested miR-214 transported from osteoclast in semaphorin 4D-rich exosomes inhibited osteoblasts by inhibiting ATF4.[9] In addition to studies indicating that miR-214 is involved in regulating osteoblast differentiation negatively, others have shown it is involved in the metastasis of cancer cells to bone and is a positive regulator of osteoclasts.[25,26] A major concern regarding the proposed mechanism of miR-214 in exosomes from osteoclasts being transported to osteoblasts to suppress ATF4, or other protein expression, arises from reports showing that only very small numbers of miRNAs actually are transported per exosome.[27] The numbers reported seem too low to transfer enough microRNA of any kind to affect protein expression in target cells; however, this finding is controversial. Some suspect that the number of exosomes in most studies is exaggerated grossly due to detection on lipoproteins. At the same time, much of the quantitation of exosomes that is done makes use of nanoparticle tracking, which has a resolution limit larger than the size of small exosomes.[28] Quantitative approaches in exosome biology are essential to resolve this issue and for continued progress in the field.

The third article focused on exosomes that carried receptor activator of nuclear factor kappa-ß (RANK) on their surface and presented evidence that RANK-rich exosomes, along with RANKL-rich exosomes that are released by osteoblasts, represent novel nodes in the RANKL/RANK/osteoprotegerin (OPG) signaling network that is at the heart of bone biology and orthodontic tooth movement.[4,8,29] The idea of RANK being present in exosomes is a finding similar to a study showing tumor necrosis factor receptor (TNFR) in exosomes.[30] RANK in exosomes could bind RANKL on osteoblasts to inhibit its interaction with RANK competitively in the osteoclast membrane.[8] If this is true, exosome-bound RANK would be able to regulate osteoclast function and orthodontic tooth movement in the manner of OPG. Quantitative data from that study suggested that the portion of osteoclast exosomes carrying RANK was low (one in 32 by electron microscopy). The regulatory results could be explained if the RANK-RANKL interaction was utilized to dock exosomes for fusion and a regulatory factor (e.g., miR-214) was introduced.

OSTEOCLAST EXOSOMES AS A DIAGNOSTIC TOOL FOR MONITORING BONE REMODELING AND ROOT RESORPTION

RANKL, and less commonly RANK, have been used as biomarkers from serum, gingival crevicular fluid (GCF) and urine.[31,32] The question of why these transmembrane proteins are present in a soluble form has been suggested to be because ectoproteases release them from the cell surface and/or due to isoforms that do not express the transmembrane domain.[33] However, there is no data that we could locate showing the size of soluble RANK and RANKL. If they are present because the transmembrane domain is missing, then they would be shorter than the full length membrane proteins found in osteoclasts and osteoblasts. If they are being released in exosomes, however, they may be identical in size to the versions found in the plasma membrane.

After the *in vitro* report showing RANK in exosomes from osteoclasts, two articles reported identifying RANK in circulating exosomes. One of the two reports shows that RANK in exosomes is a marker for psoriatic arthritis.[34] These data suggest that RANK and RANKL present in exosomes may prove to be biomarkers for pathologies. This may include both bone-related pathologies and due to the role of RANK and RANKL in immune cells, pathologies of the immune system. However, to gain the

greatest clinical utility, it may be necessary to separate cell-specific exosomes from body fluids. For instance, the presence of RANK-rich exosomes in oral fluids may be explored as a diagnostic marker of osteoclast activity in the presence of periodontal disease and/or in sites undergoing tooth movement. In addition, the links to disease between soluble and exosome-associated RANKL and RANK may be different and while exosome-associated RANK or RANKL may be useful biomarkers for specific diseases or conditions, the signal may be obscured by the soluble forms.

Recently, it has been documented in the literature that exosomes are found in saliva; however, the presence of exosomes in GCF has begun to be explored.[35-37] In line with this, we feel that an encouraging start has been made by our group since our data suggest that approximately 54% of the proteins detected in GCF have been reported to be found in exosomes and many of them were upregulated at sites of dentin resorption.[3] Indeed, our group has pioneered the proteomic analysis of GCF and we were able to identify some 'clastic' cell exosomal markers (e.g., the protein Annexin A8) in the GCF of children undergoing physiological root resorption (Fig. 2). We also have preliminary data showing that a large number of nanoparticles in the size range of exosomes can be ob-

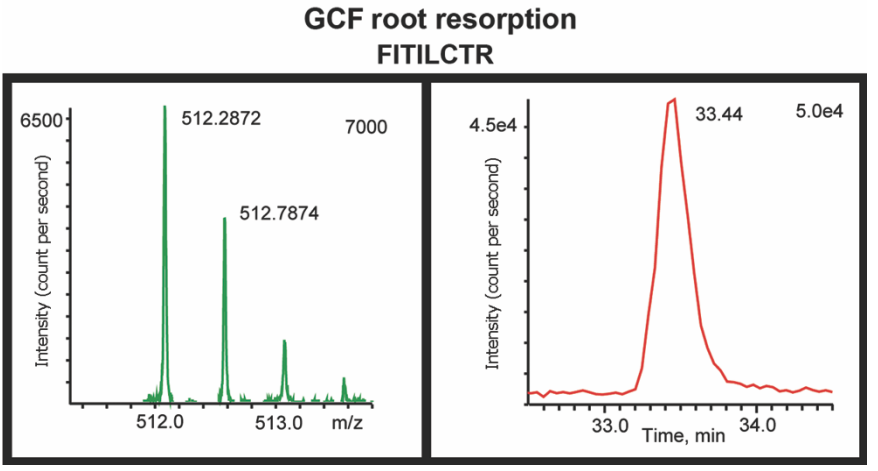

Figure 2. Mass spectrometry analysis of GCF from resorbing primary teeth. Signal intensities at peak maximum for FITILCTR, a peptide representing Annexin A8, and respective extracted ion chromatogram in red. Annexin A8 is an exosomal protein involved in acting ring formation, a process central to osteoclast resorption.

served in the GCF of patients with periodontitis using nanoparticle tracking analysis (Fig. 3). This cutting edge technique characterizes exosomes based on the rate of Brownian motion of the particles. Interested readers are referred to Gercel-Taylor and associates' article for a theoretical re-

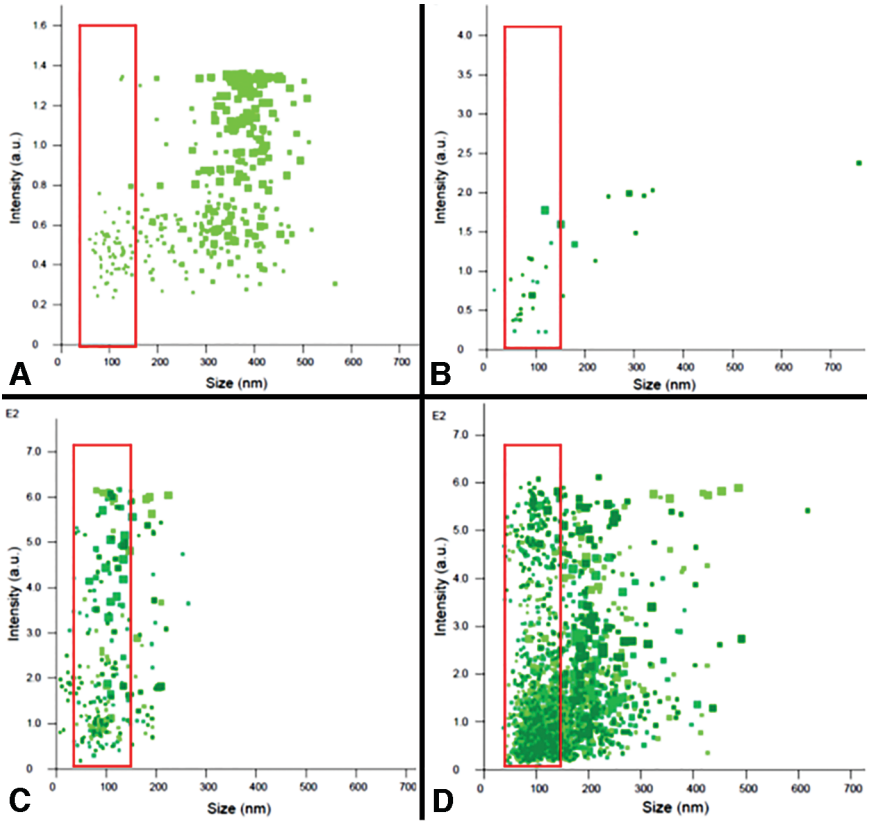

Figure 3. Size distribution and concentration of nanoparticles recovered from control and GCF samples. Analysis was performed using the NanoSight NS300 instrument (Malvern Scientific, Malvern, UK), which is equipped with a camera and particle-tracking software. Particle size between 30 and 150 nm (red box) is consistent with exosome size range. *A:* 400 nm control beads used for equipment calibration. *B:* Dilution media only. *C:* Empty GCF collection strip with dilution media. *D:* Paper strip containing GCF collected from a patient with periodontitis. Although some nanoparticles in the size range of exosomes were recovered from dilution media (*B*) and the paper strip itself (*C*), the concentration was much lower than the actual GCF sample (*D*) by two to three orders of magnitude. This is an indication that GCF may contain exosomes.

view of this technology.[28] More recently, Atsawasuwan and collaborators tested for the presence of exosomes in the GCF of patients undergoing orthodontic tooth movement.[5] The samples were collected at six time points prior to and after orthodontic tooth movement began. The authors confirmed the presence of exosomes in GCF by electron microcopy, western blots and immunostaining for exosomal markers (CD9 and CD63). In addition, they observed that miRNA-29 in exosomes seem to be overexpressed in GCF during tooth movement.

EXOSOMES AS THERAPEUTIC VEHICLES

During the past several years, data has emerged that exosomes may be useful for stimulating tissue healing. Much of the data indicates that naturally occurring exosomes (e.g., exosomes released by mesenchymal stem cells) aids healing, although the mechanism is not clear.[38-44] Perhaps most provocatively, data suggests that exosomes from young animals (or from the cells of young animals) can restore youthful characteristics when introduced into an older animal. Alternatively, exosomes from older animals will enhance aging-related conditions in young animals.[45,46] Recently, for example, serum-derived exosomes from aging patients were implicated in bone loss associated with the development of osteoporosis.[47] This immediately raises the possibility of harvesting stem cells from placental stem cells or stem cells from extracted deciduous teeth, or other “young” sources for revitalization of people as they age. Clearly, it would be best to find the mechanism of this activity so that it can be recreated in bulk and supplied to aging people as needed. Finally, while a number of studies showing the utility of exosomes, this area of research still is emerging and some caution must be exercised until the database from studies exploring therapeutic uses of exosomes is more robust.

Until now, the use of exosomes in therapeutics has involved finding the best source, either specific cell types or body fluids. It is clear now that each cell releases subsets of exosomes with specific regulatory properties. For example, osteoclasts may release a small subset of exosomes carrying RANK on their surface, which has the ability to block osteoclast formation by a paracrine mechanism as discussed previously. If it is confirmed that exosomes from a particular source can be separated (i.e., exosomes released by young mesenchymal cells), it is likely that a subset of exosomes from that source may be useful for therapeutic applications.

Nevertheless, other subsets of the exosomes from the same source may have no effect or may even counteract the therapeutic effect. Techniques are being developed to isolated subsets of exosomes. Early approaches relied on bead-based affinity separations.[48] High resolution flow cytometry and nanofluidic-based systems are under development and likely will be available widely in the near future.[49,50]

Methods for altering exosomes using various techniques for therapeutic purposes are emerging. Techniques for introducing proteins and RNAs into exosomes include strategies for both proteins and nucleic acids. Proteins can be introduced into exosomes by creating fusion proteins of the gene of interest linked to a gene encoding a protein (or protein subdomain) known to be localized to exosomes.[51,52] Oligomeric membrane-anchored proteins also tend to be trafficked to exosomes. The oligomeric protein TyA was shown to be targeted to exosomes when a site for myristoylation was engineered into the protein. RNA can be added to isolated exosomes by electroporation.[52] Certain sizes or conformations of RNA may be introduced less efficiently. The over-expression of a cargo RNA in exosome-producing cells will utilize mass action to promote inclusion of the RNAs. It is not known, however, how many RNAs can be introduced per exosomes by this method. Some miRNAs also have "zipcodes," which are sequences in the 3'-untraslated region that target the RNA to exosomes.[53]

Proprietary reagents to transfect exosomes with RNAs are available commercially. These include Exo-Fect (Systems Biosciences, Palo Alto, CA) and ExoFectin (101BIO, Palo Alto, CA). As the mechanisms involved in the targeting of native microRNAs to exosomes becomes clearer, the toolbox for exosome engineering should expand. Various means to engineer exosomes to be useful for use in the treatment of craniofacial bone defects can be envisioned. Incorporation of membrane proteins like semaphorin 4D or RANK into exosomes either could be therapeutic in itself or could be a means to target a therapeutic cargo to osteoblasts or osteocytes. Such cargo could include short interfering RNAs targeting a component that stimulates osteoclasts activity (e.g., RANKL) or inhibits osteoblasts ability to form bone (e.g., sclerostin).[54,55]

The relatively low level of knowledge regarding the regulatory mechanisms of exosomes and their roles in physiology suggests that it may be wise to focus on natural exosomes in the near future. Even then, because of the ability to regulate a target cell at multiple levels, it may be

prudent to be cautious in advancing exosomes to the clinic without extensive testing. At this point, it is unclear how effects attributed to exosomes (e.g., reversing aging) or even aiding in the healing of bone defects are achieved. It remains possible that unforeseen and dangerous side effects may become evident. Currently, it is vital to understand the underlying regulatory mechanisms of exosomes better as quickly as possible so that their therapeutic potential, which appears considerable, can be brought safely to the clinic.

CONCLUSIONS

Clinical applications of exosomes are under development in several settings both in diagnostics and in therapy. Our preliminary and published data support the hypothesis that exosomes are released from osteoclasts and that they may be useful for the identification of novel GCF biomarkers for the early diagnosis of root resorption and bone loss. In addition, exosomes are being evaluated for their potential to turn osteoclastogenesis activation pathways on or off, which will have a great impact on the management of orthodontic tooth movement and a host of craniofacial disorders.

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THE SOFT-TISSUE PARADIGM FOR GUIDING PATIENT-CENTERED ORTHODONTIC TREATMENT

David M. Sarver

ABSTRACT

The shift away from diagnosis on entirely hard-tissue-based evaluations has been a result of a broadened recognition of facial and smile appearance to the patients and the orthodontic profession. The current popularity of the "selfie" illustrates this point. This chapter covers data on growth, maturation of the lips and their relationship to the incisors evaluated from the frontal view. This data includes lip (philtrum) length, commissure height, incisor display at rest, incisor display on smile and incisor crown height. This chapter also emphasizes the importance of the clinical examination of the soft and hard tissue at rest and on smile, and the significance of these relationships and how they change over time.

KEY WORDS: growth, lips, paradigm, clinical examination, smile

INTRODUCTION

What is the Soft-tissue Paradigm and How Did the Orthodontic Profession Get There?

A paradigm may be defined as "a typical example or pattern of something; a model…" and a paradigm shift may be defined as "a fundamental change in approach or underlying assumptions." The soft tissue paradigm is simply the successor for the "Angle paradigm" in which Edward H. Angle stated that the primary purpose of orthodontic treatment is "the establishment of normal occlusion of the teeth should be the highest name of the orthodontist."[1] In other words, the primary purpose of orthodontic treatment is for the establishment of what Angle defined as normal occlusion which was dental centric. To be fair, the original Angle vision included facial appearance; however, this vision has been lost over the past century.[2] Prior to the establishment of the Angle School of Orthodontics in 1900, Angle recruited Prof. Edmund H. Wuerpel, then Head of the Washington University School of Fine Arts, who taught at the

school until Angle's death. The year 1900 can be marked as the establishment of the Angle School, as well as the establishment of the Angle paradigm. That philosophy guided orthodontics until approximately 1948 when Dewey published *Cephalometric Appraisal of Treated Result in Variations in Facial Relationships*, the first publication to introduce the use of cephalometric radiography for diagnostic, rather than research, purposes. After that time, overall soft-tissue evaluation was introduced to cephalometric analyses by many orthodontists including Tweed, Ricketts, Burstone, Subtelney, Holdaway, Merrifield, Ricketts and Peck. In 1998, the first paper identifying the soft-tissue paradigm was published.[3] How did the Angle paradigm stay entrenched for 98 years, while the soft-tissue paradigm has taken effect in a mere 20 years? In my opinion, it is due primarily to the evolution of technology (i.e., the internet with instant communication, access to information and social media).

THE SOFT-TISSUE PARADIGM

Knowledge is built incrementally. During my orthodontic career, I have been influenced by many colleagues and mentors. The readers would recognize my guidance from Dr. William Proffit immediately, but most do not know the value of my relationship with Dr. Louie Costa, a facial plastic reconstructive surgeon in Charleston, South Carolina. I first met Dr. Costa while he was an oral and maxillofacial surgery resident at the University of Alabama (Birmingham, AL). He went on to specialize in otolaryngology, followed by a fellowship in facial plastic reconstructive surgery in Birmingham. Dr. Costa spent one day per week in the Department of Oral and Maxillofacial Surgery (Birmingham), which coincided with my time teaching in the same department. I was struck by how someone previously trained as a dentist and an oral and maxillofacial surgeon evaluated patients, assessing facial characteristics first. This led me to look not just at the teeth, but the overall dental and facial appearance of each patient.

As an example, the fourteen-year-old girl in Figure 1 was treated successfully for correction of a Class II malocclusion resulting in an excellent occlusion and acceptable facial esthetics. Rather than counseling the patient in what may be perceived as the sole purpose of the orthodontist (e.g., bite correction and an improved smile), I noted that her profile was characterized by a mild chin deficiency. Is this outside of what I, as an or-

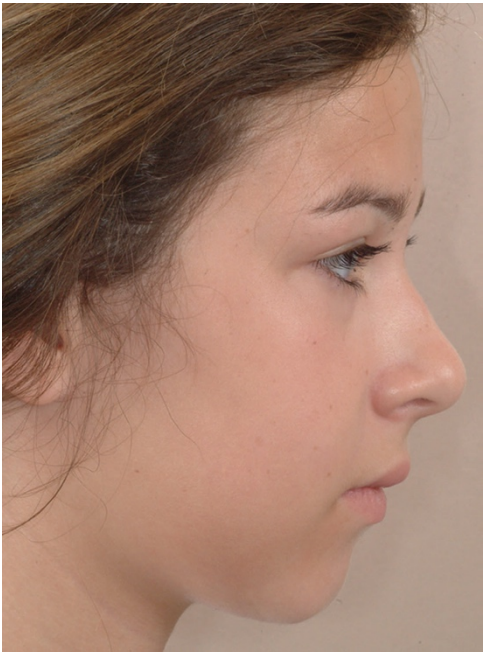

Figure 1. This young girl's profile was convex at the beginning of treatment due to her chin deficiency. Orthodontic treatment alone could offer little improvement to her facial appearance.

thodontist, should be concerned with? My philosophy—and part of my duty as an orthodontist—is to consider all aspects of esthetic treatment and the potential benefits that are important to discuss with the patient. Suggesting that she consider chin augmentation *via* inferior border osteotomy is reasonable not only because of the esthetic improvement, but also because it can be coordinated efficiently with removal of her third molars. The patient and her parents accepted this recommendation; the outcome (Fig. 2) and effect of this simple decision in patient self-esteem and quality of life is reflected clearly (Fig. 3).

The soft-tissue paradigm requires an understanding of how the soft and hard tissues and the face change through adolescence, middle adulthood and in later life; it also is important in attaining excellent facial and the smile cosmetic outcomes. Some dentists may not consider that facial esthetics have much to do with how they practice; however, because the substantial body of research over the past several decades documenting the soft-tissue changes that occur over a lifetime, orthodontists

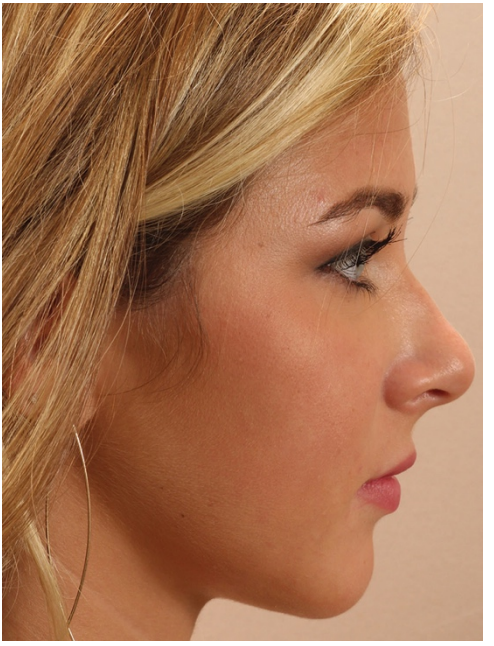

Figure 2. An inferior border osteotomy for chin augmentation was recommended at the time of third molar removal and the outcome was improved greatly.

certainly do.[3-5] Data clearly indicate that profile changes occur throughout a lifetime and relate directly to clinical decisions that must be considered in the adolescent and the adult. Consideration of facial esthetics also has a potential effect on interdisciplinary treatment decision making.[4-6]

From adolescence to adulthood, the upper lip continuously becomes thinner, while the lower lip does not, which translates to a loss of upper lip support (ages 18 to 42).[7] Of perhaps greater interest, researchers have discovered that the amount of change in both hard and soft tissue that occur between ages 25 and 42 is similar to the change between ages 18 and 25 in both males and females. My decision to shift from the Angle paradigm to the soft-tissue paradigm is knowing the long-term tissue dynamics and their effect on the face, and the fact that treatment planning in 1985 depended on a cephalogram. With this limited, cross-sectional information from a radiograph taken in 1/60 of a second in one plane space at the midline, treatment decisions considering the

Figure 3. Beyond simply looking at the profile, I recommend the oblique evaluation and images because that is the view that most of us see. This image reflects the improvement in quality of life, as well as correction of her occlusion.

changes throughout the lifetime of a patient cannot be made. Brodie stated in 1949, "Cephalometrics was never intended as the sole decision maker in orthodontic treatment plans, that its main strength was in quantification of growth and research."[8]

With this in mind, consider the eleven-and-a-half-year-old girl who was referred for treatment in 1985; her dentist expected that I would refer the patient for serial extraction because of the severity of her crowding (Fig. 4), as evidenced by the amount of crowding and blocked-out maxillary and mandibular canines (Fig. 5). The diagnostic and treatment rules of orthodontics in 1985 focused primarily on the cephalometric analysis with an emphasis on the position of the lower incisors. She had a Class I occlusion and both maxillary and mandibular primary first and second molars were present with the leeway space. Was serial extraction the best approach? The amount of information presented thus far is insufficient to make a decision. Looking at the dentition only, the answer to extraction is "yes." Without seeing the face, smile and profile, would the treatment decision with extraction of four premolars have a negative effect on her profile? The answer is no because we would be ex-

Figure 4. This eleven-and-a-half-year-old girl was a routine referral for orthodontic consultation because of the severity of her dental crowding.

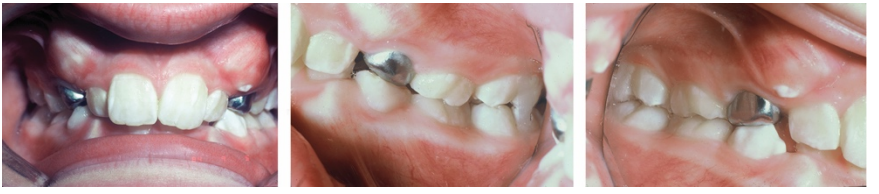

Figure 5. The patient in Figure 4 had a Class I occlusion, but her crowding was so severe that maxillary canines were blocked out. In the mid-1980s, without a doubt, serial extraction was the treatment of choice.

changing 7.5 mm premolars with 9.5 mm canines. The timing of referral was more than important; it was critical. As shown in Figure 6, her profile was flat and retrognathic with lack of lip support and vermilion display. If she had sought treatment as an adult, orthognathic surgery with advancement of both jaws may have been considered to improve her facial appearance. Because she was nearing her growth spurt, the option of growth guidance was available, which began at eleven and a half years of age. Cervical headgear was chosen because of its anterior-posterior effect and its extrusive force vector, capable of increasing her slightly short lower facial height. After approximately nine months of mandibular growth

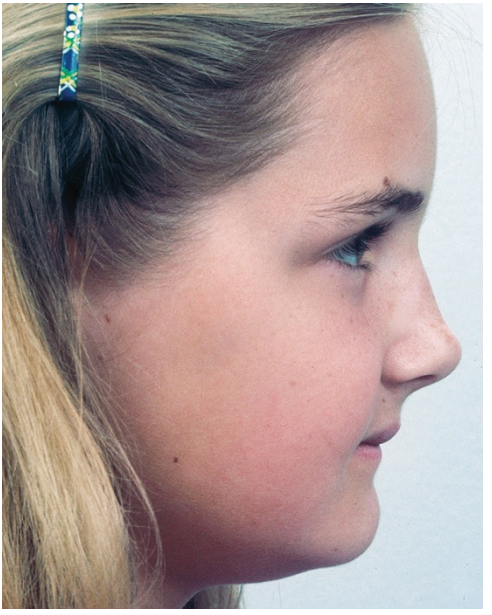

Figure 6. The macro-esthetic evaluation of the patient in Figure 4 clearly showed that her profile was flat and retrognathic, with a lack of lip support and vermilion display.

guidance *via* headgear treatment, mandibular projection was improved, as was the lower facial height (Fig. 7).

Now a treatment choice had to be made; according to the treatment planning standards of 1985, the lower incisor position was in good position cephalometrically; to tip it forward or advance it would be considered an unstable movement and not beneficial cosmetically. But when the total facial esthetics were evaluated, removal of the four premolars could not be reconciled because of the flat profile and poor lip support. In other words, rather than accept things as they were, if possible, the decision was made to enhance her facial appearance. To achieve our goals, incisor advancement was performed with the combination of advancement utility arches and springs.

At age 14, the patient's final treatment profile showed maximum lip support and projection of her lower face (Fig. 8). The outcome was rewarding, but seeing the patient 30 years later was more so, still with impressive facial esthetics (Fig. 9).

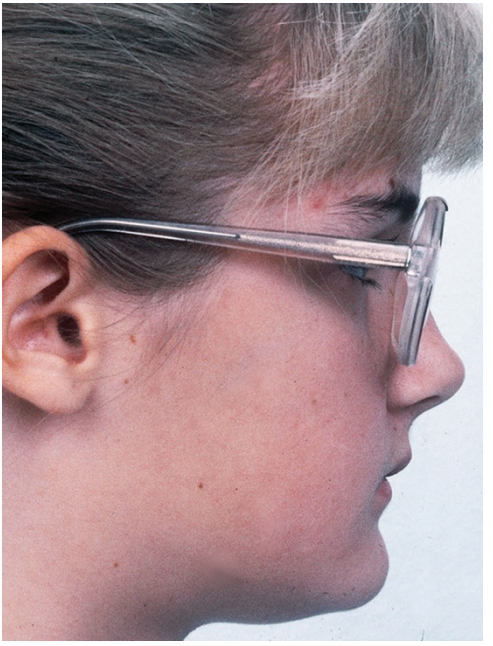

Figure 7. At the end of the first phase of growth modification treatment, mandibular projection was improved, as was lower facial height.

Figure 8. Rather than serial extraction, orthodontic advancement of the incisors was chosen in order to support soft tissue.

THE SYSTEMATIC CLINICAL EXAMINATION

A more globally oriented diagnostic regimen requiring a thorough knowledge of both craniofacial and soft tissue changes that will equip the diagnostician to direct appropriate treatment is essential in a complete diagnostic approach that includes both the functional and esthetic demands of today's orthodontic environment. In the era of the

Figure 9. An important aspect of the soft-tissue paradigm is designing treatment with soft-tissue growth, maturation and aging in mind. Thirty years after the culmination of treatment, this patient's facial appearance still benefited from our orthodontic choices.

soft tissue paradigm, hard-tissue records (e.g., cephalometric radiograph and models of the teeth) are secondary to the clinical exam. The systematic clinical examination is designed to document and quantify important soft-tissue relationships when the patient is at rest.

The value of the systematic clinical examination is two-fold. First, it makes the clinician be thorough and consistent so as not to miss anything of diagnostic significance. Secondly, it functions well with an interdisciplinary team, providing a homogenized diagnostic approach to facial and smile esthetics among involved dentists and dental/medical specialists.

It is recommended that the following sequence of events take place as part of the initial clinical exam:

1. Upper lip length: measured from the base of the nose to the philtral tubercle.
2. Commissure height: measured from the base of the nose to the commissure perpendicular to the philtrum measured in upper lip length.
3. Upper incisor at rest: have the patient open the mouth slightly (Bjorn Zachrisson recommends repeating the word "Emma") and measure the tooth display at rest. This measurement is important because it is repeatable and the start of the assessment of incisal edge position in its relation to the maturation and aging process.

4. Upper lip length on smile: it is not intuitive to most orthodontists why this part of my clinical exam is recommended. In my checklist for potential etiologies of the gummy smile (Fig. 12), smile mobility is the most obscure. What exactly is a hypermobile smile, how much is too much movement and how much is not enough? To answer this question, McEntire documented the average amount of upper lip elevation from rest to sustained smile position generally was approximately 25%.[8]
5. Millimeters of upper incisor display on smile: the maxillary incisor crown does not always show on smile and the amount of tooth display on smile guides us regarding how much vertical tooth movement is needed to attain complete incisor display on smile.
6. Incisor crown length: using a micrometer for as much accuracy as possible, crown height is measured and related to:
    a. The amount of tooth display on smile in the case of incomplete incisor display; and
    b. The contribution of short crown height in the case of excessive gingival display on smile.

This systematic clinical examination has been part of my clinical practice for many years; Boohaker has assessed our clinical data on a sample size of approximately 6,800 patients.[9] This large sample size provides sufficient data for an excellent cross-sectional analysis of how these soft- and hard-tissue elements change with growth, maturation and aging. The findings, in summary, are:

1. The philtrum and commissure lengthened steadily from adolescence to late adulthood. Their change in length was disproportionate, with the philtrum outpacing the commissure height, resulting in a flattening of the upper lip vermilion and decrease in vermilion display.

2. Upper incisor display at rest reached its maximum around ages 13 to 14 and decreased steadily afterward.
3. Maxillary incisor display on smile reached its maximum around age 25 and decreased moderately afterward.
4. Gingival display on smile reached its maximum around age ten and decreased precipitously over the ensuing decades, more so in males than in females.
5. Incisor crown length reached its maximum between ages 21 to 25 and changed very little after that.

The systematic clinical examination, resulting data and how the checklist approach to treatment is applicable is illustrated with the twelve-year-old girl presented in Figure 10. The patient's initial referral was prompted by the dentist's suggestion that an orthodontic consultation was indicated because of her Class II deep bite—the functional reason for orthodontic treatment (Fig. 11). Using this patient as an example, without an interdisciplinary team and homogenized diagnostic approach, if she was seen initially by an oral surgeon, the recommendation might emphasize surgical maxillary impaction after growth was complete. If she was seen by a periodontist initially, crown lengthening likely would be the treatment of choice; if a cosmetic dentist was consulted, crown lengthening with the possibility of porcelain veneers possibly would have been the treatment recommendation of choice.

Figure 10. This twelve-year-old girl presented with a convex profile due to moderate mandibular deficiency and the etiology of her Class II malocclusion. She had a short lower facial height with significant lip incompetence and a gummy smile.

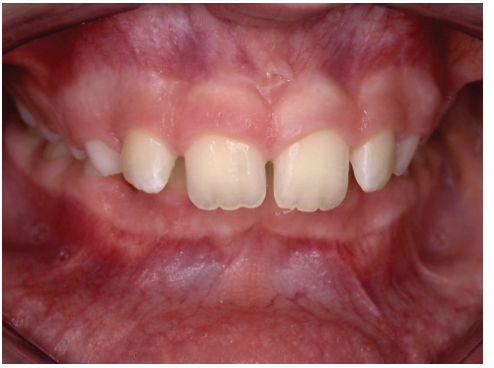

Figure 11. Original malocclusion was characterized by a Class II deep overbite.

The systematic clinical examination starts with the global approach of macro-, mini- and micro-esthetic evaluations by beginning from the outside in.[10] I recommend this be conducted in order, the reason of which will be illustrated later. With lips in repose and then on smile, we made note of:

1. Her short lower facial height;
2. A short philtrum height relative to commissure length;
3. Excessive incisor display at rest; and
4. Excessive gingival display on smile. Her profile was convex due to mandibular deficiency, the etiology of her Class II malocclusion.

In our recommended diagnostic regimen, we have defined all possible etiologies of all possible smile issues and a case of excessive gingival display on smile will be illustrated. The checklist of potential etiologies for a gummy smile include (Fig. 12):

1. Vertical maxillary excess: the clinical characteristics include excessive incisor display at rest, lips apart posture, lip strain and excessive lower facial height.
2. Short crown height: short crown height has two basic etiologies—gingival encroachment and incisor attrition. Gingival encroachment in an adolescent can in-

Figure 12. Checklist of potential etiologies for excessive gingival display on smile.

clude delayed active eruption or delayed passive eruption; it can include gingival hypertrophy in both an adult and an adolescent.

3. Short philtrum height: depending on the patient's age, the ideal philtrum position is 2 to 3 mm shorter than the commissure height. As will be demonstrated later, this is highly variable with age.
4. Hypermobile smile: elevation of the upper lip on smiling varies between persons. How do we tell when someone has a hypermobile smile? Empirically, if the patient does not have an excessive incisor display at rest and has normal crown height and facial height, then excessive gingival display would be attributable to excessive elevation of the upper lip on smiling.
5. Retroclined or super-erupted maxillary incisors: these are seen most often with dentoalveolar compensation for a Class II skeletal relationship.

With the patient's lips in repose followed by smiling, our systematic clinical examination quantified the problem list and utilization of a checklist approach allowed a treatment plan to be formulated.[12]

Macro-esthetic Evaluation and Quantification of the Problem List

1. Short lower facial height: equal thirds of lower facial height is accepted as the most desirable vertical facial proportionality. The lower facial height valuation is the macro-esthetic area over which we have the most influence and control.
2. Lip incompetence of 5 mm.
3. Convex profile with mandibular deficiency: this is the etiology of this patient's Class II malocclusion.
4. Mini-esthetic evaluation and quantification (Fig. 13).
5. Philtrum height of 15 mm: the absolute measurement is not important, but what is significant is its relationship to the maxillary incisor and proportional relationship to the commissures of the mouth. This relationship changes significantly over time. Based on the Boohaker data, it is not uncommon to find a short philtrum height in the adolescent.[9] This changes dramatically over time and the difference can be explained by the differential of vertical lip growth over the long term because in a patient's lifetime, the philtrum length increases at a greater rate than the commissure length, contributing to the flattening and aging of the upper lip in repose, and also to decreased incisor display at rest and on smile.
6. Maxillary incisor display of 8 mm at rest.
7. Maxillary central incisor display of 8 mm (100%) on smile.
8. Gingival display of 7 mm on smile.
9. Retroclined maxillary incisors (in compensation for the mandibular deficiency).
10. A consonant smile arc.
11. Micro-esthetic evaluation and quantification.
12. Crown height of 8 mm. The expected crown height at her age would be greater than 8 mm, more in the range of 9.0-10.5 mm.
13. Delayed active or passive eruption.
14. A thick periodontal phenotype.
15. Treatment plan design.

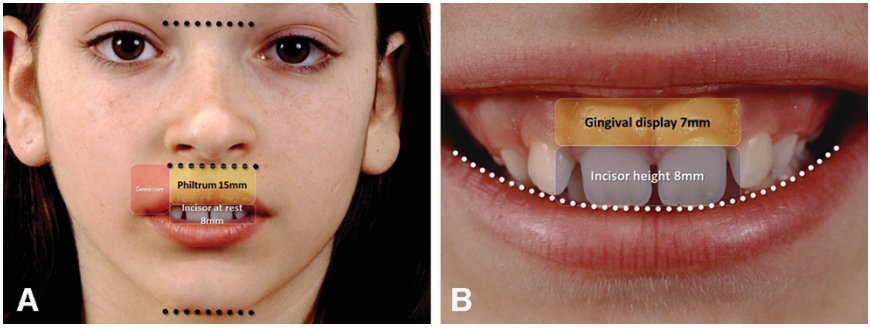

Figure 13. *A:* Our mini-esthetic evaluation revealed a philtrum height of 15 mm, much shorter than the commissure height. The patient also had a maxillary incisor display of 8 mm at rest and her philtrum height was so short that all of the maxillary incisors were shown at rest. *B:* On smile, she had 7 mm of gingival display and a consonant smile arc.

In addition to correction of the functional issues of the Class II deepbite, the esthetic treatment plan is determined by the clinical examination and its coordination with the checklist that we have generated for each problem. For example, the checklist for etiologies of the gummy smile and how it was applied to this patient shows:

1. Vertical maxillary excess: the clinical characteristics of vertical maxillary excess include a long lower facial height (generally with lip incompetence), excessive incisor display at rest and gummy smile. Because this patient had a short lower facial height, we can eliminate vertical maxillary excess from the problem list, thus not requiring treatment.
2. Short philtrum in relation to commissure height: growth will help as shown in the previous data, but will it be enough?
3. Short crown height: we measured the maxillary central incisors to be 8 mm in length, so if that does not improve with growth, crown lengthening will be needed.
4. Hypermobile smile: the smile curtain was not significantly more than 25%, hypermobility of the lip was eliminated from the problem list, thus not requiring treatment.

5. Upright maxillary incisors: maxillary incisors were upright in compensation for her mandibular deficiency, which results in an increase in gingival display. Treatment required was orthodontic uprighting of the maxillary incisors.

Treatment Plan and Summary

Treatment consisted of fixed appliance therapy with growth modification (high pull headgear) for improvement of the skeletal relationship. The deep overbite was approached with reverse-curve lower archwires to open the deep bite, thus increasing the lower facial height. Improvement in gingival display on smile was a result of orthodontic uprighting of the maxillary incisors and exceptionally favorable growth of the philtrum. Before completion of fixed appliance treatment, the incisor crowns were still 8 mm in length. A referral to the periodontist revealed that altered active eruption had taken place, so the crowns were restored to appropriate crown height.

At the end of orthodontic treatment, the patient's frontal facial proportions were ideal and lip incompetence resolved nicely (Fig. 14*A*). Her smile was only slightly gummy (Fig. 14*B*), but ideal for a fourteen-year-old female since we know that her gingival display will decrease with time. Seven years after completion of treatment, the youthfulness of her smile and appearance was maintained (Fig. 15).

Management of the macro-esthetic ramifications of the soft tissue paradigm is a discipline that, frankly, requires years of experience to incorporate into day-to-day practice. However, its application to smile design is much easier for most orthodontists to incorporate into practice quickly and the interaction of soft tissue with hard tissue determines the placement of fixed appliance (what used to be a standardized one-size-fits-all approach). For example, the twelve-year-old girl in Figure 16 was referred by her dentist for consultation regarding improvement of deep overbite and dental malalignment. The clinical examination revealed two major characteristics that greatly guided treatment design: 1) her short incisor crown height contributing to her gummy smile; and importantly, 2) she had a consonant (ideal) smile arc with ideal vertical position of the incisal edges. A primary objective in smile design is to attain or maintain an ideal vertical incisal edge position.

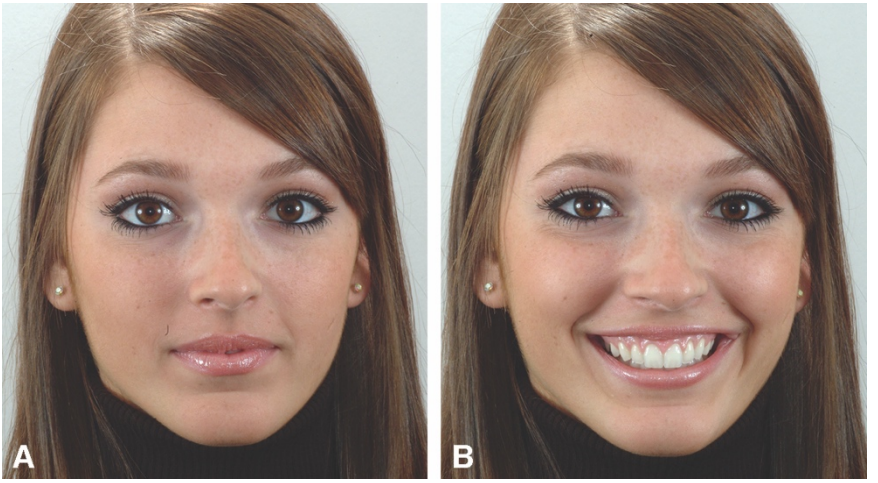

Figure 14. *A:* At the completion of orthodontic treatment, frontal facial proportions are ideal and lip incompetence was resolved because of the differential in philtrum and commissure growth. *B:* In the final result, the patient's smile was only slightly gummy. Since she was fourteen years old, this was not problematic because a reduction in gingival display over the next several decades was expected.

Figure 15. As anticipated, the patient's facial and smile appearance seven years later were maintained well.

Part of the clinical assessment includes crown height. In this case, the initial periodontal probing depths on the maxillary incisors were 4

Figure 16. This twelve-year-old girl was a routine orthodontic referral for a consultation regarding her Class I deep overbite malocclusion.

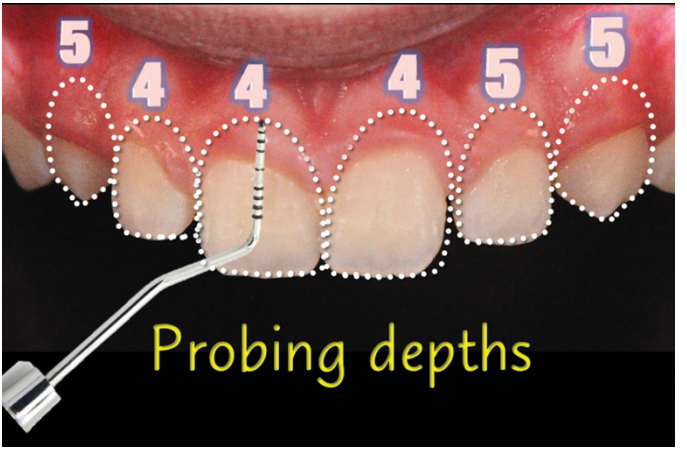

Figure 17. As part of our clinical examination, paradigm probing revealed 4 mm sulcular depths on the four incisors and 5 mm on the canines—an indication of altered passive eruption.

mm (Fig. 17), an indication of altered passive eruption. The patient and her mother were aware of the gummy smile, but had no idea that it could be improved; they simply accepted it as what it was. The use of digital imaging helped communicate what a simple gingivectomy would offer: 1) a re-

duction in gingival display on smile while maintaining incisal edge position; and 2) appropriate crown height so that the orthodontic brackets could be placed in such a way as to maintain that vertical incisal edge position, also described as smile arc protection. If we had accepted the short crown height prior to appliance placement, the brackets would have had to be placed either in what appeared to be the middle of the tooth (resulting in incisor intrusion; Fig. 18) or against the gingival margin, which would result in a undesirable oral hygiene situation.

Treatment Sequence

The gingival shape and contour based on the periodontal probing depths were visualized. This was followed by removal of the excess gingival tissue (Fig. 19) to attain ideal crown height (in this case, a diode laser was used).

The maxillary posterior brackets were placed first; the vertical level of the posterior teeth leaves little room for vertical variation for bracket placement. Visualization of the posterior bracket slots relative to the anterior teeth assist the ability to see the esthetic line of occlusion. The maxillary anterior brackets then were placed to remain level with the posterior teeth, so a straight archwire will maintain vertical incisor position (Fig. 20). After leveling and alignment, bite opening and Class II correction followed. At the culmination of fixed appliance treatment, the pa-

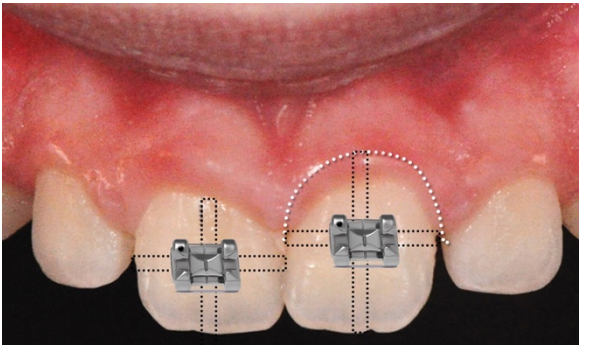

Figure 18. Why recommend crown lengthening before bracket placement? This illustration demonstrates the existing right central incisor and the left central incisor, factoring in her probing depths, reaches the white dotted line. The difference in the bracket height placement if her altered passive eruption had not been considered also is illustrated.

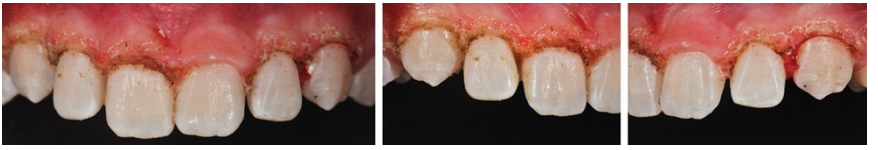

Figure 19. Designing treatment to protect ideal vertical incisal edge position, a diode laser excised excess gingival tissue to attain ideal crown height so that ideal bracket placement could be performed.

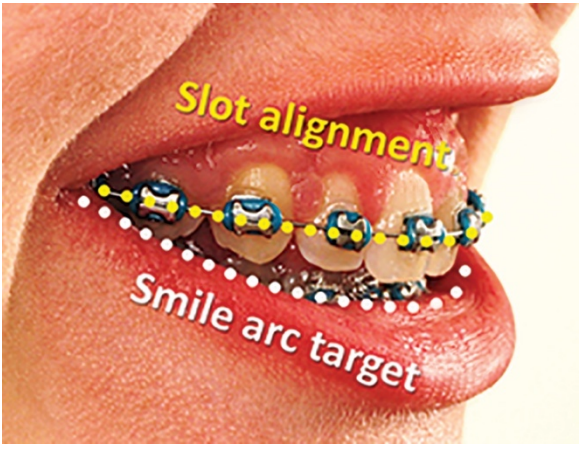

Figure 20. Brackets were placed progressing from the posterior to the incisor area so that the vertical incisal edge position could be maintained with a straight wire.

Figure 21. The patient's final smile was exceptional with consonance of smile arc, complete incisor display and esthetic smile width.

tient's final smile was exceptional (Fig. 21) with maintenance of her smile arc, complete incisor display and nice smile width.

CONCLUSIONS

The soft-tissue paradigm has been evolving since the turn of the 21st century; designing treatment to address patient's individual needs also has been embraced by the orthodontic profession. In addition to the dental centric goals, addressing the patient's overall appearance is an important determinant in treatment choice and design. Understanding how soft tissue changes over time represent the next vista in orthodontic research, helping the orthodontist design treatment that protects or improves the appearance of adolescent patients for a lifetime.

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SOFT TISSUE AND FACIAL ESTHETIC DIAGNOSIS ALLOWING PERSONALIZED RADIOGRAPHIC EXPOSURES

Mohamed I. Masoud

ABSTRACT

This chapter is based on a lecture presented at the 45th Annual Moyer's Symposium on the theme of *Effective, Efficient and Personalized Orthodontics: Patient-Centered Approaches and Innovations.* It starts by discussing the importance of finding a reference for orthodontic diagnosis that does not involve use of radiographs since that would allow orthodontists to collimate radiographs to include only the area of interest for individualized orthodontic patient care instead of the current one-size-fits-all approach. It then goes on to evaluate the stability of the eyes as a reference compared to the cranial base and explores the relationship between traditional cephalometric measurements and measurements that rely on the eyes and true horizontal (TH) instead of the cranial base. The chapter concludes with the clinical applications of these concepts including shielding sensitive tissue to the effects of radiation and the viability of more affordable small format, portable, 3D facial cameras.

KEY WORDS: 3D photogrammetry, orthodontic diagnosis, craniofacial growth, ALARA, cephalometrics

INTRODUCTION

For over 80 years, orthodontic diagnosis and planning have relied on the cranial base viewed in cephalometric radiographs as a reference to determine the position and orientation of the jaws and teeth. This has resulted in orthodontic patients routinely having their entire crania exposed to ionizing radiation before, during and after orthodontic treatment, regardless of the severity of their condition or the extent of orthodontic treatment being planned. Although orthodontic exposures involve far less ionizing radiation than medical computerized tomography (CT) imaging, the public health risk introduced by the specialty stems for the repeated exposure of a large pediatric population to

small doses of radiation. Children are known to be twice as vulnerable to the effects of radiation as adults with scholastic effects lasting at least four decades after the exposure.[1-3] Because there is no safe dose of radiation, the concept of As Low as Reasonably Achievable (ALARA) was adopted by the International Commission on Radiological Protection.[4] The two basic principles of ALARA are justification and optimization.[5] Orthodontic practitioners are unable to affect an area outside the upper and lower jaws, but cannot practice optimization since cephalometric analyses being taught at orthodontic training programs involve the exposure of the cranial base (Fig. 1). Despite the widespread use of cephalometrics in orthodontic diagnosis and planning, studies have failed to justify their impact on orthodontic decision making.[6,7] This has resulted in many parts of the world making it prohibitive to take cephalometric radiographs and/or full-field cone-beam computed tomography (CBCT) exposures at the end of orthodontic treatment, despite their importance from medico-legal and quality improvement perspective, since they do not benefit the individual patient directly.[8,9] This situation has created a need to develop non-radiographic methods for the quantification and documentation of the initial orthodontic discrepancy and the evaluation of treatment outcomes.

In 2017, our group published a method that involved three-dimensional (3D) dentofacial photogrammetry imaging, and the use of the eyes and the true horizontal (TH) line using natural head position as references instead of the cranial base, along with adult male and female references to which patients can be compared (Figs. 2 and 3).[10] Manosudprasit and colleagues have demonstrated that this method can result in treatment-planning decisions comparable to those obtained from traditional orthodontic records.[11] The following sections evaluate the long-term stability of the eyes and compare measurements that use the eyes as references to traditional measurements that depend on bony landmarks in the cranial base. Long-term stability of the eyes and the ability to predict traditional cephalometric measurements from non-cranial-base-dependent measurements would allow orthodontists to have a reference for diagnostic measurement so that radiographic exposures can be limited to the area directly affected by treatment.

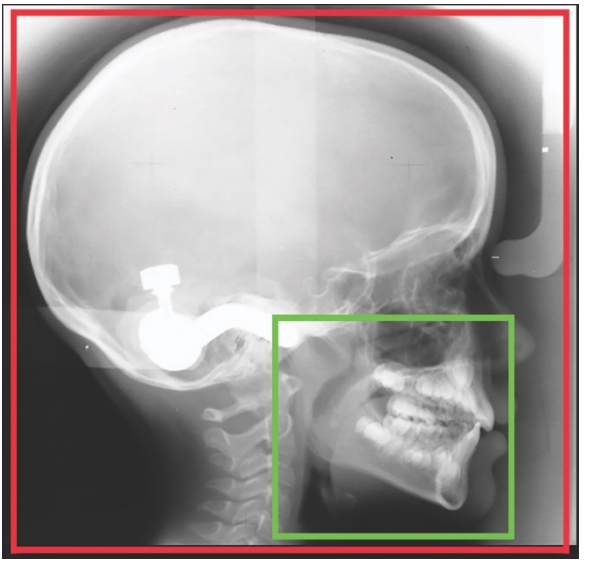

Figure 1. Green border represents the area of interest for the orthodontist. Red border represents the area often exposed to perform a traditional cephalometric analysis.

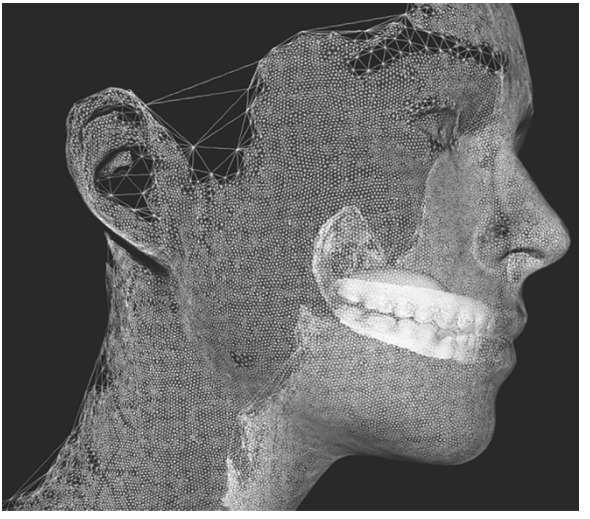

Figure 2. Facial and dental image representing adult female standard. Image was obtained by averaging 3D facial and dental images of the female models. Facial photographs were obtained using the Vectra M3 Imaging System (Canfield Imaging Systems, Fairfield, NJ); dental images were generated using the Ortho Insight scanner (Motion View Software, Chattanooga, TN).

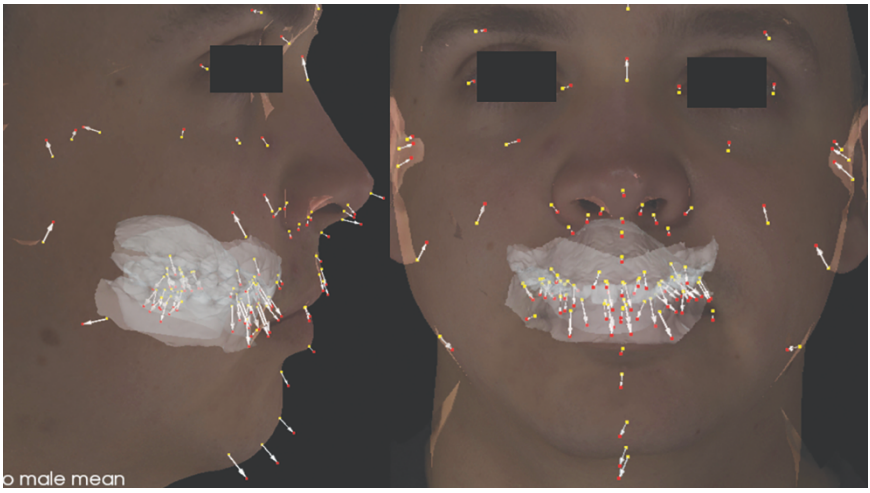

Figure 3. Sample male patient scaled to male standard with arrows pointing from the patient's landmark to the standard's landmarks.

ARE THE EYES AS STABLE AS THE CRANIAL BASE?

The eyes are considered neural tissue that generally completes growth during the first decade of life. Ophthalmology literature suggests that the eyes undergo minimal changes to their size and position between the ages of 5 and 19.[12,13] A cross-sectional cephalometric study suggests that the difference between the mean distance from the cornea to Sella before and after puberty is comparable to the difference between the mean distance from Sella to Nasion at the same ages.[14]

Since no study in the literature had examined the longitudinal stability of the eyes, we decided to use the cephalometric radiographs from the Harvard/Forsyth Growth Study to compare changes of Sella to the position of the cornea to changes of the position of Nasion relative to Sella.[15] The decision to compare to Nasion was made because most of the measurements of the most popular cephalometric analyses are dependent on Nasion.[16]

Seventy-six subjects were selected from the sample based on the availability of cephalometric radiographs before the pubertal growth spurt (age 8 years +/- 1 year), as well as after pubertal growth spurt (age 18 years +/- 1 year). Figure 4 demonstrates the tracing of the landmarks used to obtain the necessary measurements for the study. The maximum convexity of the cornea was designated as C point and was

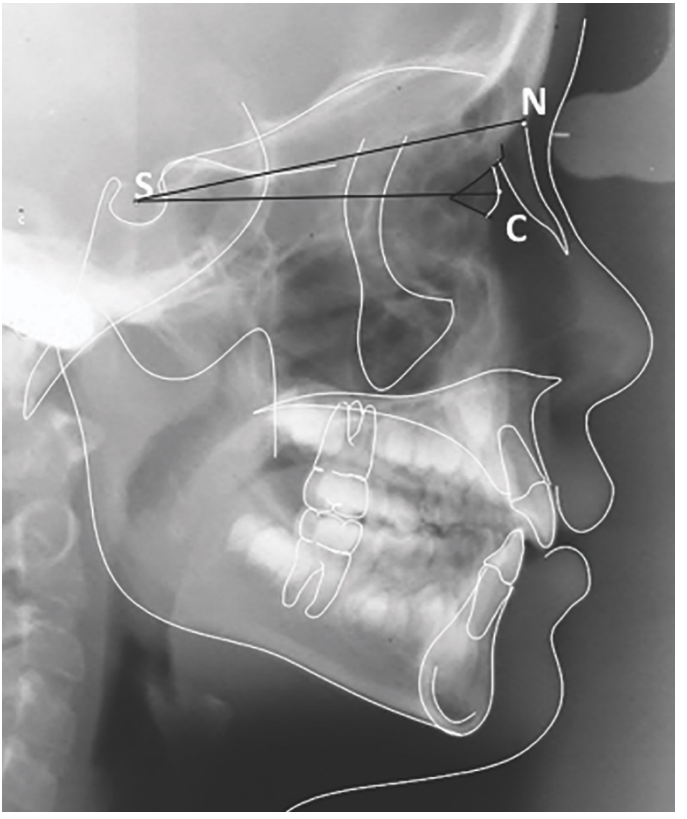

Figure 4. Landmarks and measurements used to evaluate stability of the cornea relative to Nasion. S = Sella; N = Nasion; C = cornea point.

visible clearly on the majority of the cephalometric radiographs. Any subject with radiograph quality that did not allow accurate localization of the necessary landmarks was excluded from the study. Two senior orthodontic residents performed all the tracings and had an average Intra-class Correlation Coefficient (ICC) above 0.9. At age 8 years, the mean distance from Sella to Nasion was 64.36 mm +/- 3.21 mm, while the mean distance from Sella to C point was 60.38 mm +/- 3.64 mm. At age 18 years, the mean distance from Sella to Nasion was 69.98 +/- 2.79 and the distance from Sella to C point was 65.89 +/- 3.26. A paired t-test showed no difference between the change in the distance from Sella to Nasion and the distance from Sella to C point between ages 8 and 18 years (P = 0.57).[15]

HOW DO MEASUREMENTS TO THE EYES RELATE TO TRADITIONAL CEPHALOMETRIC MEASUREMENTS?

To answer this question, we performed a traditional Steiner analysis on the radiographs from the sample mentioned above (Fig. 5) and correlated those measurements to comparable cephalometric measurements that utilize the eyes and natural head orientation instead of the cranial base (Fig. 6).[17] The angle between A point, Nasion and B point (ANB), mandibular plane to a plane connecting Sella and

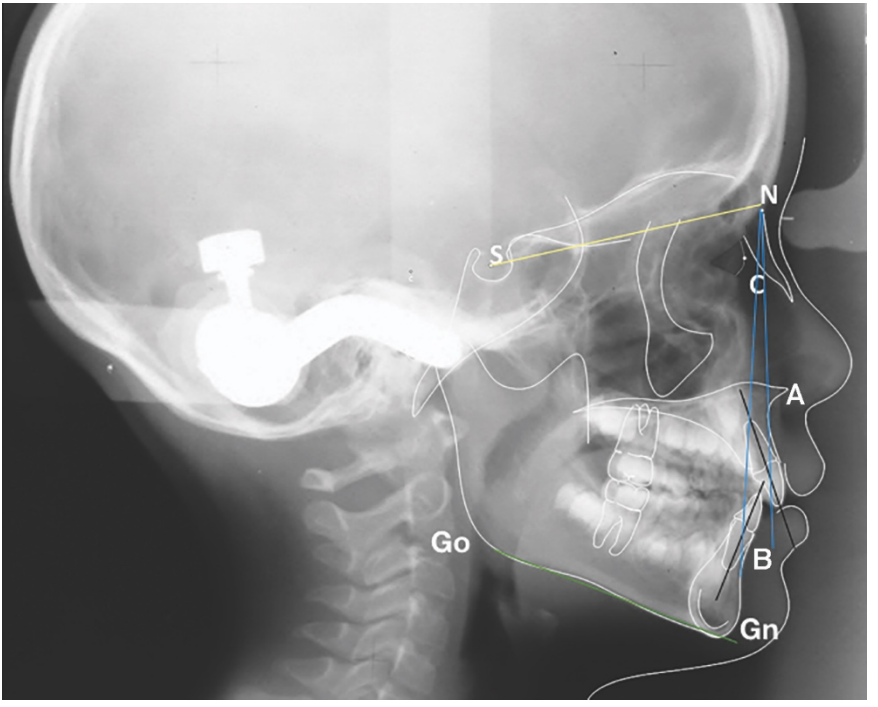

Figure 5. Traditional Steiner analysis measurements used. C = cornea point, maximum convexity of the cornea; S = Sella, the geometric center of Sella turcica; N = Nasion, the most anterior point on the frontonasal suture; A = A point, the innermost point on the contour of the pre-maxilla; B = B point, the innermost point on the anterior contour of the mandibular symphysis; Go = gonion, the most inferior posterior point on the gonial angle of the mandible; Gn = gnathion, the most interior anterior point on the symphysis of the mandible.

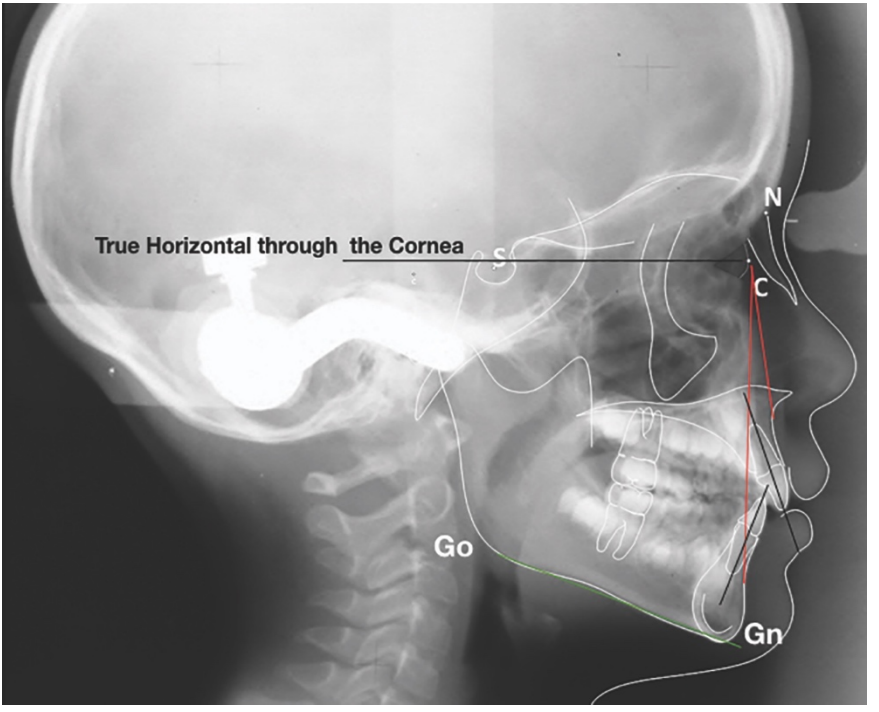

Figure 6. Modified Steiner analysis measurements that use the eyes and natural head position instead of the cranial base. C = cornea point, maximum convexity of the cornea; S = Sella, the geometric center of Sella turcica; N = Nasion, the most anterior point on the frontonasal suture; Go = gonion, the most inferior posterior point on the gonial angle of the mandible; Gn = gnathion, the most interior anterior point on the symphysis of the mandible.

Nasion (SN) and all the dental measurements had strong or very strong statistically significant correlations with the corresponding measurements that did not rely on the cranial base (Figs. 7 and 8). On the other hand, the angle between Sella, Nasion and A point (SNA), and the angle between Sella, Nasion and B point (SNB) correlated poorly with the corresponding non-cranial base measurements. The poor correlation can be attributed to the individual variation in the position of Sella which often makes those measurements unreliable.[18]

A follow-up study investigated the relationship between 3D photogrammetry measurements using the cornea and natural head orientation to traditional cephalometric measurements.[19] Twenty con-

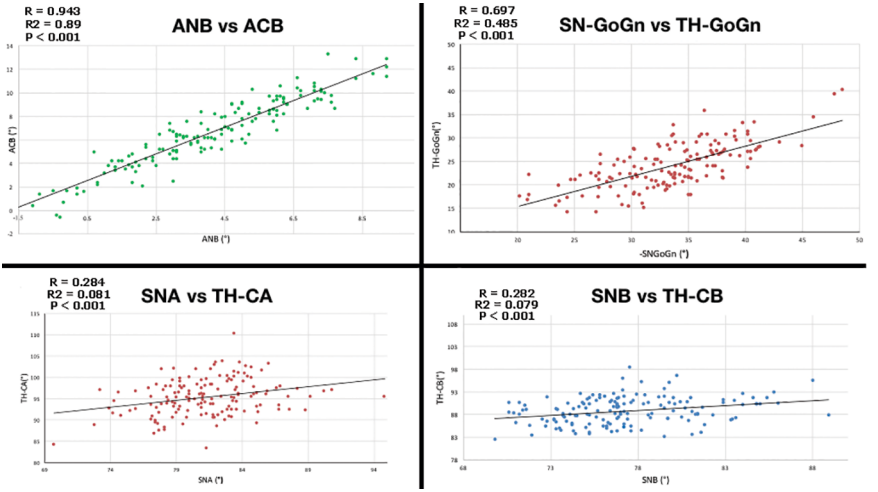

Figure 7. Correlation between skeletal cephalometric measurements using Sella (S) and Nasion (N) and corresponding measurements that use natural head position for True Horizontal (TH) and the cornea point (C). C = cornea point, maximum convexity of the cornea; TH = true horizontal based on natural head orientation; S = Sella, the geometric center of Sella turcica; N = Nasion, the most anterior point on the frontonasal suture; A = A point, the innermost point on the contour of the pre-maxilla; B = B point, the innermost point on the contour of the mandibular symphysis; Go = gonion, the most inferior posterior point on the gonial angle of the mandible; Gn = gnathion, the most interior anterior point on the symphysis of the mandible.

secutive orthodontic patients (ten males and ten females) between the ages of 13 and 36 years old who all were above their pubertal growth spurts based on cervical vertebral maturation had cephalometric radiographs, as well as 3D dental and facial images taken as part of their initial records.[20] The Steiner cephalometric measurements from Figure 5 were correlated with comparable 3D photogrammetry measurements in Figure 9. Each patient served as his/her own control resulting in measurements from twenty cephalometric images being correlated with measurements from twenty photogrammetry images of the same individuals. The results indicated that the maxilla-mandibular relationship (ANB), mandibular plane angle, lower face height, lower incisor position, lower incisor inclination and the upper incisor inclination all had statistically significant positive correlations with the corresponding 3D photogrammetry measurements (Table 1). The correlation coefficients for these

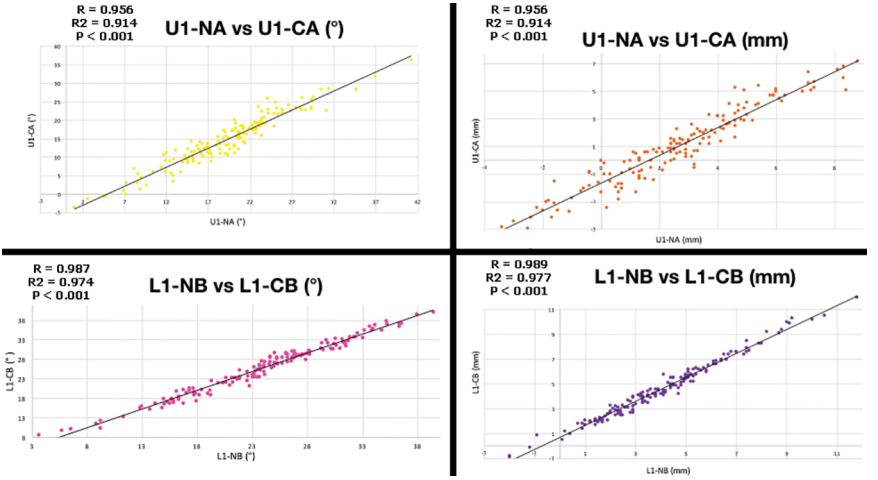

Figure 8. Correlation between dental cephalometric measurements using Nasion (N) and corresponding measurements that use Cornea (C) and natural head position. The maximum convexity of the cornea, C = cornea point, the most anterior point on the frontonasal suture; N = Nasion; the innermost point on the contour of the premaxilla; A = A point; the innermost point on the anterior contour of the mandibular symphysis; B = B point; the most inferior posterior point on the gonial angle of the mandible; Go = gonion; the most interior anterior point on the symphysis of the mandible; Gn = gnathion; L1 = lower incisor; U1 = upper incisor.

measurements ranged between 0.64 and 0.89 and were comparable to the correlation between different cephalometric measurements intended to quantify the same parameter. For example, the correlation between ANB and the comparable 3D photogrammetry measurement was 0.77, whereas the correlation between ANB and Wits was not significant statistically and the correlation between ANB and Harvold was 0.78. Similarly, the correlation between the lower incisor to NB and the corresponding 3D photogrammetry measurement was 0.82, while the correlation between the lower incisor to NB and the lower incisor to the mandibular plane was 0.77. These findings were interesting, particularly since the root position was estimated on the 3D photogrammetry records using the crown anatomy. A regression model controlling for age, race and ethnicity demonstrated that cephalometric measurements could be predicted accurately from 3D photogrammetry measurement (Table 1). For example, if the angle between soft tissue A point and soft

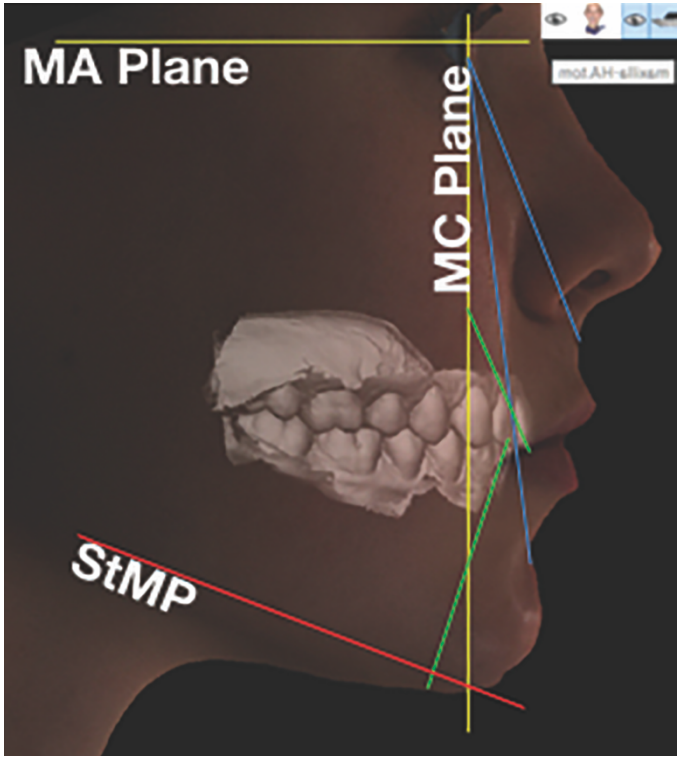

Figure 9. 3D photogrammetry measurements that correspond to traditional Steiner analysis. MC = coronal plane perpendicular to true horizontal passing through the cornea of the eyes; MA = axial plane parallel to true horizontal passing through the cornea of the eyes; StMP = soft tissue mandibular plane tangent to the soft tissue lower border of the mandible.

tissue B point relative to the eyes is 12°, the regression model would predict an ANB angle of 1.4°.

CLINICAL APPLICATIONS

The direct clinical applications of this information are that it allows practitioners to collimate radiographs to avoid exposing the cranial base and limit exposures to the area relevant to orthodontic treatment based on the needs of each patient. A comprehensive case that involves growth or orthognathic surgery may require radiographically exposing

the maxilla and mandible, whereas a limited tooth movement case to align the lower incisors on an adult patient may require only radiographically exposing the teeth and supporting structures. Moreover, collimating

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→ Table 1. Summary of estimates from multi-variable linear regression model. * = regression model is adjusted for the effects of age (adult *versus* adolescent), sex and race. ** = statistically significant for regression set at $p < 0.05$. Outcome = constant + parameter estimate of predictor variable. **LATERAL CEPHALOMETRIC MEASUREMENTS:** SNA = angle between Sella, Nasion and A point; SNB = angle between Sella, Nasion and B point; ANB = angle between A point, Nasion and B point; 2D LAFH (lower anterior face height) = distance from anterior nasal spine to menton; 2D TAFH (total anterior face height) = distance from Nasion to menton; U1-NA (°) = angle between most proclined upper central incisor long axis to Nasion-A point line; U1-SN (°) = angle between most proclined upper central incisor long axis to Sella-Nasion line; L1-MP (°) = angle between most proclined lower central incisor long axis to mandibular plane; L1-NB (°) = angle between most proclined lower central incisor long axis to Nasion-B point line; L1-NB (mm) = distance between most protruded lower central incisor tip to Nasion-B point line; U1-NA (mm) = distance between most protruded lower central incisor tip to Nasion-A point line; MP-SN = angle between mandibular plane to Sella-Nasion line; MP-FH = angle between mandibular plane to Frankfurt horizontal line (porion to orbitale); Wits = difference in distance between the perpendicular lines from A and B points onto the occlusal plane. **3D PHOTOGRAMMETRY MEASUREMENTS:** StAM-MC = angle formed between soft tissue A plane to irises and coronal plane through the irises; StBM-MC = angle formed between soft tissue B plane to the irises and coronal plane through the irises; (StA-MC)-(StB-MC) = distance between soft tissue A point and soft tissue B point relative to coronal plane through the irises; StAM-StBM = angle formed between soft tissue A plane to irises and soft tissue B plane to the irises; StMP-MA (mandibular plane angle) = angle formed between mandibular plane and axial plane through the irises; 3DLAFH (lower anterior face height) = distance between soft tissue menton and subnasale; 3DTAFH = distance between soft tissue menton and trichion; U1-MC (°) = angle formed between the most proclined upper incisor long axis and coronal plane through the irises; U1-MC (mm) = distance between the most protruded upper incisor tip to coronal plane through the irises; L1-MC (°) = angle formed between the most proclined lower incisor long axis and coronal plane through the irises; L1-MC (mm) = distance between the most protruded lower incisal tip to coronal plane through the irises mm; L1-MP (°) = angle formed between the most proclined lower incisor long axis and the soft tissue mandibular plane.

Predictor variable (photogrammetry)*	Outcome variable (cephalometric)	Constant	Parameter estimate	95% CI		R^2	P value
				Lower bound	Upper bound		
STAP-MCP (°)	SNA (°)	81.561	-0.092	-0.635	0.451	0.126	0.723
STBP-MCP (°)	SNB (°)	79.576	0.81	0.575	0.413	0.278	0.73
STAP-STBP (°)	ANB (°)	-11.49	1.074	00.792	10.357	0.865	**<0.0001****
(SA-MCP) – (SB-MCP)	Wits (mm)	-4.794	0.689	00.239	10.138	0.56	**0.005****
3D LAFH (mm)	2D LAFH (mm)	-30.765	1.398	00.881	10.915	0.844	**<0.0001****
3D TAFH (mm)	TAFH (mm)	-6.278	0.982	00.393	10.57	0.705	**0.003****
MP-MAP (°)	MPSN (°)	12.789	0.58	00.211	0.95	0.698	**0.005****
MP-MAP (°)	MPFH (°)	2.055	0.625	00.22	10.031	0.522	**0.005****
U1-MCP (°)	U1-NA (°)	11.517	0.651	00.33	0.972	0.626	**0.001****
U1-MCP (°)	U1-SN (°)	93.166	0.513	00.258	0.767	0.672	**0.001****
U1-MCP (mm)	U1-NA (mm)	3.419	0.18	-0.256	0.616	0.436	0.39
L1-MCP (°)	L1-NB (°)	5.738	0.678	00.456	0.9	0.872	**<0.0001****
L1-MCP (°)	L1-MP (°)	79.5	0.761	00.328	10.194	0.548	**0.002****
L1-MCP (mm)	L1-NB (mm)	1.596	0.297	-0.044	0.637	0.649	0.083

to avoid exposing the cranial base allows additional shielding of surrounding sensitive tissue (e.g., the brain, pituitary gland, thyroid gland and lenses of the eyes; Fig. 10). Most shielding of this sort is not compatible with traditional radiographic exposures (i.e., panoramic and cephalometric radiographs). This concept becomes even more important as the profession transitions from two-dimensional (2D) to 3D radiographs that allow modification of the field of view and resolution, which results in the effective dose of a CBCT limited to the maxilla and mandible being comparable to that of a panoramic radiograph while providing more information.

Traditional six-lens 3D facial cameras used in photogrammetry are prohibitively expensive and generally are not offered with software

Figure 10. Additional lead shielding that is compatible with CBCT imaging limited to the upper and lower jaws.

packages that allow combining the dentofacial components with the facial images. Additionally, software do not allow for comparison of the acquired patient images to an established standard or pre-treatment records. However, small format portable 3D facial cameras with orthodontic software packages currently are available for approximately 1/3 of the price of traditional 3D facial cameras without any loss of image accuracy.[21]

With advances in technology and affordability, 3D photogrammetry may be expected to become a standard component of orthodon-

tic records as software applications that support this technology become more available and allow the integration of patient diagnosis and treatment planning. Additionally, 3D photogrammetry also may have potential application in orthodontic appliance fabrication and construction.

CONCLUSIONS

1. The cornea point is at least as stable as Nasion.
2. 3D photogrammetry measurements relating the jaws to each other and incisor orientation have a strong positive correlation with corresponding traditional cephalometric measurements and can serve as cephalometric predictors.
3. Radiographic images remain necessary for orthodontic diagnosis, but can be limited to the area relevant to treatment.

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THE QUEST AND REALITY OF PERSONALIZED TREATMENT FOR THE SKELETAL CLASS III PATIENT

G. Thomas Kluemper, Lorri Ann Morford, James K. Hartsfield Jr.

ABSTRACT

Successful treatment of the Class III skeletal pattern is difficult at any age. The challenge is compounded by early presentation of the malocclusion and the decision of whether or not to treat during active growth. This would be made easier if the relative probability of success could be determined for each growing patient. The validity of such an estimate depends on the vector and magnitude of future growth, a predictive measure that has to be discovered yet. Consequently, the provider is left with a clinical question that has gone unanswered since the inception of the specialty: is the potential benefit of treatment worth the risk/cost, both direct and indirect? In the current climate in which data on the benefit of such treatment is inconclusive, this chapter offers five diagnostic considerations to help the provider navigate the turbulence of available treatment options for the growing Class III patient. Genetics is one of these diagnostic considerations that has been questioned to help treatment planning for Class III malocclusions. Multiple associated genetic factors have been suggested and specific mutations in four genes in five families have been identified. However, there is insufficient data to predict the effect of the mutation on its respective protein and then to know how that would affect growth accurately. This will require future investigation to see if there is a correlation between genotype and phenotype that would be useful clinically. The most important "genetic test" the practitioner can do today is to review the patient's individual and family history.

KEY WORDS: early Class III treatment efficacy, genetics, orthodontics

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INTRODUCTION

Successful treatment of the skeletal Class III malocclusion is difficult with patients of any age, especially the pre-adolescent, growing child. While the reasons for this difficulty are many, the primary challenge is that successful treatment depends heavily on correctly predicting the magnitude and vector of future dentofacial growth. While there is discussion about determining the timing of dentofacial growth, to date, no one has developed an accurate or clinically practical method for predicting the amount and trajectory of dentofacial growth.[1-6] So what orthodontists are left with is a question that Peter Ngan proposed over a decade ago in his classic paper of 2006: "Is early treatment of Class III malocclusion worth the burden?"[7] Precisely what this question means in clinically practical terms is: Does the benefit of early Class III treatment outweigh the treatment cost? In this case, "the benefit" of early treatment refers to the ability to resolve the patient's skeletal and occlusal discrepancies in such a way that skeletal and occlusal balance is achieved without the need for surgery. "The cost" refers to more than simply the direct financial cost of two-phase treatment: it also refers to the very real indirect costs to the patient and their family of multiple years in a course of treatment that relies on the patient's potential growth.

Examples of these costs can include:

- Direct costs of two- *versus* one-phase treatment;
- Indirect costs of missing work for one or both parents to transport child to and from orthodontist office for phase I treatment;
- Indirect cost of exhausting patient compliance during early years, only to have none left when needed most during traditional phase II treatment;
- Indirect cost of unintentionally, yet unavoidably moving teeth during growth modification, only to reverse such movement to maximize benefit of orthognathic surgery if needed;
- Indirect cost of time out of school, band, sports and other extracurricular activity; and
- Indirect cost of potential insults to the enamel and periodontium related to the presence of orthodontic

hardware over extended period. Both types of insult can be irreversible. The enamel damage in the form of while spot lesions, or frank decay, most often are irreversible. The periodontal compromise is less frequent and most often reversible. On occasion, however, the insult is significant and irreversible. If one is not careful, the well-intended provider can find him/herself "chasing overjet" and allowing the desire to succeed in phase I treatment override the evidence that such efforts are putting the teeth in a compromised periodontal position, from which reverse treatment is no longer an option (Fig. 1). Of course, use of temporary anchorage devices (TADs) and/or plate anchorage in early orthopedic treatment can mitigate some of these risks significantly, but it does not eliminate them as expression of growth or muscle function may alter the outcome.[8-10]

The orthodontic literature is replete with studies that support the expectation of an immediate positive skeletal and dental outcome from an early phase of treatment involving an anteriorly directed force on the maxilla.[11-16] An example of such a response following fourteen months of facemask (FM) therapy in a nine-year-old female can be seen in the initial/progress cephalometric tracing superimpositions illustrated in Fig-

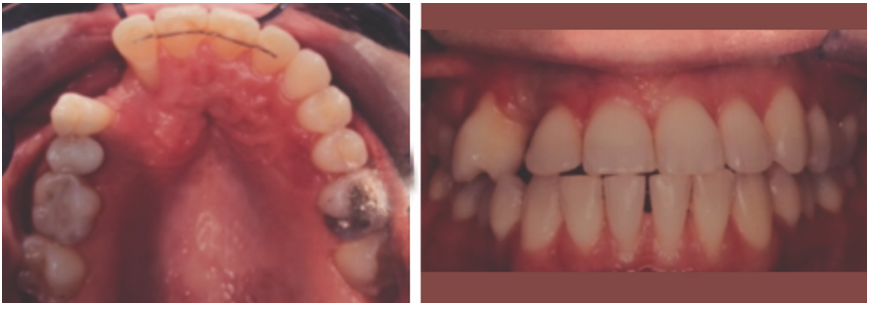


Figure 1. Clinical photos of a young adult female with an extended history of two phases of Class III treatment. She has lost her upper right canine due to traumatic occlusion and a lack of periodontal support, and is about to lose the adjacent lateral incisor for similar reasons. Her current treatment plan includes extraction of upper left premolar, orthodontic retraction of remaining anterior teeth and a Le Fort I maxillary advancement.

ure 2. This superimposition shows a forward and downward displacement of the maxilla along with a corresponding downward displacement of the mandible following FM treatment. The primarily skeletal change illustrated in Figure 2 can be differentiated clearly from the primarily dental effects shown in Figure 3. This superimposition of an eight-year-six-month-old Caucasian female is composed of the initial/progress tracings following thirteen months utilization of a 2x4 appliance in the upper arch to procline the incisors combined with a lower lip bumper to preserve leeway space, another commonly practiced approach to the young Class III malocclusion. Figure 3 shows the significant proclination and mild extrusion of the upper incisors, the corresponding extrusion and tipping of the upper molars, the mild proclination of the lower incisors and the restraint of forward movement/eruption of the lower first molars.

While the short-term changes during early orthopedic treatment observed for the patient shown in Figure 2 and others like her are promising, the more important question is whether the early orthopedic treat-

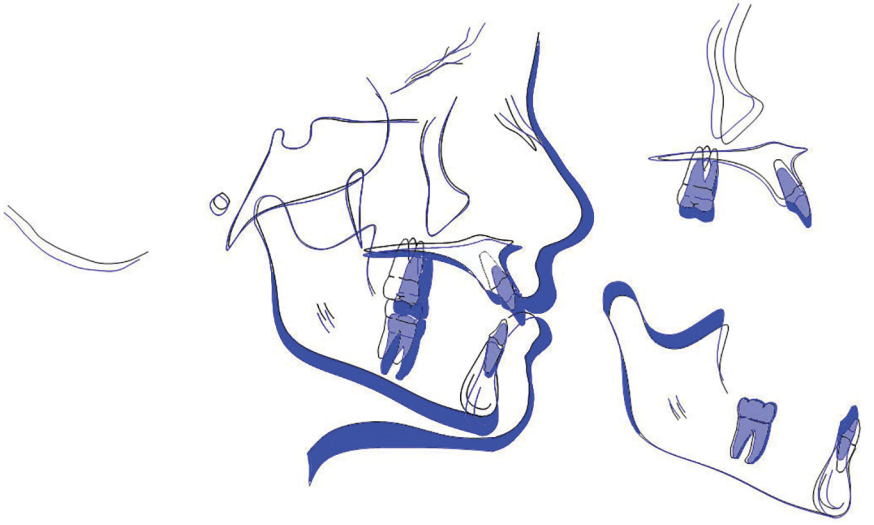


Figure 2. Superimposition of pre- and post-treatment changes following fourteen months of reverse-pull headgear therapy (termed facemask [FM] therapy) in a nine-year-four-month to ten-year-six-month Caucasian female.

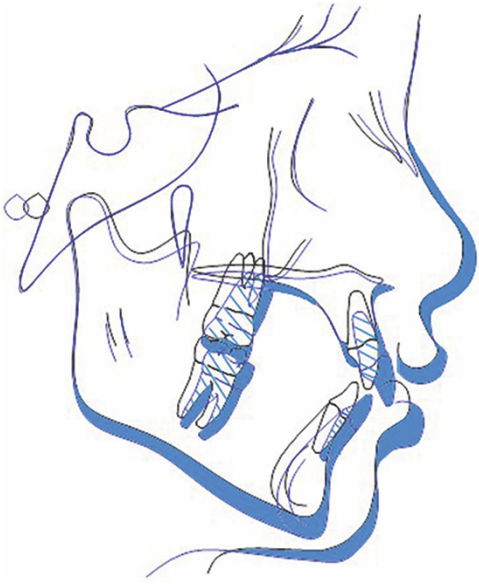


Figure 3. Superimposition of pre- and post-treatment changes following thirteen months use of a 2x4 appliance to procline upper incisors and a lower lip bumper to preserve leeway space.

ment has a lasting benefit. In other words, does such a phase of treatment make a significant enough difference that by the time the patient has completed her/his craniofacial growth, s/he truly achieves the desired skeletal, facial and dental corrections without surgery? In the end, this important clinical question can be answered only with the assistance of good data on the long-term stability/success of early treatment. A recent systematic review and meta-analysis has suggested that the long-term outcome of early treatment is not nearly as favorable as one would hope. However, the authors acknowledge that a solid body of evidence for the long-term stability of early Class III treatment is lacking sorely in the orthodontic community.[17]

Given the relative lack of evidenced-based outcome data on phase I treatment of the Class III malocclusion, how does the conscientious clinician develop a personalized plan of treatment for the young Class III patient? The purpose of this chapter is to propose a reasonable strategy for developing such an approach in the presence of uncertainty.

A REASONABLE PROPOSAL

In orthodontic circles, it is not uncommon to hear the following approaches to the treatment of the Class III patient:[18]

- "I start as early as I can and do everything possible to avoid surgery;" or
- "I never do early treatment, but wait until growth is complete."

For obvious reasons, no one position can represent a personalized method of treatment and is no better than a "one-size-fits-all" campaign in shoe wear. Moreover, considering the evidence that exists, albeit weak, neither of these two extreme positions can be supported as an overall practice strategy for the treatment of Class III patients.

There are several indicators, clinically and otherwise, that provide a glimpse into the variation of severity of the skeletal discrepancy. Not all Class III malocclusions are created equal. While some Class III cases may be caused by a single gene variation (Mendelian inheritance, i.e., monogenic gene effect), numerous cases appear to be a composite of or affected by multiple gene influences (i.e., polygenic), which work together to create the observed Class III trait.[19] This may be found particularly in individuals or families showing variable expressivity and incomplete penetrance of the Class III traits. As we learn more about the genetic blueprint for certain malocclusions, our treatment may become more personalized. But short of those breakthroughs, there are a few useful diagnostic indicators that can help the provider better diagnose and subsequently construct a more personalize plan of treatment for the Class III patient. One might think of them as landmarks on a map to assist with the journey of Class III treatment. The five such landmarks are as follows:

- Pseudo Class III (result of functional shift);
- Age of patient;
- Severity of discrepancy;
- Patient goals for treatment; and
- Family history/genetic predisposition.

Each of these indicators will be discussed individually.

Pseudo Class III Malocclusion

The so-called Pseudo Class III malocclusion is a function of a Centric Relation-Centric Occlusion/Maximum Intercuspation (CR-CO/MI) anterior slide that can be difficult to diagnose due to patient resistance/posturing, yet a proper diagnosis can make all the difference in the design of an effective treatment plan. This sub-type of malocclusion generally entails two distinct positions of the mandible in the sagittal plane when teeth are in contact. In centric relation (CR), when the condyle is seated in the glenoid fossa, the upper and lower teeth interdigitate with one another in a more balanced, or Class I relationship. However, in the Pseudo Class III, there typically is an occlusal interference, usually involving the canines or incisors, that forces the mandible to shift away from the balanced or Class I relationship and into maximum intercuspation (MI). In the Pseudo Class III case, this shift away from the interference is forward and often lateral as well, positioning the mandible into a more prognathic position (Fig. 4). The implication of this shift not only is on the occlusion, but also on overall facial balance as well (Fig. 5). Clearly, the orthodontic treatment plan for this patient differs significantly, depending upon whether you treat him in CR rather than MI.

Age of Patient

By definition, early treatment (or phase I treatment) implies that the timing of the treatment occurs before phase II treatment that traditionally occurs in the late mixed, or early permanent dentition. There is an

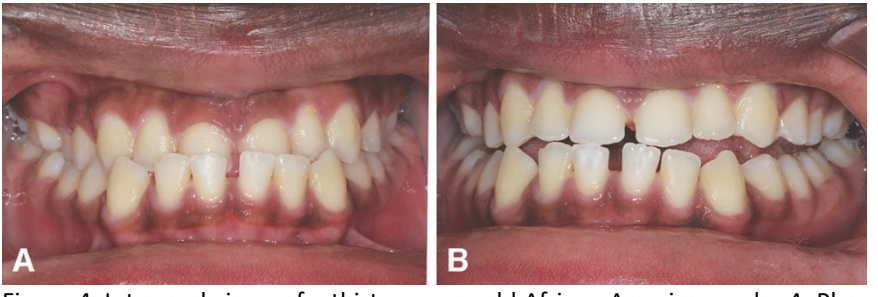


Figure 4. Intra-oral views of a thirteen-year-old African-American male. *A:* Photograph of the patient's occlusion in maximum intercuspation (MI). *B:* Image of the patient's occlusion in centric relation (CR).

Figure 5. Lateral profile photos of patient in Figure 4. *A:* Patient in MI. *B:* Patient in CR.

important reason for this timing, especially in Class III treatment. Unlike the mandible, the maxilla experiences downward and forward displacement in growth before intramembranous ossification at the posterior and superior circummaxillary sutures. Consequently, the best timing for the protractive forces used in early Class III treatment is during the most active period of such growth, which is prior to the adolescent peak height velocity curve and within the range of six to nine years of age.[14,15] Hence, the age of the patient for whom early Class III treatment is being considered clearly is an important factor. Orthopedic treatment at a later stage of growth is more likely to have a dental component than a skeletal component. The crucial point is that skeletal response to protraction forces in the maxilla is age dependent, with the maximum response to protraction therapy occurring earlier than later. Consequently, one is served well to consider the implications of this reality when planning treatment for Class III patients and counseling them on the relative prognosis for each treatment option.

Severity of Discrepancy

On one hand, the severity of an early Class III discrepancy is an intuitive indicator of future severity. Thus, it is a reasonable tool with which to predict the likelihood of the average response to protraction therapy providing enough of a correction to achieve skeletal, facial or oc-

clusal balance. As with other such predictors, however, it is most useful with the Class III patterns that represent the two extremes of the spectrum. In children with a mild Class III skeletal pattern, a phase I approach most likely will be successful when planning treatment. The opposite conclusion would be true for the severe skeletal discrepancy.

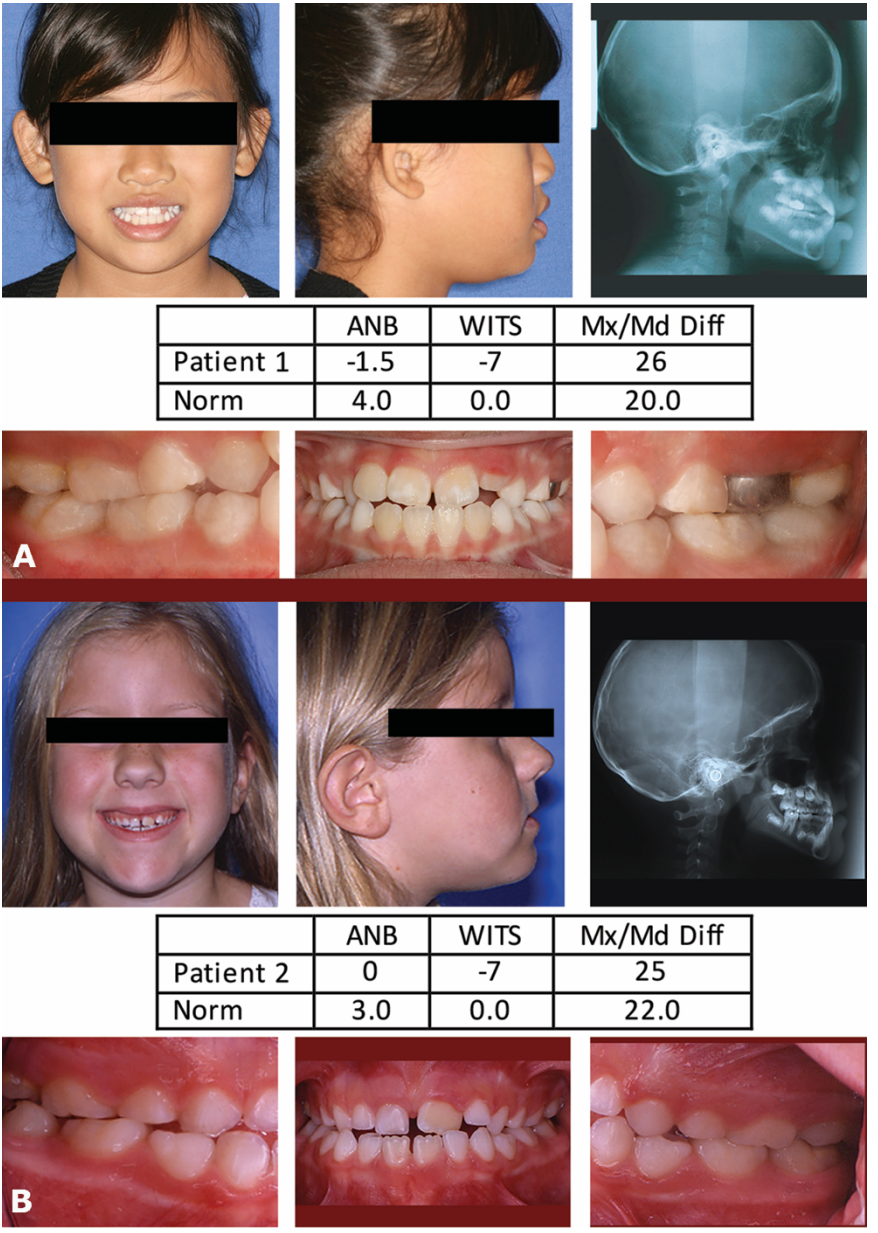
For patients whose Class III pattern lies somewhere in the middle, severity of the discrepancy becomes less predictable. In Figure 6, the records of two young girls are shown, both within four months of eight years of age and nearly identical in all diagnostic measures of their Class III malocclusion. Based upon the severity of malocclusion alone, one would predict with a reasonable degree of confidence that each would respond similarly to a phase I round of maxillary protraction therapy. In fact, that was not the case at all. Though both were compliant with their FM treatment and demonstrated a favorable outcome, the girl in Figure 6*A* maintained her correction throughout her adolescent growth, while the patient in Figure 6*B* proceeded to grow into a relatively severe Class III skeletal malocclusion for which a combined surgical/orthodontic approach was her best and eventual treatment option. In addition to the apparent difference in ethnicity—which, in general, is associated with a difference in incidence—if a patient's family history is known, it may give the clinician a clue, but not a guarantee, as to how the patient will grow.

Patient Goals in Treatment

Consideration of the patient's goals for treatment is appropriate, particularly in the comprehensive treatment of the Class III patient. Except for the craniofacial anomaly patient, or potentially the individual with an obstructed airway, there are only two overall reasons that an individual will seek treatment to resolve the skeletal discrepancy involved in a Class III malocclusion:

- To achieve a better bite; and
- To improve facial appearance.

For potential patients who are motivated merely by achieving a better bite, it likely will be enough to maximize the dental compensations for the skeletal pattern; one exception may be the severe Class III skeletal pattern for which even maximum dental compensation is not sufficient



	ANB	WITS	Mx/Md Diff
Patient 1	-1.5	-7	26
Norm	4.0	0.0	20.0

	ANB	WITS	Mx/Md Diff
Patient 2	0	-7	25
Norm	3.0	0.0	22.0

Figure 6. Two girls, each within four months of eight years of age, nearly identical in all diagnostic components of their Class III malocclusion.

to achieve a functional occlusion. For individuals who are motivated primarily by the facial implications of their Class III malocclusion, it likely does not matter if the orthodontist can work wonders with the dentition. Maximizing dental compensations does nothing to improve facial balance and sometimes even emphasizes the appearance of mid-face deficiency or mandibular prognathism. Consequently, eliciting the patients' feelings regarding their malocclusion and facial esthetics is paramount to personalized treatment.

Due to the reluctance of some individuals to share their feelings about self-image and facial appearance, it can be difficult to elicit such personal information. The key to success in this area is the clinician's ability to construct a patient/provider relationship based upon mutual trust. Though sometimes difficult, it cannot be circumvented. Inserting our own value system into the process is an exercise in futility as we often are fooled by the choices our patients make when given the option of orthognathic surgery *versus* camouflage treatment.

It is likely that most orthodontists would be pleased with outcome of early FM therapy in the patient illustrated in Figure 7. Comparing her initial records at 8.5 years of age with her pre-phase II progress records at almost 15 years of age, one can appreciate the relative improvement in her skeletal and facial balance, as well as her anterior occlusion. Yet when given the option of orthodontics only *versus* an orthodontics/surgical treatment plan, she chose the orthodontics/surgical option due her displeasure with the Class III implications on her facial esthetics.

Similarly, most orthodontists likely would think that the patient in Figure 8 would not be pleased with the extreme dental compensations employed to achieve positive anterior overjet (OJ), or the relative midface deficiency in her profile. However, she was perfectly happy with both and chose to continue with her orthodontics-only treatment to completion.

Family History/Genetic Predisposition

Personalized ("Precision") Orthodontics. In 2008, the President's Council of Advisors on Science and Technology emphasized that the term *personalized medicine* "refers to the tailoring of medical treatment to the

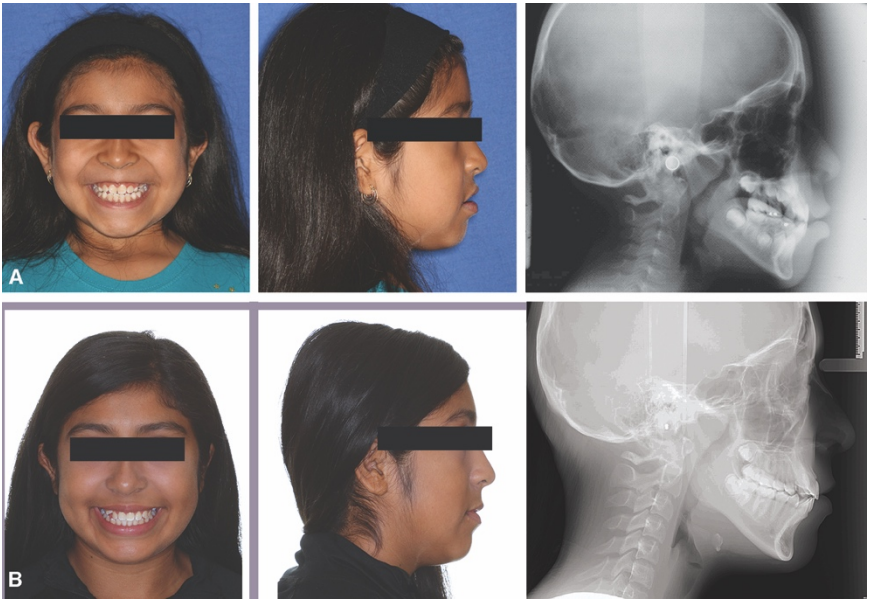


Figure 7. *A:* Initial records of eight-year-six-month old female prior to FM therapy. *B:* Progress records of same patient at fourteen years of age following fourteen months of FM therapy, more than three years of observation and prior to Phase II treatment.

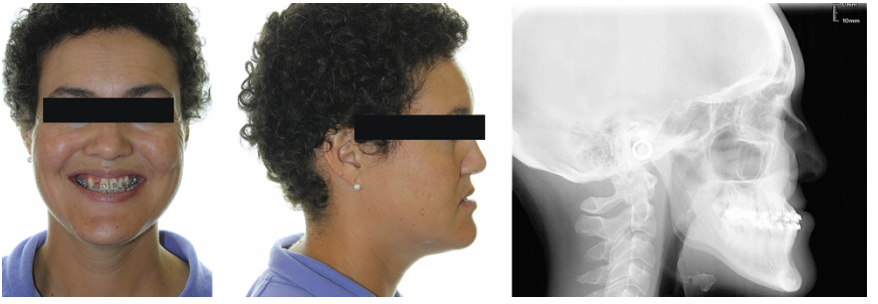


Figure 8. Progress records of adult female in final stages of ortho-only, "camouflage" treatment for Class III skeletal malocclusion. She was pleased with substantial dental compensations to achieve positive overjet/overbite and was not concerned with her concave profile; she rejected surgical correction.

individual characteristics of each patient. It literally does not mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into sub-populations that differ in their susceptibility to a particular disease or their response to a specific treatment."[20] The term *precision medicine* has been used by some to

take the place of *personalized medicine*, to encompass specifically the inclusion of an individuals' genetic characteristics to aid in classifying the individual into the appropriate diagnostic category, increasing the likelihood of a more consistent or favorable response to targeted treatment. Although the emphasis often is on how genomics may do this, proteomics, metabolomics, epigenomics, transcriptomics, microbiomics and bioinformatics in combination now can generate more focused 'systems biology perspective' from the 'big data' set which can be included in this definition and process.[21] This concept has been explored under the term *personalized* or *precision orthodontics*, with ongoing discussion of the promise and challenges of incorporating this into orthodontic practice.[22-24]

Genetics will help in clinical practice through the identification of specific genetic factors and factor variations that can influence the craniofacial traits that are identified within an individual, not by using heritability estimates of a sample that can change within the sample and cannot be predictive for an individual, even within the sample.[25] However, since there is practically no aspect of orthodontic practice that can be predicted or explained precisely by only one mutation in one gene, the expectation that genetics will be a crystal ball that tells all is unfounded. It most likely will be a combination of genetic factor effects and variations that will be central to enhancing our understanding of the genetic influence(s) that act in/on the development of complex oral-facial phenotypes and responses to treatment.

Genetics and Class III Malocclusion

Based on its more frequent clustering within families than other sagittal skeletal jaw growth discrepancies, it has been suggested that a genetic component most likely is involved in the Class III malocclusion. Studies have shown that this phenotype can occur in families with an autosomal dominant mode of inheritance, variable expressivity and incomplete penetrance, and that phenotype arises due to a major gene effect and polygenic/multi-factorial influence.[19,26] In other words, the phenotype runs strongly in families, but can vary in how severely it affects members of the same family (variable expressivity); the appearance of the phenotype can even skip a generation (incomplete penetrance).

From a treatment perspective, Class III "skeletal" malocclusion (often referred to as mandibular prognathism) is understood to be due

to a short maxilla, long mandible, or both when examined in the sagittal plane. Thus, a concept of treating the jaw(s) at variance with some statistical norm is reinforced. However, based on morphometric and other studies, this is a simplification that may serve for clinical diagnosis and treatment planning, but is likely to be insufficient for studies associating the clinical development of Class III malocclusion with genetic markers (i.e., genotype-phenotype correlation).[27-30] Based on the number of subtypes of clinical morphology found in Class III malocclusion patients, are we likely to have as many or more genetic factors associated with the subtypes?

Prior to genetic analysis of individuals and families with Class III skeletal malocclusion, the question was whether there was one, or only a few, genetic markers that were the primary driving factors. It was hypothesized that resolving this question and determining which factors were involved could make it more likely to forecast the Class III skeletal growth pattern and growth timing of a patient. For example, would knowing the gene(s) involved in "late" growth help who more likely would grow out of a phase I reverse headgear negative overjet correction? Would it help to determine if a further sagittal (or also vertical) growth discrepancy would occur in the mid or late teens, making a camouflage treatment plan less advisable *versus* waiting for orthognathic surgery?

Generally speaking, many genetic studies compare individuals who have a Class III skeletal malocclusion to those who do not. In Genome-wide Association Studies (GWAS) of the Class III phenotype, the subjects chosen for analysis are not related to each other in order not to confound the results of this type of analysis. One problem with many of the GWAS studies, however, has been that if Class III malocclusion is as heterogeneous morphometrically as it seems to be, this type of study involving many affected and unaffected who all come from different families will be less likely to pinpoint a contributing factor, since it is likely that many contributing factors may be present among all the represented families.[31]

In contrast, Genetic Linkage Analysis studies have been performed on large families and require a different type of statistical approach than GWAS to account for the shared DNA in common among the family members, which is not linked to the phenotype being studied. To

date, family linkage analyses in combination with DNA sequencing technologies have been more effective in the identification of genetic mutations that are thought to cause Class III malocclusion than the association studies of Class III. For those who are interested, more information on these different types of studies may be found elsewhere.[32]

In studies of Asian subjects, genetic linkage and association studies have identified multiple loci and candidate genes connected to the Class III phenotype including 1p22.3, 1q32.2, 1p35-36 (Matrillin-1, *MATN1*; Erythrocyte Membrane Protein Band 4.1, *EPB4.1*; Heparin sulfate proteoglycan 2, *HSPG2*; Alkaline phosphatase, *ALPL*), 3q31.2, 4p16.1, 6q25, 12q13 (Collagen, type II, alpha 1, *COL2A1*), 14p24.3 and 19p13.2.[33-39] By comparison, several unique loci were identified in linkage analysis of the Class III phenotype in multiple South American families including 1p22.1-22.2, 3q26.2, 7p21, 11q22.2-q22.3, 12q13.13 and 12q23.[40,41] In an association analysis of Class III malocclusion cases with a U.S.-based population compared to Class I and comprised of multiple ethnic backgrounds (European, African, Hispanic and Asian), the SNP rs10850110 within the Myosin 1H gene (*MYO1H*) on chromosome 12q24.11 was found to be associated with Class III.[42] A recent study also found it to be associated significantly in a Brazilian sample.[43]

While numerous genetic loci have been associated with Class III, so far causal genetic mutations have been identified within four unique genes in five families with Class III malocclusions;

1. Various mutations in the Dual Specificity Phosphatase 6 (*DUSP6*) gene (c.545C>T; p.Ser182Phe; rs139318648) within a family from Estonia and missense mutations 1907 C> T (p.Thr365Ile) and 1930 T>C (p.Tyr373His) in a Malaysian Malay family;[44,45]
2. A mutation in the Rho GTPase Activating Protein 21 (*ARHGAP21*) gene (Gly1121Ser) within an Italian family;[46]
3. A mutation in the Fibroblast Growth Factor-23 (*FGF23*) gene c.35C>A (p.Ala12Asp) in a Chinese family and three unrelated (sporadic, i.e., non-familial) individuals;[47] and
4. A (c.2680A>C) p.Ile742Thr mutation in the gene termed “A Disintegrin-Like and Metalloprotease

(Reprolysin Type) with Thrombospondin Type 1 Motif, 1" or *ADAMTS1* was identified in a Chinese family.[48]

Additional genetic studies on Class III malocclusion have suggested the *FGFR2, COL1A1* and *TBX5, MYO1H, GHR* and *FGF10, SSX2IP, PLXNA2, RASA2, TCF21, CALN1* and *RORA* genes to be associated with the phenotype.[49-51]

As stated previously, large family studies have been the most successful in identifying causal genetic mutations and/or contributing mutations for Class III, possibly due to reduced genetic heterogeneity of the Class III phenotype within a family compared to that observed within a general population. In future studies of large numbers of unrelated individuals diagnosed with a Class III malocclusion, it will be important to subclassify Class III patients morphologically with a combination of cephalometric and/or geometric morphometric information to study the genetics of the predominant sub-type(s) of skeletal and dental Class III cases across families better.[27,29] This type of approach would answer the question of whether Class III patients with a similar subtype also will have similar genetic factors in common, or if this primarily will be the case among affected members of a family.

Investigations into muscle fiber composition variation have been observed in vertical dimension malocclusions (e.g., deepbite, openbite) and mandibular asymmetries, muscle fiber compositions varied to a lesser degree in malocclusions affecting the sagittal dimension. Still, type IIA (from the *MYH2* gene) and IIX (from the *MYH1* gene) myosin heavy chain (MHC) protein expression was increased in the masseter muscle of individuals with mandibular prognathism.[8,54] Class III deepbite cases showed an increased amount of type I and hybrid type I/II muscle fiber areas in the masseter muscle, compared to normal and openbite cases.[54]

Epigenetic factors also may influence muscle fiber types, vertical and/or sagittal dimension variations and malocclusion types. Increased gene expression of histone deacetylase 4 (from the *HDAC4* gene) was associated with increased gene expression of the fast type IIX MHC (*MYH1*) and decreased gene expression of slow type I MHC (*MYH7*) in subjects diagnosed with Class II. Increased gene expression of lysine acetyltransferase 6B from the *KAT6B* gene correlated negatively with type IIX MHC

(*MYH1*) gene expression in Class III malocclusions.[55] Overall, expression of both the *KAT6B* and *HDAC4* genes were elevated in masseter muscle from patients with Class III malocclusions compared to individuals diagnosed with Class II.[10,55] It has been proposed that the KAT6B protein could play a potential role in mandibular prognathism through its ability to activate the runt-related transcription factor 2 gene (*RUNX2*), which encodes an osteogenic transcription factor.[10] These studies of how the genetic variation can affect muscle variation—which, in turn, can affect variation in morphology from Class II to Class III and from deep to open bites—are areas for research in the correction and stability of correction of facial morphology variation and skeletal malocclusion. Better understanding the genetics of muscle composition and how muscle can be reprogrammed prior to surgical correction of either Class II or III surgical cases may aid greatly in reducing the number of surgical relapse cases—and also may assist in the identification of late and/or slow growers.

Application of Genetic Testing to Class III Malocclusion

Given the numerous "sub-types" of Class III malocclusion and the numerous genetic factors that have been involved either directly (so far four of them), indirectly, or suggested to be involved in the etiology of Class III malocclusion, there is not a single gene test that can be applied in practice. What has developed in medical genetics when a phenotype has multiple sub-types (sub-phenotypes) and is heterogeneous genetically is the use of "gene panels" to test a patient. While initially these panels often consisted of specific markers or DNA variations associated with the phenotype, with the progress of technology into "next-generation" DNA sequencing, the panels often consist of the sequencing of several selected genes. This may apply one day to Class III malocclusion as well (Fig. 9), but not until extensive investigation into the most common genetic variations associated with Class III malocclusion are discovered so that they may be considered for inclusion on such a gene panel. Then extensive clinical research must be performed to see how the genetic variants when known are associated with clinical patterns of development of the Class III malocclusion sub-types, including the effect on growth and size the maxilla and mandible, and their response to whatever treatment we prescribe.

So what is the practitioner to do? While the field of oral and craniofacial genetics expands to learn more about the genetic factors that

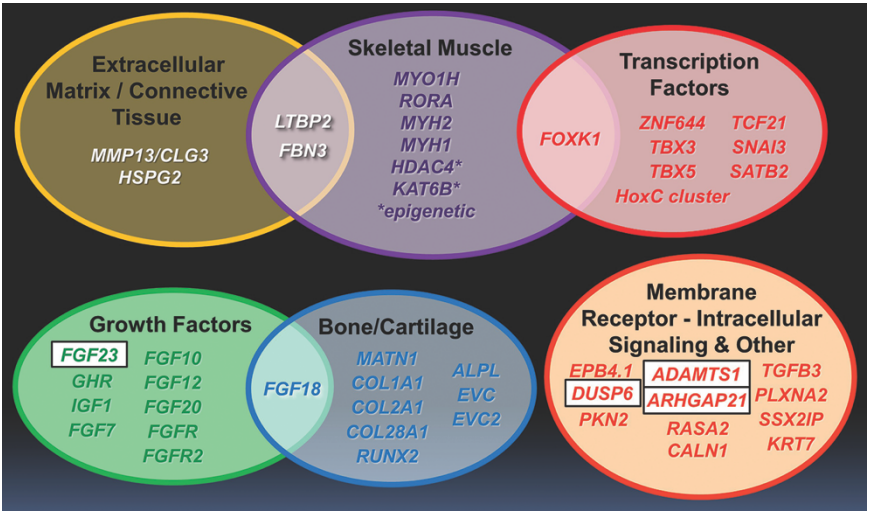


Figure 9. Proposed candidate genetic factors influencing Class III, based on references in the text.[10,33-55] The four genes in boxes have been found to have specific mutations associated with Class III in one, or in the case of *DUSP6*, two families. This is not intended to be an exhaustive review of genetic factors suggested to have influenced the development of Class III malocclusion. The point is to show the complexity from a clinical genetics diagnostic perspective of construction of a gene panel that possibly could predict development of a Class III malocclusion. In addition, other factors, particularly in family studies, are expected to be discovered. Figure by author LAM.

would help to treat individual patients better, it should not be overlooked that practitioners today could start to take and consider a detailed family history in the diagnosis and treatment planning of malocclusion.[32] While it may be imprecise, this can be used to help understand the approximate likelihood that the patient or a sibling also may develop Class III malocclusion, which still may vary in its severity, even within the same family.

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THE EFFICIENT TREATMENT OF CLASS II AND CLASS III MALOCCLUSIONS: PATIENT-CENTERED DECISION MAKING IN DENTOFACIAL ORTHOPEDICS

Lorenzo Franchi and James A. McNamara Jr.

ABSTRACT

The aim of this chapter is to evaluate patient-related factors that potentially can improve the efficacy and efficiency of Class II and Class III treatment. Two factors that possibly can improve the efficacy of treatment have been analyzed: 1) timing of treatment, defined on the basis of reliable indicators of individual skeletal maturity; and 2) individual patient responsiveness.

Functional appliances used for the treatment of Class II malocclusion are effective in altering short- and long-term mandibular growth and mandibular sagittal position if active treatment includes the pubertal growth spurt. To predict individual patient responsiveness, mandibular morphology should be evaluated at puberty. Good responders to functional jaw orthopedics (FJO) for the treatment of Class II malocclusion associated with mandibular retrusion are characterized by a small mandibular angle.

Optimal timing for Class III malocclusion occurs during the prepubertal phases of development when the circummaxillary sutures offer less resistance to maxillary protraction compared to the pubertal phase. Individual patient responsiveness to combined rapid maxillary expansion (RME) and facial mask (FM) therapy can be assessed by analyzing the craniofacial features at the start of treatment. Although it remains difficult to achieve a reliable prediction of long-term treatment outcomes of orthopedic treatment of Class III malocclusion using methods related to the pre-treatment cephalometric dentoskeletal characteristics, unsuccessful cases seem to be characterized by high-angle vertical skeletal relationships and a large gonial angle.

KEY WORDS: growth modification, Class II malocclusion, Class III malocclusion, treatment timing, individual patient responsiveness

INTRODUCTION

The efficacy of treatment of Class II and Class III skeletal imbalances in the growing patient by means of functional jaw orthopedics (FJO) or other appliances that can produce growth modification remains a controversial issue in contemporary literature. Specifically, there still is ongoing debate as to whether removable or fixed functional appliances can induce short- and long-term stimulation of mandibular growth and mandibular sagittal displacement in growing patients affected by Class II malocclusion associated with mandibular retrusion. Similarly, when dealing with Class III malocclusion, the greatest controversy involves the long-term stability of early correction of this skeletal imbalance. This chapter is an attempt to decipher this controversy on the efficacy of FJO for the treatment of Class II and Class III skeletal imbalances by means of a patient-centered decision-making approach.

Probably the most interesting part of "evidence-based medicine" is so-called "patient-centered care" where the focus is mainly on the appropriateness of treatment on one hand and on the biological responsiveness of the individual patient on the other.[1] Orthodontic treatment is "appropriate" when it meets the patient's expectations in terms of correction of the patient's main complaint, esthetic and functional satisfaction, favorable cost/benefit balance and positive impact on the quality of the patient's life.

One of the most exciting research scenarios of contemporary and future times will be the discovery of those biological characteristics of the individual patient (both anatomical and genetic biomarkers) that can influence the individual response to a given treatment modality substantially. The same orthodontic appliance delivered by the same orthodontist may give completely different results in different patients with the same type of dentoskeletal malocclusion. The variation in response depends on factors such as individual skeletal maturation (timing of treatment), genetic predisposition to react to orthodontic/orthopedic forces, intensity of bone turnover and others.

In particular, two patient-related factors that potentially might improve the efficacy of Class II and Class III treatment will be discussed in this chapter: 1) timing of treatment, defined on the basis of reliable indicators of individual skeletal maturity (e.g., increases in stature,

hand-wrist method, cervical vertebral maturation [CVM] method); and 2) individual patient responsiveness.[2-4]

TREATMENT TIMING FOR CLASS II MALOCCLUSION

Among systematic reviews that have appeared recently in the literature, the one by Perinetti and colleagues has the merit of having focused specifically on the role of treatment timing on the short-term effects produced by removable functional appliances in pre-pubertal *versus* pubertal Class II patients.[5-7] To be included in the systematic review and meta-analysis, the studies had to be randomized controlled clinical trials (RCTs) or either prospective or retrospective controlled clinical trials (CCTs). The most important inclusion criteria were:

1. Longitudinal studies, either prospective or retrospective, on healthy growing subjects treated for skeletal Class II malocclusion due to mandibular retrusion;
2. Use of removable functional orthodontic appliances;
3. Use of a reliable indicator of individual skeletal maturity to assess treatment timing that had to be either pre-pubertal or pubertal; and
4. Use of matched control groups of untreated Class II malocclusion subjects in a similar growth phase.

According to the electronic search, a total of 2,835 articles were retrieved; among these, only eleven studies were eligible for meta-analysis (see Perinetti and associates for further details).[7] Figure 1 illustrates the forest plot, a graphical display of estimated results from several clinical studies that addressed the annualized changes in total mandibular length (Co-Gn or Co-Pg) in the pre-pubertal and pubertal treated Class II patients with respect to corresponding untreated Class II controls. The results from this forest plot clearly show the fundamental role of treatment timing on the amount of supplementary mandibular growth that can be gained by using different types of removable functional appliances. Regardless of the type of appliance used, the overall annualized supplementary mandibular growth was less than 1 mm (0.9 mm) in the pre-pubertal subgroup while it was more than 3x greater (2.9 mm) in the pubertal subgroup (P = 0.0002). Similarly, when considering the supplementary annualized changes in mandibular ramus height

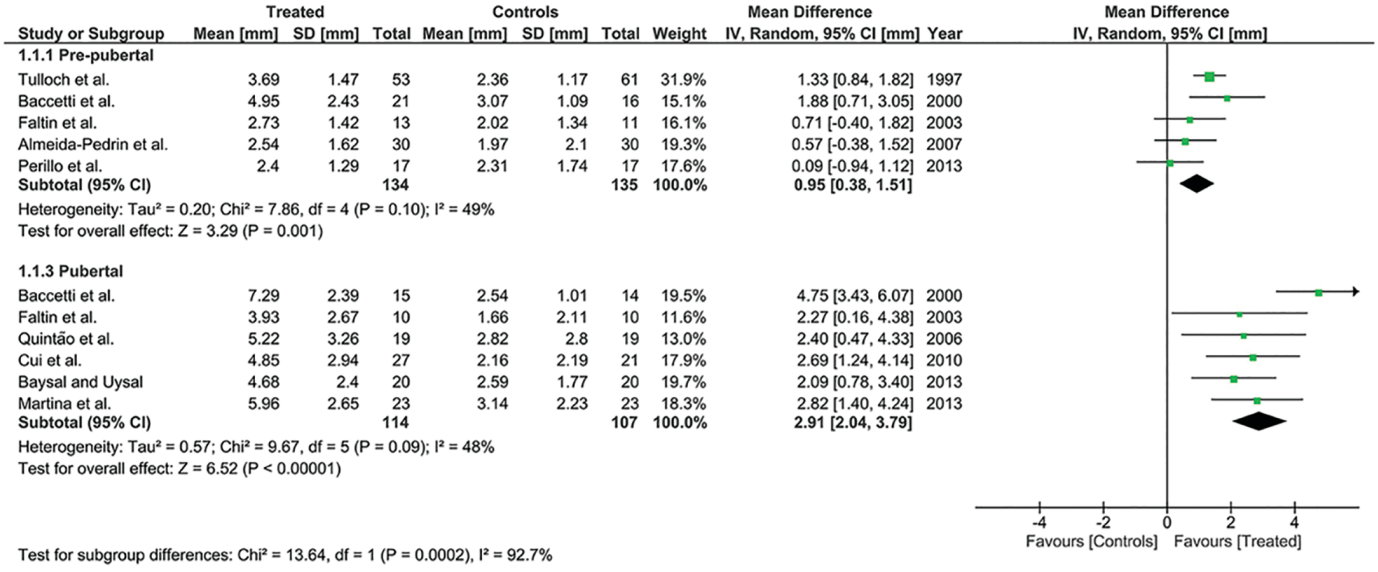

Figure 1. Forest plots for the annualized changes in total mandibular length in the pre-pubertal and pubertal subgroups. Printed with permission of PLOS ONE; Perinetti and coworkers, 2015.[7]

(Co-Go; Fig. 2), a greater amount of change was observed in the pubertal group (2.2 mm) with respect to the pre-pubertal subgroup (0.0 mm).

The results of this meta-analysis confirmed the findings of previous meta-analyses.[5-7] Thiruvenkatachari and associates reported that the ANB angle showed significantly greater decreases when treatment with removable functional appliances was performed at puberty with respect to treatment carried out before puberty (-1.4° *versus* -0.9°, P = 0.0003).[5] Koretsi and colleagues found that only 10 of the 17 studies included for the meta-analysis reported the skeletal growth stage at the start of treatment.[6] Specifically, six studies performed treatment before puberty, three included pre-peak and peak patients and only one included peak patients (see Koretsi and coworkers for details).[6] The majority of these studies, therefore, started treatment at a pre-pubertal growth stage. This finding can explain why the authors wrote in the conclusions: "the short-term evidence indicates that removable functional appliances are effective in improving Class II malocclusion, although their effects are mainly dentoalveolar, rather than skeletal."

The results of these meta-analyses indicate that if the aim of treatment is to try to stimulate mandibular growth effectively, it is prudent to include the pubertal growth spurt in the active treatment period with a removable functional appliance. Treatment of Class II skeletal imbalance associated with mandibular retrusion begun during the pre-pubertal period can produce a correction only at a dentoalveolar level, with no significant effect achieved in terms of effective mandibular growth stimulation.

The use of removable functional appliances at puberty followed immediately by fixed appliance therapy to refine the occlusion for the comprehensive treatment of Class II dentoskeletal imbalance is characterized by several favorable features. First, this type of approach can induce an effective amount of mandibular growth stimulation (almost 3 mm, as shown by Perinetti and colleagues).[7] Moreover, this treatment protocol can be considered an efficient approach with shorter treatment duration when compared with a typical two-phase treatment when removable functional appliances are applied before puberty (2.3 years *versus* 3.4 years on average).[8-10] This approach also is efficient with shorter treatment duration of fixed appliance therapy with respect to overall treatment with fixed appliances used in combination with fixed functional appliances (1.2 *versus* 2.3 years on average).[8]

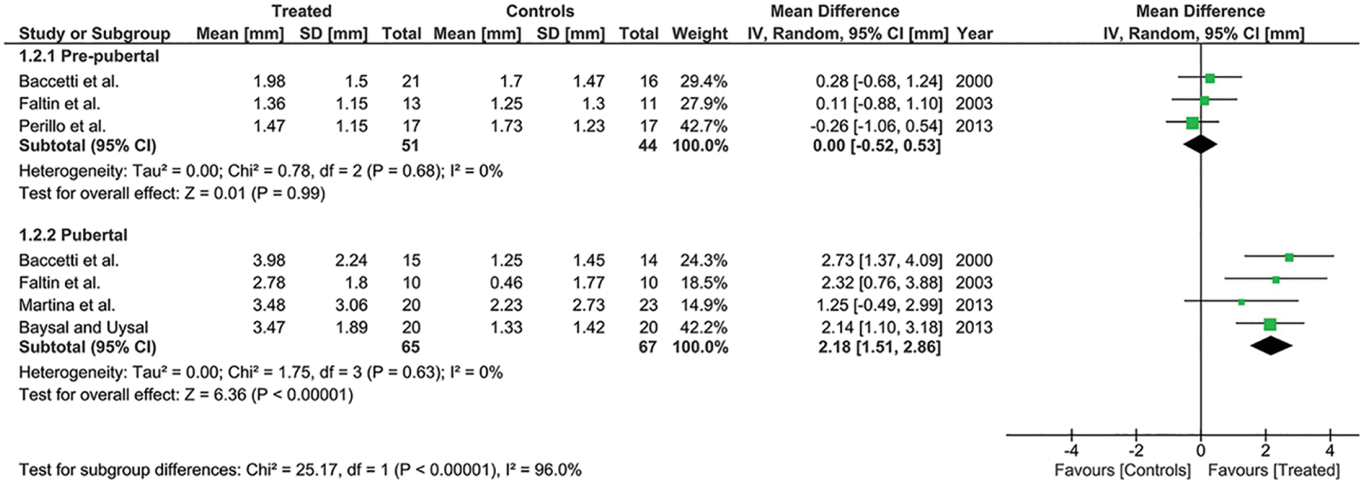

Figure 2. Forest plots for the annualized changes in mandibular ramus height in the pre-pubertal and pubertal subgroups. Printed with permission of PLOS ONE; Perinetti and colleagues, 2015.[7]

Finally, the use of removable functional appliances at puberty followed immediately by fixed appliance therapy is characterized by two aspects that potentially should favor long-term stability of treatment outcomes. The first aspect is that when treatment with removable functional appliances is started at puberty, comprehensive treatment will end at a late post-pubertal phase of development in the majority of the patients (CS 5, according to the classification of vertebrae maturation) when the residual amount of active mandibular growth is minimal; it is not different from the residual amount of mandibular growth shown by untreated Class I subjects.[4,11,12] In addition, creating a stable Class I intercuspation at the end of comprehensive treatment also favors long-term stability.[13]

Role of Treatment Timing on the Long-term Outcomes of Class II Treatment

The role of treatment timing on the long-term dentoskeletal effects of Class II treatment with removable functional appliances followed by full-fixed appliance therapy was analyzed recently by our research group.[14] A group of 46 patients (23 females and 23 males) with Class II division 1 malocclusion consecutively treated either with the Bionator (26 subjects) or Activator (20 subjects) were collected. Class II patients were retrieved from an orthodontic practice (Bionator) and from the records of patients treated at the Department of Orthodontics at the University of Rome Tor Vergata (Activator). Lateral cephalograms were available at three time points: T1, at the start of treatment (mean age: 9.9 ± 1.3 years); T2, at the end of treatment with functional appliances (mean age: 11.9 ± 1.3 years); and T3, at long-term observation after completion of growth (CS 5 or CS 6 according to the CVM method, mean age: 18.3 ± 2.1 years).[4] The treated sample was compared to a control group of 31 subjects (16 females and 15 males) with untreated Class II division 1 malocclusion that were selected from the *American Association of Orthodontists Foundation* Craniofacial Growth Legacy Collection (http://www.aaoflegacycollection.org). The treated and control samples were divided into pre-pubertal and pubertal groups according to skeletal maturity observed at the start of treatment (for further details, refer to Pavoni and associates).[4,14]

When analyzing the short-term (T1-T2) changes in the pre-pubertal groups, a significant amount of mandibular growth stimulation in the treated sample *versus* the untreated Class II controls was record-

ed (Co-Gn +2.3 mm, P = 0.006), while no significant mandibular advancement occurred during this interval (Pogonion to Nasion perpendicular +0.9 mm, P = 0.347). During the post-treatment T2-T3 interval, a significant relapse in mandibular growth occurred in the pre-pubertal treated group with respect to the pre-pubertal control sample (Co-Gn -3.0 mm, P = 0.049) while no significant differences were recorded between the two groups in terms of mandibular advancement (Pog to N perpendicular 0.0 mm, P = 0.996).

The analysis of the overall long-term T1-T3 period showed that treatment performed before puberty was not able to produce significant changes either in mandibular growth or chin advancement when compared to the growth changes in the pre-pubertal untreated sample (Co-Gn -0.7 mm, P = 0.632; Pog to N perpendicular +0.9 mm, P = 0.479). These findings were similar to those reported by Wieslander who analyzed the long-term effects of early treatment with the headgear-Herbst appliance in pre-pubertal children with severe Class II malocclusions.[15] The significant 2.0 mm short-term therapeutic increase of the Co-Gn distance decreased to 1.2 mm after retention and it was not different significantly from control values at the age of 17 years, four months.[15]

When treatment was performed at puberty, however, the short-term changes of both mandibular growth and advancement were significant statistically (Co-Gn +3.7 mm, P = 0.000; Pog to N perpendicular +2.2 mm, P = 0.007). No relapse occurred during the post-treatment T2-T3 period (Co-Gn +1.8 mm, P = 0.131; Pog to N perpendicular +1.1 mm, P = 0.274). Therefore, treatment performed at puberty resulted in favorable long-term mandibular changes in terms of both mandibular growth stimulation (Co-Gn +5.5 mm, P = 0.000) and chin advancement (Pog to N perpendicular +3.1 mm, P = 0.001).

These favorable mandibular skeletal changes can be considered significant not only at a statistical level, but more importantly, at a clinical level (3.0 to 5.0 mm) as they can contribute substantially to the improvement of skeletal Class II relationship in the long term. The results of this long-term study confirmed those of a previous study that found a 5.1 mm increase in total mandibular length in patients treated at puberty

with the Bionator who were examined about eight years after FJO and compared with untreated Class II controls.[16]

Thus, if the aim of treatment is to produce favorable skeletal mandibular changes (effective mandibular growth stimulation and chin advancement), the start of treatment with removable functional appliances should be postponed until puberty. On the other hand, if the correction of the Class II problem requires mainly dentoalveolar modifications, treatment timing can be initiated before puberty.

INDIVIDUAL PATIENT RESPONSIVENESS FOR CLASS II MALOCCLUSION

If treatment timing can be regarded as the fourth dimension in orthodontic diagnosis, individual patient responsiveness to treatment can be defined as the fifth dimension. The concept of individual patient responsiveness to FJO for Class II malocclusion can be understood easily by means of the scatterplot shown in Figure 3. This scatterplot depicts the individual bi-annualized increases along total mandibular length of 27 Class II patients treated at puberty with the Fränkel type 2 (FR-2) appliance.[17] Even though all patients were treated at the optimal time from a maturational perspective, individual responsiveness to treatment varied widely with patients showing minimal mandibular growth response (1 to 3 mm) and patients showing maximum mandibular growth response (8 to 13 mm).

From a clinical standpoint, it would be useful to predict before treatment with FJO which patient is going to show a favorable amount of mandibular growth (good responders) and who is going to exhibit an unfavorable growth response (bad responders). In 2006, we published a study to identify pre-treatment cephalometric variables for the prediction of individual mandibular outcomes of FJO followed by fixed appliances in Class II patients treated at the peak in mandibular growth.[18] This study was performed on 51 subjects (24 females, 27 males) with Class II malocclusion. First-phase therapy was accomplished with a Twin Block appliance in 16 subjects, a stainless-steel crown Herbst in 15 subjects and an acrylic splint Herbst in 20 subjects. Lateral cephalograms were available at the start of treatment with FJO and at the completion of fixed appliance therapy. All subjects received FJO at the peak in man-

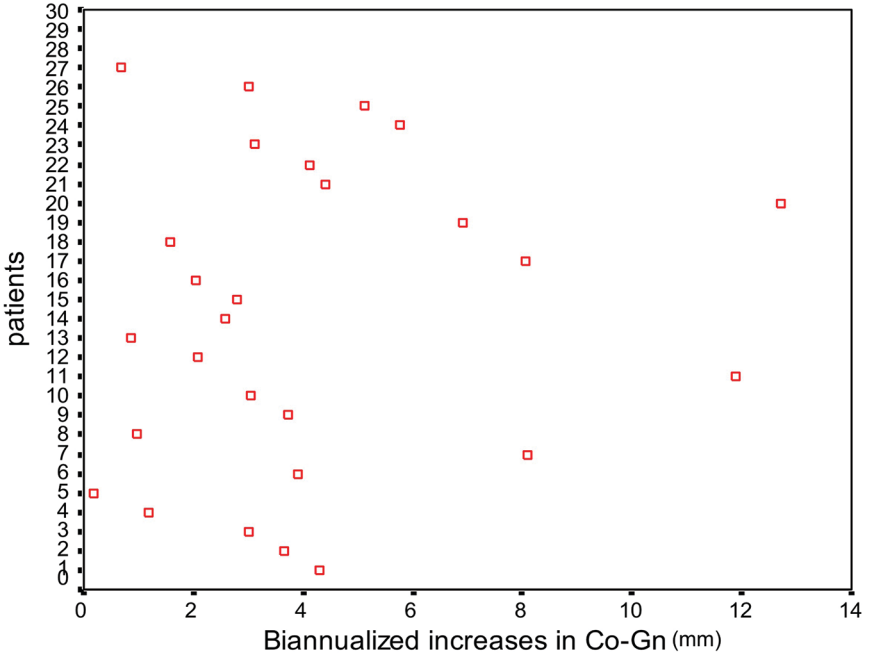

Figure 3. Scatterplot of the individual bi-annualized increases along total mandibular length (Co-Gn) of 27 Class II patients treated at puberty with the Fränkel type 2 (FR-2).

dibular growth (CS 3 at T1). Individual responsiveness to Class II treatment including FJO was defined based on the T2-T1 increment in total mandibular length (Co-Gn) when compared with untreated Class II subjects. The cut-off value to define a clinically significant amount of supplementary elongation of the mandible in treated subjects in two years was set at 5.3 mm.

Discriminant analysis identified a single predictive parameter (the so called "mandibular angle" Condylion-Gonion-Menton [Co-Go-Me]) with a classification power (prediction accuracy) of 80%. Pretreatment vertical and sagittal parameters were not able to improve the prediction based upon the mandibular angle. The analysis of the individual patient values for the Co-Go-Me angle indicated that the "bad responders" were those Class II patients who presented at puberty with a mandibular angle greater than 128°. In these patients treated with FJO at puberty, the amount of mandibular growth was 4.2 $\pm$ 1.2 mm, values

that were slightly greater than the amount of mandibular growth shown in two years by untreated Class II subjects (3.3 ± 1.5 mm).[11] Treated patients presenting with pre-treatment values of the mandibular angle between 124 to 128° can be classified as "good responders" as they are exhibiting an amount of mandibular growth of 6.8 ± 2.8 mm in two years of comprehensive treatment with FJO followed by fixed appliances. Finally, Class II patients presenting with pre-treatment values of the mandibular angle smaller than 123° can be regarded as "best responders" as their amount of mandibular growth was 7.3 ± 2.1 mm during two years of comprehensive treatment.

The mandibular angle Co-Go-Me also was identified as a significant predictor in another study in which discriminant analysis was performed on the pre-treatment cephalometric variables in a sample of 28 patients (14 females and 14 males) treated at puberty with the acrylic splint Herbst appliance followed by fixed appliances.[19] In this study, discriminant analysis was applied on pre-treatment cephalometric variables to predict a significant amount of advancement of the soft tissue chin (soft tissue Pogonion) with respect to a vertical line passing through Subnasale and perpendicular to the Frankfort horizontal. The cut-off value for a clinically significant chin advancement was set at 2.5 mm. The smaller the pre-treatment values of the mandibular angle the greater was the advancement of the soft tissue chin.

Recently, D'Antò and coworkers analyzed a sample of 43 Class II pubertal patients (22 males and 21 females, mean age: 11.1 ± 1.6 years) treated with the Sander bite jumping appliance with acrylic covering the lower anterior teeth.[20] The post-treatment cephalograms were taken prior to the start of fixed appliance therapy when a tendency to Class III molar relationship was achieved or after 15 months of treatment. Also in this sample, the pre-treatment Co-Go-Me mandibular angle was a significant predictor for the increases in mandibular length. Greater increases in mandibular length occurred during treatment of patients with smaller Co-Go-Me pre-treatment values.

The results of these studies clearly indicate that the ideal candidates for FJO at puberty are those Class II patients who, at puberty, are showing small pre-treatment values for the mandibular angle. In other words, pubertal patients who present with a small mandibular angle are characterized by a favorable mandibular growth potential. This concept

was described three decades ago by Petrovic and associates who demonstrated that the mandibular growth rate (e.g., the potential responsiveness of the individual subject to FJO aimed to stimulate growth at the mandibular condyle) is significantly greater in the presence of anterior growth rotation of the mandible than in the presence of posterior growth rotation of the mandible.[21-23] It is confirmed, therefore, that the mandibular morphology with a small mandibular angle, that is a typical feature of anterior growth rotation according to the classical concepts by Björk, is characterized by an elevated growth potential.[24]

TREATMENT TIMING FOR CLASS III MALOCCLUSION

One of the most commonly used protocols for the treatment of Class III malocclusion in the growing patient is rapid maxillary expansion (RME) combined with maxillary protraction with the facial mask (FM). Franchi and colleagues performed a study in 2004 to assess the optimal treatment timing of RME/FM followed by fixed appliances. The treated sample consisted of 50 subjects (30 females, 20 males).[25] Lateral cephalograms were analyzed at T1 (the start of RME/FM therapy) and at T2 (the observation after RME/FM and fixed appliance therapy at CVM stage 5 or 6, classified as post-pubertal).[4] The treated sample was compared to a control group of 24 subjects with untreated Class III malocclusion.

The treated sample was divided into two groups according to the stage of dental development at T1: early treated group (ETG; 33 subjects) if they were either in the deciduous or early mixed dentition (erupting permanent incisors and first permanent molars) and late treated group (LTG; 17 subjects) if they were in the late mixed dentition (erupting permanent canines and premolars). The mean age of the ETG was 7.4 $\pm$ 1.2 years at T1 and 14.5 $\pm$ 1.7 years at T2. All patients of ETG started treatment at a pre-pubertal phase of development (CS 1).[4] The mean age of the LTG was 10.7 $\pm$ 1.3 years at T1 and 15.2 $\pm$ 1.5 years at T2. Most patients in the LTG (about 70%) started treatment at puberty (CS 3 stage).[4]

The control sample was divided into two groups, the early control group (ECG, 14 subjects) and the late control group (LCG; ten subjects). The mean age of the ECG was 7.0 $\pm$ 1.4 years at T1 and 15.0 $\pm$ 2.2 years at T2, while the mean age of the LCG was 10.7 $\pm$ 1.8 years at T1

and 16.0 ± 1.6 years at T2. The treated and control groups were matched for race, sex, mean age at observation periods, mean duration of observation intervals, CVM stages and craniofacial characteristics at T1.

Treatment with RME/FM is most effective when it begins before puberty at an early developmental phase of the dentition (early mixed or late deciduous) rather than during later stages of development close to puberty. A significant orthopedic advancement of the maxilla that can withstand further maxillary modifications occurring during the active growth period can be achieved only by treating Class III patients during the early developmental phases. About 2 mm of supplementary forward movement of the maxilla are maintained in treated patients at a post-pubertal observation when compared with untreated subjects. Class III subjects treated during later stages of development close to puberty had only a 0.7 mm advancement of the maxilla at T2, an amount of growth that is not clinically or statistically significant.

These results agree with the previous findings of Melsen and Melsen on human autopsy material that evaluated the maturational changes of the palato-maxillary suture.[26] This suture represents a region of resistance to maxillary protraction with the facemask as it connects the posterior portion of the maxilla (palatal bone) to the cranial base (pterygoid process). Melsen and Melsen found that disarticulation of the palatal bone from the pterygoid process is possible only on skulls from the infantile and juvenile (early mixed dentition) periods.[26] Attempted disarticulation in the late juvenile and adolescent periods often is accompanied by fracture of the heavily interdigitated osseous surfaces.

When considering the mandibular changes both early and late treated groups showed a significant restriction of mandibular growth with respect to the corresponding control groups (3.6 mm in approximately seven years and 4.8 mm in about 4.5 years, for early and late treated subjects, respectively). According to Franchi and associates, therefore, the optimal treatment timing for Class III malocclusion with RME and FM is during the early developmental phases when significant favorable pre-pubertal modifications in both maxillary and mandibular structures can be achieved.[25] Late treatment, close to puberty, can produce only a significant restriction of mandibular growth.

Other sutures that offer resistance to maxillary protraction are the zygomaticomaxillary sutures (ZMSs).[27] The advantage of these an-

terior circummaxillary sutures—with respect to the palato-maxillary sutures that are too thin—is that their morphology can be evaluated by means of a cone-beam computed tomography (CBCT).[28] The morphology of the oblique and tortuous ZMS can be determined in the sagittal view, at the infra-orbital (superior) and infra-zygomatic (inferior) portions of the suture. Angelieri and coworkers described five maturational stages of the ZMSs (Fig. 4) that are very similar to those of the midpalatal suture.[28,29] In most immature stage (stage A), the ZMS is a uniform high-density line, with little or no interdigitation. In stage B, the suture can be described as a thicker scalloped high-density line with some interdigitation. Both A and B stages are pre-pubertal.[30] In stage C, which typically can be seen in the pubertal phase of development, the suture is characterized by two thin, parallel, scalloped, high-density lines that are close to each other and separated by small low-density spaces.[30] In stages D and E, the suture becomes fused partially and totally, respectively. In stage D, fusion occurs in the most inferior part of the suture (infra-zygomatic portion), while region [region – omit] a suture still can be identified in the infra-orbital [add RETION here]. Finally, in stage E, fusion of the suture has taken place and no suture can be recognized in either the inferior or superior portions.

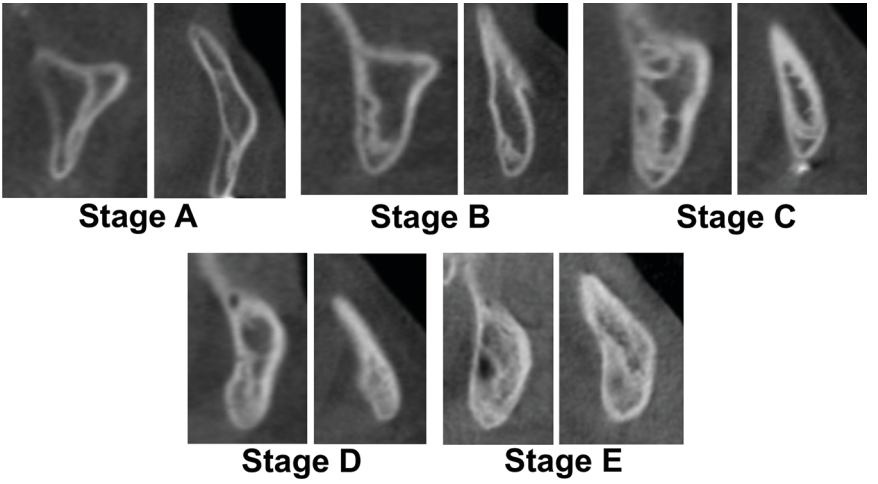

Figure 4. The five maturational stages of the zygomaticomaxillary suture (ZMS). Printed with permission from Wiley and Sons; modified from Angelieri and associates; see text for explanation of the stages.[28]

Recently, Angelieri and coworkers evaluated the influence of the maturational stages of the ZMSs on the amount of maxillary protraction produced by RME/FM and bone-anchored maxillary protraction (BAMP) protocols in growing patients with Class III malocclusion.[31] The RME/FM group was comprised of 18 patients (15 females and three males) with a mean age of 8.3 years (range from 5.6 to 10.7 years), while the BAMP group was comprised of 22 patients (twelve females and ten males) with a mean age of 11.8 years. For all patients, CBCT images were available at the onset (T1) of therapy and after approximately ten months for the RME/FM group and after twelve months for the BAMP group (T2). All patients were staged at T1 according to the maturational stages of the ZMSs. Nine patients showed stage A, 18 presented stage B and ten exhibited stage C.

The antero-posterior displacement of the maxilla was assessed as sagittal changes in Point A after registration of the T1 and T2 CBCTs on the anterior cranial base.[31] This study showed that the stage of ZMS maturation was associated significantly with the amount of maxillary protraction. A significantly greater forward displacement of the maxilla was found when treatment with either BAMP or RME/FM was performed at the more immature (pre-pubertal) ZMS maturational stages A and B compared to the pubertal stage C (1.3 mm and 1.4 mm, respectively).[30] The pubertal stage C is characterized by an interdigitated ZMS with bony bridges along the suture that presumably hampered the forward displacement of the maxilla, reflecting less maxillary protraction, compared to stages A and B for both groups. The results of this study confirmed that the optimal timing for Class III malocclusion is during the pre-pubertal phases of development when the circummaxillary sutures offer less resistance to maxillary protraction compared to the pubertal phase.

INDIVIDUAL PATIENT RESPONSIVENESS FOR CLASS III MALOCCLUSION

The concept of individual patient responsiveness to early orthopedic treatment Class III malocclusion with RME and FM is related to the possibility of predicting the long-term stability of this type of therapy in the individual Class III patient. In 2004, Baccetti and colleagues performed a study to identify some cephalometric variables predictive for

the long-term (post-pubertal) outcome of early orthopedic treatment of Class III patients with RME and FM followed by a phase with fixed appliances.[32] Lateral cephalograms of 42 patients (20 boys and 22 girls) with Class III malocclusion were analyzed at the start of treatment (mean age 8.5 years $\pm$ 2 years, at CS 1). All patients were re-evaluated at T2 (mean age 15 years $\pm$ 1.8 years, at CS 5 or 6) after a mean period of 6.5 years that included active treatment with fixed appliances plus retention.

Failure of treatment at T2 was defined as the concurrent presence of Class III permanent molar relationship, negative overjet and Class III profile. According to this rationale, the sample was divided into two groups: successful (30 patients, 71%); or unsuccessful (twelve patients, 29%). After application of discriminant analysis to a total of eleven linear variables and eight angular variables, three cephalometric measurements were selected as significant predictors for long-term treatment outcomes: the length of the mandibular ramus (Co-Goi); the angulation of the cranial base (measured as the posterior angle between Ba-T and the stable basicranial line [SBL]; and the inclination of the mandibular plane to the cranial base (Mand Pl-SBL; Fig. 5). The prediction accuracy of the selected three-variable model was 83%. The probability of predicting unsuccessful cases was 69% (positive predictive value [PPV]) while the probability of predicting successful cases was 90% (negative predictive value [NPV]).

The results of the discriminant analysis allowed the derivation of an equation that can be used for the calculation of the individual patient score (IPS):

IPS = (0.282*Co-Goi) + (0.205*Ba-T-SBL) + (0.12*ML-SBL) - 29.784.

The IPS can be compared to the so-called “critical score” that has a value of 0.4065. Each new patient with Class III malocclusion witha IPS lower than the critical score will be treated successfully with early RME/FM therapy. Conversely, each new Class III patient with an IPS higher than the critical score can be predicted to respond poorly to early orthopedic treatment. The results of this study, therefore, showed that the craniofacial features of a bad responder are: 1) excessive length of the mandibular ramus (e.g., increased posterior facial height); 2) acute cranial base angle; and 3) steep mandibular plane angle.[32]

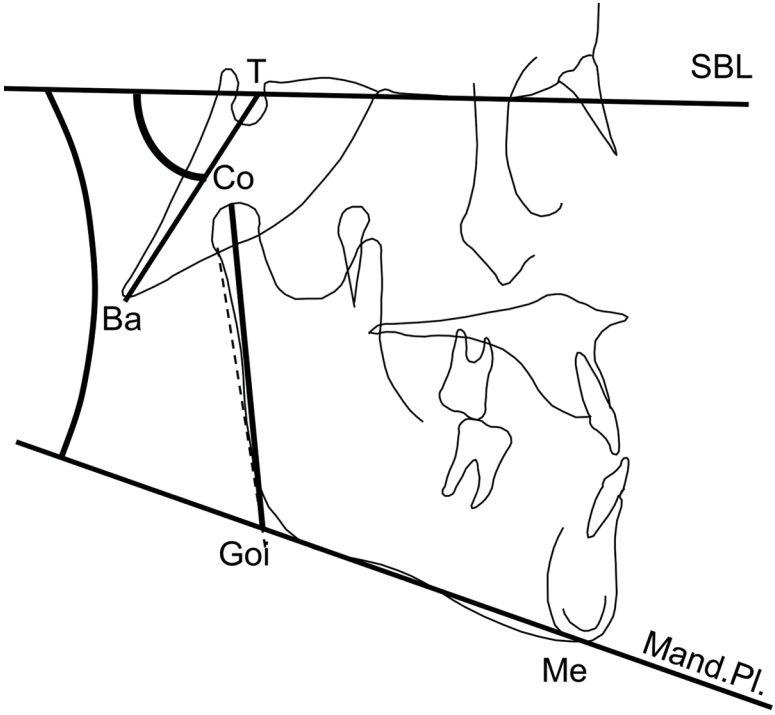

Figure 5. Predictive measurements for early orthopedic treatment of Class III malocclusion: Co-Goi = length of the mandibular ramus; SBL = angulation of the cranial base, measured as posterior angle between Ba-T and the SBL; Mand Pl-SBL = inclination of mandibular plane to cranial base. Printed with permission from Elsevier; modified from Baccetti and associates.[32]

In 2011, Fudalej and coworkers performed a systematic review on the prediction of the outcome of different types of orthodontic/orthopedic treatments of Class III malocclusion in growing patients.[33] The gonial angle was identified most frequently (in five of fourteen publications) as a significant predictor of treatment outcomes. Specifically, a large gonial angle was a significant predictor for the unsuccessful Class III treatment.

Another study on the long-term stability of RME and FM therapy analyzed the craniofacial features of unsuccessful *versus* successful cases. Masucci and colleagues reported prevalence rates of successful and unsuccessful cases (73% and 27%, respectively), percentages similar to those reported by Baccetti and associates.[32,34] The unsuccessful

cases were characterized by a modest degree of compliance during active treatment with the FM. Moreover, the unsuccessful cases showed a significantly greater gonial angle (+3.8°), a significantly greater downward inclination of the mandibular plane to Frankfort horizontal (+4.1°) and a significantly greater mesial molar relationship (+1.5 mm) when compared to the successful cases.

When dealing with the prognosis of early Class III treatment in the individual patient, we agree with the conclusions of a recent study by Choi and colleagues who suggested that clinicians need to be careful when trying to predict the long-term outcomes of orthopedic treatment of Class III malocclusion using any method based on the pre-treatment cephalometric dentoskeletal features.[35] In particular, the patient and his/her parents always should be informed on potential errors in prediction and on the possibility of unsuccessful outcomes.

CONCLUSIONS

Treatment efficacy and efficiency of Class II and Class III malocclusions in the growing patient can be reached if patient-related factors also are considered. Functional appliances are effective in altering short- and long-term mandibular growth and mandibular sagittal position if active treatment is performed at puberty. Mandibular morphology should be evaluated at puberty to assess patient responsiveness; good responders are characterized by a small mandibular angle.

Optimal timing for Class III malocclusion is during the pre-pubertal phases of development when the circummaxillary sutures offer less resistance to maxillary protraction compared to the pubertal phase. The long-term success rate for RME/FM is 70 to 75%. In general, it is difficult to achieve a reliable prediction of long-term treatment outcomes of orthopedic treatment of Class III malocclusion using methods related to the pre-treatment cephalometric dentoskeletal characteristics. The most common pre-treatment craniofacial features of unsuccessful cases seem to be high-angle vertical skeletal relationships and a large gonial angle.

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PERSONALIZED PRECISION INTEGRATION OF AUGMENTATION AND IMPLANT SURGERIES WITH ACCELERATED ADULT ORTHODONTICS FOR SYNERGIZED INTERDISCIPLINARY CARE

Jeff C.W. Wang

ABSTRACT

Interdisciplinary care has become a much-appreciated approach to provide optimal treatment for our patients. However, there are several challenges to synergize multi-disciplinary treatment and values from different clinicians and specialists, including better communication and reasonable treatment time. Each patient presents with unique conditions and specific needs that deserve personalized attention; each patient also deserves a collaborative team that will provide a well-coordinated treatment process for the best outcome and long-term stability. Surgically-facilitated orthodontic therapy (SFOT) is a newly developed interdisciplinary approach that can facilitate tooth movement and expand the orthodontic boundaries of tooth movement by inducing regional acceleratory phenomenon (RAP) and bone grafting to facilitate orthodontic treatment. The details of its benefits and mechanisms are described in this chapter.

In addition, local selective precision application of corticotomy with augmentation and implant therapy in adult patients will be introduced, which also is a practical approach to create synergy. Integrating surgeries at an early stage of orthodontic treatment not only shortens the treatment time by having a jump start in tissue healing, but also induces RAP to accelerate the desired precision tooth movement. Each patient has various treatment needs related to having dental implant therapy, which offers creative ways to conduct an integrated approach that fits personal needs. If planned properly, dental implants also can provide absolute anchorage to facilitate orthodontic treatment. This integrated approach will provide an excellent opportunity to maximize communication and deliver quality treatment outcomes in a reasonable timeframe for our patients.

KEY WORDS: interdisciplinary, augmentation, implant, adult, accelerated orthodontics

INTRODUCTION

Every patient who requires interdisciplinary care presents with different complaints and unique needs that warrant individualized treatment planning and options. An increase in demand and popularity for adult orthodontics has made orthodontic therapy an integral part of the ideal comprehensive treatment in many interdisciplinary cases. Although orthodontic therapy sometimes might be considered optional for the patient clinically, it should be acknowledged that incorporating orthodontic treatment often can provide a better treatment outcome. In situations where restoring compromised partially edentulous spaces with dental implants are of interest, adjunctive orthodontic treatment with bone augmentation often is required prior to implant placement to develop an ideal implant site. Using the current conventional sequential treatment workflow with an "orthodontic treatment first and implant later" approach, treatment can take three to five or more years to complete the entire case. Therefore, a personalized precision integrated approach that can provide an efficient and effective interdisciplinary treatment approach is proposed in this chapter. In addition to treatment planning, the treatment sequence also should be tailored for the best synergized process and results for the patient. There are many creative ways to integrate surgical augmentation therapies during active orthodontic treatment that will reduce the total treatment time significantly and also will foster better communication.

Although it was estimated that approximately 23% of patients receiving orthodontic treatment are adults, it is unknown how many cases were involved in interdisciplinary treatment.[1] Certainly, many patients are in need of interdisciplinary care, but the two major hindrances for patient acceptance are treatment time and cost. Reducing total treatment time may be the first step to increasing patient acceptance. As chair time is decreased, the overall cost may be reduced as well. Even though patients may be able to afford the fees, they may not have the time or resilience to complete a lengthy treatment. Additionally, communication and coordination for interdisciplinary treatment pose a major challenge for clinicians. The conventional sequence of multi-disciplinary treatment requires each specialty to conduct their treatment procedures at a specific time. This process may occur without simultaneous communication as the treatment progresses. In this chap-

ter, augmentation and implant therapy with adult orthodontic treatment will be discussed regarding how it can be integrated to enhance the collaborative effort for a unified interdisciplinary care.

INTERDISCIPLINARY TREATMENT PLANNING

Urgent care and disease control together always comprise the first step in the comprehensive treatment planning. This process also allows time for sophisticated discussion among team members toward a comprehensive treatment effort, especially if orthodontics and full-mouth rehabilitation are involved. It is important that all clinicians are in agreement regarding the treatment before presenting it to the patient. The lead clinician should coordinate the sequence of the overall therapy, including a draft for the treatment plan, timing and pricing to facilitate communication, as well as making sure all of the clinicians agree with the treatment. Otherwise, the patient may make several visits to talk with the team clinicians separately, become confused about the proposal before the team reaches a consensus and may decline treatment. Basic clinical records and a draft of the treatment should be prepared in advance so that a productive team meeting can occur. The patient should be presented with an organized, professional and coordinated treatment blueprint with itemized options and costs that represents the collaborative efforts of the entire team. Only when the patient understands and values the overall treatment will s/he consent and commit to treatment.

Patient education is an essential part of comprehensive patient care and should include explanation of oral health conditions and discussion of the treatment. Visual aids are essential to assist the discussion of the treatment options with the patient, including images of orthodontic appliances, dental implants and/or different types of prosthesis. With advancements in digital technology, digital workflow can be a powerful tool when presenting a provisional plan along with an image of the final results. This will provide personalized precision patient education that is pertinent to each patient's unique condition, rather than verbally conveying the idea or handing over brochures with general information.

It also is important to manage patients' expectations and to discuss the treatment's limitations (e.g., whether the discrepancy of the

gum line or gummy smile can be addressed; whether minor black triangle or longer implant crown still may be present after the overall treatment; and/or whether a second bone grafting for a severely resorbed ridge or soft tissue augmentation may be needed in certain areas). Additionally, if the patient opted for clear aligners, s/he must understand that attachments on the anterior teeth may compromise her/his esthetic appearance during treatment. The patient also should understand that parts of the overall plan may be subject to change, depending on the progress of the treatment and his/her response to the therapy.

Although patient education and managing expectations is not the main focus of this chapter, it is key for the patient's acceptance of the treatment. Initial planning of the integrated treatment sequence also needs to occur at this stage. More communication must occur if an integrated approach will benefit the interdisciplinary team and the patient while developing an optimal treatment plan.

TREATMENT SEQUENCE AND INTEGRATION

Conventional Sequence with the Status Quo: Ortho First, Implant Later

The main focus of this chapter is to challenge the conventional treatment sequence of orthodontics that involves implant therapy for patients with restorative needs. Typically, implant placement is performed either during the finishing stages or after completion of orthodontic treatment, while bone augmentation therapy is performed during different phases of orthodontic treatment. In some cases, implants can be placed earlier to provide absolute anchorage to facilitate tooth movement, which requires a more personalized plan with a precise treatment sequence.

New Proposal: Personalized Precision Integration of Augmentation and Implant Therapy

The conventional sequence for interdisciplinary treatment with orthodontics and implant-supported restorations always begins with orthodontic treatment because after the implant fixture is placed, its location cannot be changed; therefore, the implant may not be angled or located ideally. The wrong implant position could compromise orthodontic movement and alignment of the adjacent teeth; because of this, orthodontic treatment usually happens before implant therapy. Ortho-

dontic treatment usually requires the most time among the interdisciplinary treatments, ranging from one to three years or more depending on the case's complexity and clinician's experience. By the time orthodontic treatment is completed, another six to eight months is needed for the implant site to develop if bone grafting is required for a staged ridge augmentation procedure is needed. Additionally, subsequent implant osseointegration and final restorations may require another four to six months. This means that if everything goes as planned, treatment can take at least three to four years to accomplish. Patients usually do not want to commit to this kind of comprehensive treatment schedule and/or s/he gets frustrated and tired in the middle of the process. Figure 1 shows an adult male patient who was referred for implant therapy after a three-year orthodontic treatment. During the consultation, the need for mandibular edentulous ridge augmentation was noted and maxillary first molar implant site required a sinus lifting procedure. In order to perform the treatment in stages—including augmentations, implant placement and restorations—another 18 months were needed, thus the total treatment time took approximately five years to complete.

Is it possible to speed up the entire process to reduce total treatment time? With the goal of providing a personalized precision and integrated interdisciplinary treatment plan within a reasonable time, implants often can be placed before or during the orthodontic treatment. For that purpose, the implant site has to be determined and adequate space for it has to be established (or it must be available at the beginning of the treatment). For bone grafting and other augmentation procedures—which also is a critical part of implant site development—

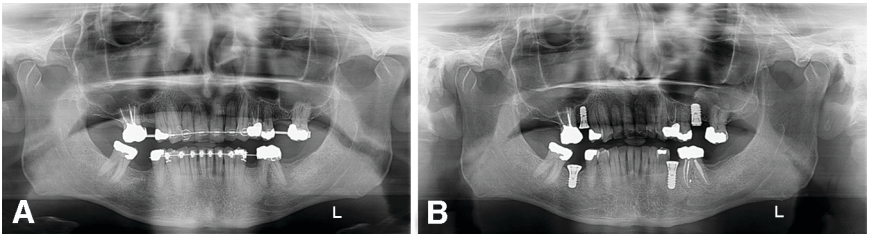

Figure 1. Conventional sequence for interdisciplinary treatment took close to five years to complete. *A:* Orthodontic therapy completion. *B:* Ridge and sinus bone augmentation and implant therapy were completed after orthodontic treatment.

almost every case can be performed efficiently during orthodontic treatment.

Challenge the Status Quo: Bone Augmentation for Implant Therapy During Active Orthodontic Treatment

Before debating if we can foresee the future of placing implants during active orthodontic treatment, the first question to challenge the status quo may be: can a bone grafting procedure be performed during the early phase of orthodontic treatment for implant site development? Two proof-of-principle case reports with split-mouth comparison demonstrated that simultaneous ridge augmentation and molar uprighting can be performed effectively together without complications (Fig 2).[2] Accelerated implant site development was achieved with up to 5 mm horizontal alveolar ridge augmentation and 3 mm mesial-distal

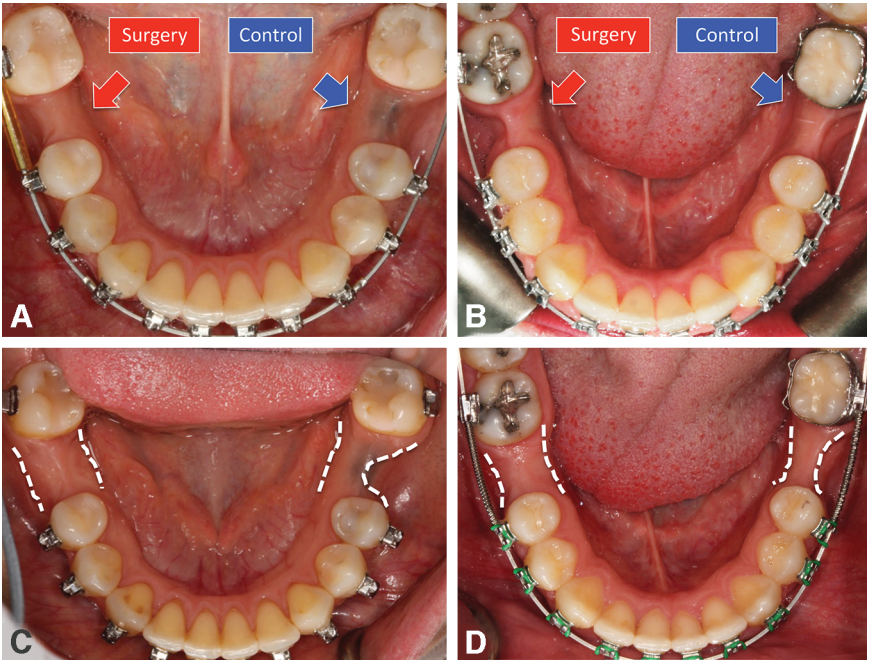

Figure 2. Pilot proof-of-principle cases with a split-mouth design comparison for simultaneous ridge augmentation and accelerated molar uprighting. *A-B:* Before surgery and symmetrical biomechanics. *C-D:* Five months after surgery; #30 site is ready for implant placement, yet #19 site still requires ridge augmentation.

space creation. The requisite six months for the bone graft to mature can occur during active orthodontic treatment and, thus, can reduce total treatment time significantly. Additionally, these surgical procedures temporarily accelerate the tooth movement. The speed of molar uprighting compared to the contralateral side is about 1.5 to 1.8x faster (Fig. 3), yet the speed can be much faster if the re-activation process can be coordinated better. It also was found that the speed over the control side without surgery moved slightly faster, from which we hypothesized that there is a systemic acceleratory phenomenon in addition

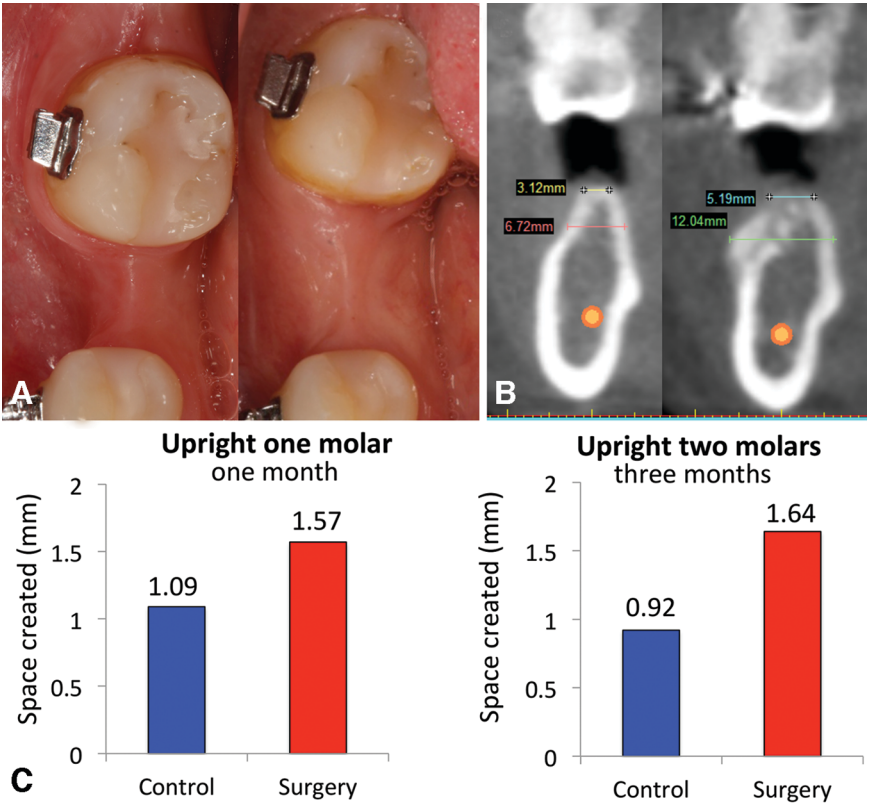

Figure 3. Accelerated implant site development. *A:* Pre- and five months post-surgery showed successful buccal-lingual horizontal ridge augmentation and mesial-distal space creation for ideal implant prosthetics. *B:* Pre- and post-surgery CBCT revealed ~5 mm horizontal gain. *C:* The speed of second molar uprighting comparing to the control side is about 1.5 to 1.8 times faster.

to the regional acceleratory phenomenon (RAP). The details regarding RAP—why and how the procedure accelerates the tooth movement—will be discussed later.

Missing first molars with mesially-tilted second molars may be the most common clinical scenario that applies to this integrated approach.[3] Adjunctive orthodontic treatment for proper restoration should apply to implant-supported restorations.[4,5] In summary, simultaneous ridge augmentation and molar uprighting for implant site development can be performed effectively during orthodontic treatment.

Sinus Lift Bone Augmentation During Active Orthodontic Treatment

Sinus pneumatization in adults is a challenging situation for implant therapy and for orthodontic treatment. Sinus pneumatization is common following tooth loss and adds complexity to the implant therapy to replace the tooth. It requires an advanced bone grafting procedure called sinus lift bone augmentation through a lateral window over the buccal cortical wall of the sinus. As early as the 1980s, Boyne and James published the technique of maxillary sinus lift, after which the approach and materials have advanced significantly to reach a success rate close to 97%; this is considered the most predictable bone augmentation given the defect is contained favorably.[6,7] However, the healing time for the bone graft to mature will take from six to ten months, depending on the amount of the bone grafting materials that are placed.

For conventional sequence (Fig. 1), maxillary left sinus lift was performed after completion of the orthodontic treatment, which delayed the implant placement for at least six months. Given that significant tooth movement was not expected, the sinus lifting procedure could have been performed at an earlier time to have the site ready for implant placement during the finishing stage of orthodontic treatment. This would have reduced approximately ten months of the total treatment time (six months for sinus lift healing and four months for implant osseointegration in a grafted site). Lateral sinus lift can be performed during the earlier stage of orthodontic treatment to allow the bone graft to mature (Fig 4). It is likely that bone grafting and opening of the lateral window (a form of controlled trauma to the cortical bone) may facilitate molar uprighting and alignment as well.

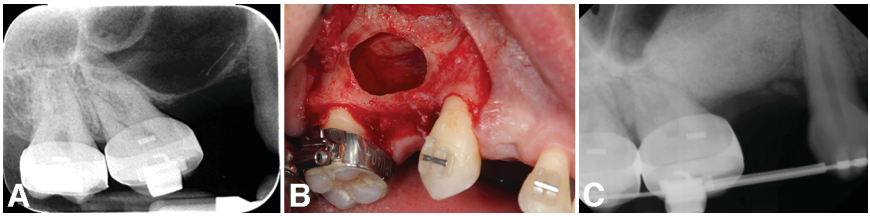

Figure 4. Lateral sinus lifting augmentation procedure during active orthodontic treatment. *A:* Pre-operative radiograph shows significant sinus pneumatization. *B:* Lateral sinus window with intact sinus Schneiderian membrane. *C:* Post-operative radiograph shows stable bone grafts in the sinus.

Orthodontic movement may become difficult as the roots of the tooth engages the cortical bone of the sinus. Although there have been case reports that demonstrate successful closure of a single tooth or multiple teeth space in a sinus pneumatized edentulous area, the speed in which tooth movement occurs is slow, as described in a systematic review.[8-10] Sinus lift augmentation may be performed to facilitate tooth movement in areas of pneumatization. It can be hypothesized that tooth movement will be easier to achieve in the grafted site. Currently, more prospective clinical studies are needed in this field. However, given the rare indication and heterogeneity of the patient condition, it is a challenge and almost impossible to conduct a controlled clinical trial to assess the effect of sinus lift augmentation to facilitate space closure. However, performing a sinus lifting procedure for implant therapy during active orthodontic treatment should be considered as an option.

Implant Placement During Active Orthodontic Treatment

Placing a dental implant during active orthodontic treatment remains controversial and it definitely is an area that still needs development for more generalized applications, especially considering advancements in technology. The concept of using dental implants as a device to provide absolute anchorage is not new. In 1984, the first published animal study on rabbits demonstrated that osseointegrated implants would remain stable, even with continuous orthodontic forces.[11] Use of “mini-implants” or temporary anchorage devices (TADs) to provide anchorage in orthodontic treatment has become popular and

is reported to have a 87.8% success rate when placing them in the alveolar bone compared to 93.8% over the palate.[12]

Using a prosthetic dental implant to facilitate orthodontic treatment is possible, but is less popular than using a TAD, perhaps due to the complexity of treatment planning and difficulty in predicting the ideal final position of the dental implant in most cases. [13,14] The benefit of using a dental implant rather than a TAD, however, is that the dental implant can be used later to restore partial edentulism. Therefore, especially from the patient's perspective, the cost of a TAD may be considered extra, whereas the fee for the dental implant can be considered to be offset for prosthetic use. Currently, the complexity of treatment needs from a multi-disciplinary team may seem to be overwhelming; thus, most clinicians still prefer to postpone the dental implant placement. However, there are still cases that indicate placing the dental implant at an early stage to facilitate orthodontic treatment.

Interestingly, placing a dental implant also may accelerate the orthodontic movement of the adjacent teeth. Figure 5 demonstrates a simple case scenario of placing a dental implant in the location of a missing mandibular first molar during the process of active molar uprighting. A wax-up of the future tooth #19 implant crown was fabricated considering a provisional prediction of the final position of the second molar after orthodontic treatment. An area where two crowns were overlapping can be appreciated (Fig. 5*B*). A surgical guide for implant placement was made to facilitate the implant osteotomy (Fig. 5*C*). The healing period was uneventful, but the second molar moved much faster when compared to the speed before implant placement. There was approximately 2.5 mm mesial-distal space created in two months and the implant was temporized to serve as an absolute anchorage to facilitate the remaining orthodontic work (Fig. 5*D,E*). This case demonstrates the effect of implant osteotomy for accelerated orthodontic tooth movement that can be considered in subsequent similar cases for a preprogrammed implant placement for a predicted future restoration.

As mentioned earlier, given advancements in digital technology, we may be able to predict better and provide precision to implant therapy with computer-guided surgery. Although more information and structured protocol is needed, it is the time to start thinking about how

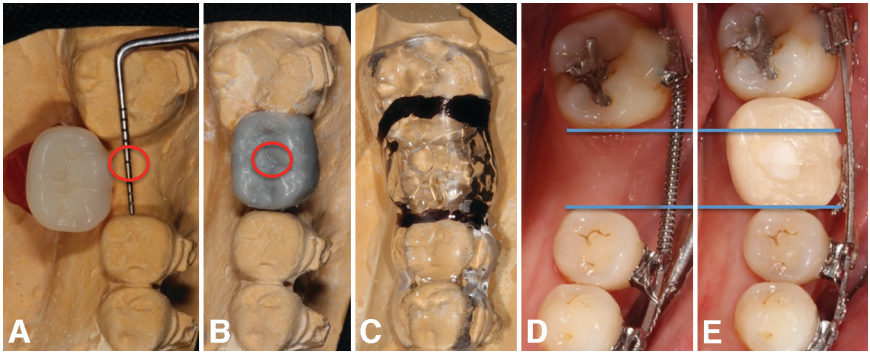

Figure 5. Pre-programmed implant placement with provisional orthodontics. *A:* Prediction of future implant crown after second molar urighting. *B:* Wax-up of the future crown. *C:* Surgical stent with the visualization of the overlapping area between the implant crown and second molar. *D:* Pre-op clinical exam. *E:* Two months post-implant placement showed accelerated molar uprighting (gain of 2.5 mm space in two months).

we can integrate augmentation and implant therapy during active orthodontic treatment.

RATIONALE AND MECHANISM OF ACTION

The major benefits of integrating surgeries during orthodontic treatment are jump starting tissue healing and enhancing communications to synergize treatment to reduce total treatment time. Additionally, the benefits of accelerating and facilitating adjacent tooth movement can impact many cases. Some might argue that a local temporary effect of RAP will not change much of the total treatment time. Nonetheless, sometimes the question is not if it will work, but how to make it work best. If augmentation procedures are required for the patient, why not take the advantage of the opportunity? The following is the historical background of RAP effect and how it evolved from a basic finding into new approaches and an emerging field.

From RAP to Periodontally Accelerated Osteogenic Orthodontics (PAOO)

In 1983, RAP first was described by an orthopedic surgeon, Dr. Harold Frost.[15] He found that surgical wounding of the cortical bone causes a transient burst of bone remodeling in the extremity long bone,

which was observed in a conventional radiograph. At that time, it merely was a subtle observation for academic discussion without much attention or clinical application. Yaffe and colleagues later observed RAP in the jaw bone in a rat animal model.[16] It was not until the Wilcko brothers' published first two cases that RAP had its first clinical application to accelerate orthodontic treatment. When they performed interdental corticotomy, they also observed alveolar bone deficiency (e.g., dehiscence or fenestration defects). Therefore, they combined the corticotomy with a bone grafting procedure for augmentation and termed it periodontally accelerated osteogenic orthodontics (PAOO) or an accelerated osteogenic orthodontics (AOO) procedure.[17] Their initial case reports consisted of teenagers who required decrowding and alignment; this led to the controversy regarding the risk and benefits of this type of aggressive treatment.

Nevertheless, there was continuous development and investigation of the approach. Many human randomized controlled clinical trials (RCTs) were conducted to evaluate effectiveness; animal studies from different groups also looked into mechanism at the histologic, cellular and molecular levels. In addition, alveolar ridge bone augmentation seemed to facilitate further expansion of the orthodontic wall with sagittal correction of the incisal relationship and compensation for transverse deficiency of the malocclusion. The field's focus has transformed from accelerating tooth movement to augmenting the ridge to expand the alveolar housing and facilitating orthodontic treatment and ultimately providing long-term health on the periodontium.

HOW FAST AND HOW LONG DOES RAP EFFECT LAST?

The Case of Corticotomy-assisted Accelerated Orthodontics (CAO)

The most common questions are: 1) how long does RAP effect last? and 2) how fast can the tooth move? Although many factors underlie the answers, there are a number of human clinical studies that have a good overall picture of the RAP effect. The classic pilot study by Aboul-Ela and associates demonstrated that the velocity increased to approximately 2x faster for the first two months compared with approximately 1.6x during the third month.[18] Most human clinical trials are performed in similar context with a split-mouth design to retract canine with or without decortication to close a pre-molar space.[19,20] Our

group conducted a systematic review and meta-analysis on the acceleratory effect from the corticotomy in retracting canine.[21] On average, the speed is 2x faster for three months and the total treatment time is reduced by 50%. When evaluating the time course of the RAP effect during the four-month period, there are two peaks of accelerating effects (Fig. 6), which is in agreement with the animal study that demonstrated two peaks of accelerating phenomenon coupled with changes in bone remodeling markers.[22] Another group counted the number of osteoclasts and found it to be consistent with the pre-clinical findings to have two peaks of osteoclastogenesis. It was hypothesized that there was an activation of local resident osteoclasts that accounted for the first peak and recruitment of new cells for another wave of bone remodeling.[23] The exact molecular mechanism is thought to be linked with inflammation and RANK-mediated bone remodeling.[24] This mechanism is not elucidated fully and currently is under investigation.

How Much Trauma is Needed to Induce RAP?

What kind of trauma is sufficient to induce RAP and achieve the desired clinical effect to facilitate orthodontic treatment? Currently, there is insufficient data to provide a more specific recommendation. This question may depend on a case-by-case scenario, host response and clinician preference. Minor tooth movement may need only flapless micro-perforations, yet major maxillary arch expansion may require se-

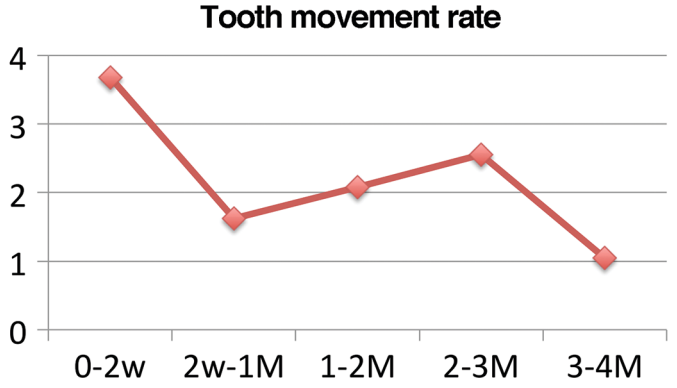

Figure 6. Weighted mean of the faster tooth movement for each time period from the meta-analysis of the randomized clinical trials.[19] W = weeks; M = months.

lective decortication around the palatal roots of the molars to facilitate movement.

In Yaffe's animal studies, the procedures did not involve drilling the cortical bone, rather, they only raised the flap of the alveolar bone.[16] With the repositioned flap, there was a transient widening of the periodontal ligament (PDL) space shown on the radiographs. It later was proposed that flap elevation alone might be sufficient to induce the RAP effect.[25,26] Thus, it may not be necessary to traumatize the bone to induce RAP, though it is likely that the degree of trauma is correlated positively to the strength and duration of RAP approaches, but there are limitations regarding the amount and location of bone grafting that can be placed for augmentation procedures.

As to the specific size and depth of the corticotomy in relationship to the desired clinical benefits and time course, this area needs more study.

BEYOND THE SPEED: RIDGE AUGMENTATION TO EXPAND THE ORTHODONTIC WALLS

The border of orthodontic tooth movement was confined by the alveolar housing, called the "orthodontic wall."[31] Many orthodontic treatment plans were limited or affected by the border of the alveolar bone, especially in adults.[32] By combining decortication with bone grafting, the results not only increase the speed of tooth movement, but also can augment the alveolar bone to accommodate certain tooth movement beyond the previous boundaries. Using this approach, cases have been shown to demonstrate tooth movement beyond the "Proffit's envelope."[33,34]

For sagittal correction of the incisal relationships, case reports with long-term post-operative cone-beam computed tomography (CBCT) data show that the bone augmentation altered the alveolar bone deficiency over the point A and B in the short term and also in a ten-year follow-up.[35-38] Other case studies also reported using corticotomy-assisted maxillary arch expansion to correct the maxillary transverse deficiency. One of the case reports correcting significant posterior cross-bite with seven months of orthodontic treatment on a 46-year-old male demonstrated seven years of stable results without complications.[37]

Although more prospective studies are needed to assess the predictability and maximal limit of this approach, it certainly is possible to think "outside the walls" and move teeth to the desired location, more so than previously thought. A future question to consider is: "How do we optimize and maximize the potential of this approach?"

SAFETY CONCERNS AND POTENTIAL COMPLICATIONS

Since several RCTs were conducted, it was concluded in a few systemic reviews that corticotomy-assisted orthodontic therapy (decortication of the bone to facilitate tooth movement) is safe without adverse events or complications.[19,21,39] The most common morbidity that is part of the healing process is post-operative pain and swelling that lasts for the first week post-surgery.[40] Overall, corticotomy-assisted orthodontic therapy is safe if planned well and conducted by experienced clinicians.

In terms of adding the bone graft for ridge augmentation and biotype enhancement, there were fewer RCTs combining corticotomy-assisted orthodontics with the use of bone grafts. A large number of case series/reports with long-term follow-up were published without reported complications.[17,34,36,38,41,42] However, a similar approach to address periodontal defect with guided tissue regeneration and limited orthodontic also was successful.[43-45] Preliminary results show that minor orthodontic tooth movement may enhance the results of bone grafting for periodontal regeneration.[45]

Most concerns regarding the periodontium are associated with conventional orthodontic treatment, including damage to periodontium, root resorption and endodontic complications (e.g., loss of vitality). Regarding the effect to the periodontium, this also has been a concern for adult orthodontics. CAO therapy combining with bone grafting—or so-called PAOO—has been shown to enhance the biotype of the issue both for hard and soft tissues.[41,46-48]

In terms of root resorption, it always has been a concern for orthodontic treatment; yet the working hypothesis is that if we can reduce the treatment time and resistance of the bone to the orthodontic treatment, it potentially can contribute to less root resorption. There were no reports of adverse events regarding root resorption in the published clinical trial or case series, which also is confirmed in an animal

study.[19-21,41,50] If future personalized dentistry becomes reality and able to identify subjects at higher risk of significant root resorption, it may be considered contra-indicated for orthodontics overall and is unknown whether CAO can be beneficial or not.

The major concerns for this approach may be loss of tooth vitality and poor treatment planning, which may result in unwanted loss of anchorage. Although there were no adverse effects reported, limited studies specify the endodontic conditions.[51,52] This may pose the most concerning perspective because if the tooth moves too fast or too far, it is likely to compromise the neurovascular complex around the apex. Future clinical trials, therefore, should make the effort to monitor and report this potential complication. Additionally, RAP effects may cause teeth to lose their anchorage and thus, the professional will need to plan a staged approach, particularly for more complicated cases that require significant tooth movement with specific anchorage needs (e.g., orthodontic traction of impacted teeth).

An important question to address may be: will the tooth movement compromise the wound healing process and the outcome of bone grafting? Although evidence from RCTs supports the application of early orthodontic forces after CAO, there are limited studies assessing the timing of orthodontic treatment to the bone graft.[19-21] It is important to acknowledge that research is lacking and requires more studies to investigate the interaction between bone grafting and orthodontic tooth movement.

Results of various studies indicate that CAO or PAOO are considered safe with a well-coordinated team and experienced clinicians.[19-21] However, we should continue to conduct in-depth preclinical and clinical studies to optimize the use of grafting materials for the outcome of augmentation, as well as to conduct prospective clinical trials to monitor some of the potential complications and concerns for this approach in the long term.

FUTURE DEVELOPMENTS

Surgically-facilitated Orthodontic Therapy (SFOT)

Several groups have termed the approach surgically-facilitated orthodontic therapy (SFOT) to escalate the field to another level by em-

phasizing the benefits not only to facilitate orthodontic therapy, but also to emphasize the value of providing "health" to our patients—including the health of the periodontium—and to provide better airway and sleep quality.[53-55]

Currently, one of the major benefits of SFOT is to facilitate tooth movement beyond the conventional orthodontic wall boundary.[34] Additionally, it was found that alveolar bone deficiency is common and development of labial gingival recession occurs more frequently over time—from 8% immediately after orthodontic treatment to 20% and 38% after two and five years post-treatment, respectively.[56-58] Therefore, a bone grafting procedure to augment the alveolar ridge and tissue biotype can establish a better foundation for the long-term health of the periodontium.[41,47,48] It also was found that with the bone grafting to thickened alveolar ridge width over the mandibular anterior area, there is less relapse of the alignment after ten years.[38] This observation aligned with the study by Rothe and colleagues, who found that thickness of the cortical bone is associated with the degree of relapse: the thicker the cortical bone, the less relapse there will be.[59]

One of the new and controversial perspectives of SFOT is to provide better airway for patients. Proponents argue that by expanding the alveolar arch in selective cases with appropriate facial profile, teeth will not need to be extracted for alignment. The thought is that tongue space may be compromised if the arch is narrowed in some patients; the consequence is that the tongue base may collapse into the pharyngeal space and cause different degrees of sleep apnea. In some adults, sleep quality can be improved by expanding the lower arch; however, these statements are theories and anecdotal in nature. Further studies are needed to validate such benefits in the field of sleep medicine.

Personalized Precision Integration of Augmentation and Implant Therapy

It might take some time before SFOT becomes an option for the standard of care as full-arch corticotomy and bone grafting still may be considered aggressive for most clinicians and patients. In addition, not all patients are indicated for full-arch augmentation and some selective anchorage control still is required in some cases. A more local application combining the required augmentation and implant therapy for each patient can be a creative and practical solution.

In addition to the case examples described in the previous paragraphs, there are other various but unique ways of integrated approaches in each individual case. The ideal timing for different surgeries may differ case by case, including tooth extraction, which may induce RAP. Another example consists of integrating canine exposure with soft tissue augmentation with selective corticotomy to facilitate faster tooth movement (Fig. 7). Although the application of corticotomy-assisted canine exposure was demonstrated previously, soft tissue augmentation is important to achieve a healthy periodontium after the tooth is in the correct position.[60]

Furthermore, complete closure of the remaining space may be challenging in adult orthodontics. Ridge augmentation combined with selective cortication can facilitate space closure. Closing a molar space by moving the second molar mesially into a grafted site with decortication has been demonstrated.[28] More clinical studies are needed to understand the predictability of this approach, as well as the best indications of using such an approach.

Digitally-integrated Interdisciplinary Treatment

Many of the previously described approaches can be facilitated with the use of digital technology. Flapless interproximal cortication can be facilitated with a CAD/CAM surgical stent.[61,62] In the future, utilizing digital technology to facilitate the integration of augmentation and implant therapy is the key to provide predictability and precision. Clear aligners, 3D-printed scaffold and fully-guided computer implant surgery currently are available for integration. Digital technology can provide an

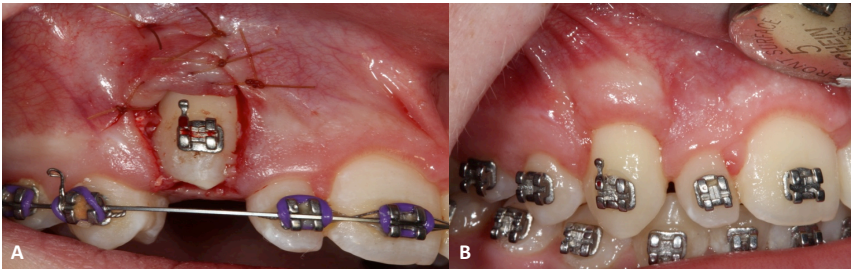

Figure 7. Simultaneous canine exposure, minor decortication and soft tissue augmentation. *A:* Immediately-post-op. *B:* Canine-forced erupted into the desired position in a few months with well-appreciated band of keratinized tissue.

excellent platform for communication between clinicians and patients.[63]

CONCLUSIONS

Individual patients present with different clinical problems and specific needs for certain procedures; therefore, it is important to provide a personalized interdisciplinary treatment plan. As comprehensive treat-ment plans for the patient are formulated, we should strive to integrate surgical (augmentation/implant) procedures at an earlier stage of orthodontic treatment to synergize our work and reduce total treatment time. Clinicians should communicate effectively and precisely to provide treatment outcome that each patient deserves for his/her unique conditions. Although more prospective clinical studies are needed in this field regarding the benefits from bone grafting and interdisciplinary care, it may be challenging to conduct an RCT as it relates to personalized dentistry. A patient-centered approach by a group of well-coordinated specialists remains the key to provide a personalized, precise interdisciplinary treatment.

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THE REGULATORY MECHANISM OF TOOTH FORMATION AND ERUPTION

Akira Takahashi, Noriaki Ono, Wanida Ono

ABSTRACT

In this chapter, we provide an overview of the current knowledge concerning root formation and eruption and their molecular mechanism. Normal tooth root formation and eruption are necessary for performing their fundamental functions (e.g., food intake and speaking). In spite of the failure of tooth root formation and eruption directly leading to death in almost all living organisms, details about the molecular mechanism of tooth root morphogenesis still are unknown. It is accepted widely that dental root formation is related closely with epithelial and mesenchymal interactions. After completion of crown formation, the epithelial tissue termed Hertwig's Epithelial Root Sheath (HERS) elongates apically and differentiates dental papilla cells into odontoblasts and dental pulp cells, and dental follicle cells into periodontal ligament (PDL) cells, alveolar osteoblasts and cementoblasts. They are the fundamental composition elements of root and periodontal tissue. Many recent studies focus on dental pulp stem cell (DPSCs) and PDL stem cells (PDLSCs) because their capabilities mediated therapy and tissue regeneration. It also should be beneficial for regenerative medicine to elucidate the mechanism of tooth root morphogenesis and generation of periodontium.

KEY WORDS: root formation, PTHrP, PTH1R, PFE, dental follicle

INTRODUCTION

Tooth eruption is important for human survival, with direct impact on fundamental functions (e.g., growth and development of the lower face, mastication for nutrition/energy intake, speech and esthetics) and for effective communication. Disorders involving tooth eruption are prevalent among the general public in a variety of forms including delayed, ectopic and failure of eruption.[1,2] Orthodontic and/or surgi-

cal approach is the first treatment choice for these patients, but in most cases, many affected teeth do not respond well to orthodontic mechanical forces and often result in ankylosis. Extraction of these teeth results in morbidity and subsequently requires prostheses with inferior functions that can compromise the patients' quality of life.

Dental root formation is initiated by the interaction of dental epithelium and dental mesenchyme after the completion of crown formation. The bi-layered epithelial sheath, called Hertwig's Epithelial Root Sheath (HERS) and dental mesenchymal cells, dental papilla and dental follicle interact with each other to form tooth root and periodontium.

Recently, though research in the area of tooth development has advanced what is known about the biological basis of tooth development, the molecular mechanism of root formation and eruption still is not understood completely. In this chapter, we summarize our current understanding of the signaling cascades and mechanisms involved in root development and eruption.

THE IMPORTANT GENES RELATED WITH TOOTH ROOT FORMATION AND ERUPTION

Tooth development is composed mainly of two distinct stages: crown and root formation. After the completion of crown formation, HERS invades apically and recruits dental papilla mesenchyme inside the HERS to become odontoblasts that produce root dentin. Then dental follicle mesenchyme is recruited to the outer surface of dentin to become periodontal ligament (PDL) cells and cementoblasts that produce cementum. HERS is accepted widely as the main region responsible for root formation. HERS and dental mesenchyme, dental papilla and dental follicle collaborate to form root through signal transduction. Subsequent bone resorption of coronal portion by osteoclasts enables teeth to erupt into the oral cavity. Recent *in vivo* and *in vitro* studies regarding tooth development—including tissue engineering and tissue regeneration—provide new understanding about tooth root formation and eruption. [28,29]

Various signaling cascades (e.g., Wnt/β-catenin, Osterix [Osx], Sonic Hedgehog [Shh] signaling pathway, interleukin-one alpha [IL-1a],

nuclear factor I [NfI] gene family and Ellis-Van Creveld [EVC] gene), as well as mechanisms involved in root development and eruption are discussed further in this chapter.

Wnt/β-catenin Signaling

The Wnt/β-catenin signaling cascade plays an important role during embryogenesis and adult tissue homeostasis. It controls gene expression and cell behavior in many tissues and also is related with various diseases.[3,4] β-catenin is expressed in both dental epithelium and dental mesenchyme during root formation.[5] Previous studies have shown that mice lacking β-catenin signaling in odontoblasts show the complete absence of roots.[5,6] In the developing molars of OC-Cre; Ctnnb1fl/fl mouse, where there is conditional β-catenin knockout in dental mesenchymal cells, dentin failed to form due to the lack of odontoblast formation in the inner layer of HERS, while the outer layer of HERS normally elongated apically. Interestingly, in spite of the failure of root formation, periodontal tissues (e.g., cementum and PDL) were formed between the crown and alveolar bone and teeth erupted even without root formation. This suggests that root formation may not be related directly with tooth eruption itself.

Similarly, mice with conditionally deleted Wntless protein which is required for the Wnt secretion in odontoblasts also displayed similar phenotype to OC-Cre;Ctnnb1fl/fl mouse.[7] In Wnt knockout mice, mandibular molars have thin dentin and short roots caused by delayed odontoblast maturation, failure of HERS extension and reduced dentin apposition. *In vivo* co-culture system of HERS cells and dental follicle cells reveal that HERS regulates the osteogenic differentiation of dental follicle cells *via* Wnt pathway.[8] These results demonstrate that the Wnt/β-catenin signaling plays essential roles in osteogenic/odontogenic differentiation in dental mesenchymal cells.

Osx

Osx is a zinc finger-containing transcriptional factor essential for osteogenesis.[9] During root morphogenesis, Osx expression has been identified in odontoblasts and dental pulp cells from Embryo 18 day (E18) to Post-natal 14 day (PN14) mice and Osx is required for differentiation and mineralization of odontoblasts and dental pulp cells.[10]

Osx is essential for odontoblast maturation in root formation.[11,12] Two independent Osx conditional knockout mice in odontoblast specific manner were generated: Col1a1-Cre;Osxfl/fl and OC-Cre;Osxfl/fl. Both Osx conditional knockout mice showed short molar roots and thin interradicular dentin. The expression of Dentin sialophosphoprotein (Dsp), osteocalcin (OC) and alkaline phosphatase (ALP) were inhibited in both mice, indicating that Osx is necessary for odontoblast maturation and root formation.

Shh

The Shh signaling pathway plays a principal role during embryonic development in many organs, tissue regeneration and carcinogenesis in various adult tissues.[13] The expression of several molecules of the Shh signaling pathway in early developing molar was reported, which suggested that the Shh signaling pathway is involved in root development.[14,15] HERS serve as the main source of Shh during both initiation and subsequent root morphogenesis. The HERS cells and apical mesenchyme of the dental papilla and follicle surrounding HERS expressed the Shh receptor Patch1 (Ptch1), agonist Smo and Gli downstream transcription.

Nakatomi and associates revealed Shh signaling is involved in root formation.[16] Shh is expressed in inner enamel epithelium, whereas its receptor Ptch1 is expressed in both inner and outer dental mesenchymal of HERS in developing tooth. In the homozygous of mesenchymal dysplasia mice that have an abnormal C-terminus of Ptch1 protein, cell proliferation of dental mesenchymal cells around HERS largely were suppressed in the period of root formation. The inhibited cell proliferation of dental mesenchyme by deletion of Shh signaling results in the delayed molar eruption and short roots. Li and coworkers examined the role of Shh signaling in root formation using a Gli1-CreERT2/loxP system.[17] Gli1, target transcription factor of Shh, is expressed in the apical mesenchyme cells close to Shh expressing epithelial cells between PN4 to PN11. In their study, Li and colleagues inhibited or activated Shh signaling by Shh inhibitor or constitutively activated Shh signaling by administering tamoxifen to Gli1-CreERT2; R26SmoM2fl/fl mice. Both inhibition and constitutive activation of Shh signaling result in the down regulation of proliferation in the apical re-

gion that resulted in short roots. This indicates that proper expression level of Shh signaling in apical mesenchyme is important and crucial for root formation.

IL-1a

The IL-1 family plays an important role in innate and adaptive immune response.[18] IL-1a also is related with tooth eruption.[19] It is located in the stellate reticulum and its receptor, type I IL-1R, is present in the adjacent dental follicle.[20] In IL-1R knockout mice, incisor eruption was delayed slightly (about one day) and molar eruption was delayed by two days relative to control mice.

NFIC

The NFI gene family encodes site-specific transcription factors essential for the development of many organs. In vertebrates, there are four NFI gene family members: Nfia, Nflb, Nflc and Nflx; the nuclear factor I C (NFIC) is known as one of critical genes for root formation. The expression of NFIC in developing molar is detected in ameloblasts, dental follicle cells and dental papilla cells, especially in the odontoblasts and pre-odontoblasts in humans and mice, while not in HERS cells.[21,22] NFIC-/- knockout mice formed normal HERS and showed normal crown formation and tooth eruption, but their root formation was disrupted significantly.[23-25] The expression of dentin sialophosphoprotein (DSPP) in NFIC-/- knockout mice was reduced significantly in the developing root. Thus, the loss of NFIC did not affect the formation of HERS, but it caused the failure of odontoblast differentiation and proliferation that leads to the failure of root formation.

EVC Syndrome

EVC syndrome is an autosomal recessive skeletal hypoplasia characterized by short limbs, short ribs and abnormal teeth. EVC and EVC2 genes are known as causal genes of this syndrome.[26] The EVC gene also affects root formation through Shh signaling in the embryonic stage.[27] In EVC-/- mice, the symmetric expression pattern of Shh and its downstream targets, Hh1 and Gli1, were altered from E13 to P0. In particular, the expression of Ptch1 disappeared at P0, which resulted in abnormal crown and root morphogenesis.

EPITHELIAL-MESENCHYMAL INTERACTION DURING ROOT DEVELOPMENT

Epithelial-mesenchymal interaction is a common feature of early stages of morphogenesis in different ectodermal organs (e.g., hair, glands and teeth). Despite tissue diversity, from the point of histogenetics, all ectodermal organs are formed by epithelial-mesenchymal interaction. The development starts from the formation of ectodermal placodes. Then they interact with adjacent mesenchyme, develop subsequent morphogenesis and finally, accomplish organogenesis. Various important factors relevant to epithelial-mesenchymal interaction in tooth morphogenesis in embryonic stage are reported.[28,29] Dental epithelium and FGFs regulates Cbfa1 expression in dental mesenchyme during the bud and cap stages.[30]

Smad4-Shh-NFIC signaling cascade for epithelial-mesenchymal interaction is required in tooth root morphogenesis.[31] Both K14-Cre; Smad4fl/fl mice (the expression of Smad4 is inhibited in epithelial cells including HERS) and NFIC-/- mice (NFIC originally is expressed in dental mesenchyme) show rootless phenotype. Shh is expressed primarily in HERS and transcription factor Gli1 activated by Shh is expressed in dental epithelium and dental mesenchyme. In K14-Cre;Smad4fl/fl mice, the expression of Shh in HERS, that of Gli1 in dental epithelium and mesenchyme and that of NFIC in dental mesenchyme are suppressed. By adding ectopic Shh into K14-Cre;Smad4fl/fl mice, the root defect and NFIC expression in dental mesenchyme were rescued partially. However, ectopic Shh are not able to rescue the root dysplasia in NFIC-/- mice. The results lead to the conclusion that Smad4 is required for Shh expression in dental epithelium. Shh released from the dental epithelium works on the dental mesenchyme to induce NFIC expression to control root development by the intermediary of Gli1.

DENTAL FOLLICLE AND OSTEOCLAST FORMATION FOR TOOTH ERUPTION

The dental follicle, a sac-like membranous tissue surrounding the developing tooth bud, regulates two distinct processes of tooth eruption and root formation. Cahill and coworkers reported that when the dental follicle surrounding a premolar was removed surgically, the

premolar failed to erupt, resulting in ankylosis of the tooth to the alveolar bone.[32] Therefore, for several decades, the dental follicle has been considered to play the central role in tooth eruption. Dental follicle includes mesenchymal progenitor cells for cementoblasts, alveolar osteoblasts and PDL cells.[33] It also is required for the formation of osteoclasts that resorb alveolar bone to create the eruption pathway.

Osteoclasts play a role in bone remodeling, osteoclast formation and function, which also is associated intimately with normal tooth eruption. Delayed tooth eruption occurs by the inhibition of osteoclast formation and function. The recruitment of active osteoclasts and subsequent alveolar bone resorption are necessary to create the eruption pathway.[34] The Runx2/Cbfa1 gene is important for recruiting osteoclasts at prompt timing for bone resorption. Its heterozygous mutation mice showed significantly delayed tooth eruption because of insufficient number of osteoclasts recruited on the surface of the eruption pathway. Colony stimulating factor-1 (CSF-1), receptor activator of nuclear factor kappa-ß ligand (RANKL) and osteoprotegerin (OPG) are known as important regulating factors for osteoclast differentiation. Their expression patterns differ temporospatially and they regulate osteoclastogenesis during tooth eruption.[35] OPG expression in the dental follicle is regulated temporally to activate osteoclast formation, which is required for tooth eruption. The presence of CFS-1 and parathyroid hormone-related protein PTHrP has been shown to inhibit OPG expression in dental follicle cells *in vitro*.[36]

PTHrP AND PFE

PTHrP Signaling and Tooth Eruption

The parathyroid hormone (PTH) behaves as a major mediator for bone remodeling and as an essential regulator for calcium homeostasis. PTHrP has diverse biological activities when compared with PTH. PTHrP not only has local paracrine/autocrine function, but it also has intracrine function in various tissues, where it regulates the cell proliferation and differentiation. As organogenesis is initiated, PTHrP signaling regulates epithelial-mesenchymal interaction in various epithelial organs (e.g., skin, hair follicles, mammary and parathyroid gland and developing teeth).[37,38] In addition, PTHrP regulates endochondral bone develop-

ment, maintains proliferation of the chondrocytes while delaying their differentiation into pre-hypertrophic and hypertrophic chondrocytes through the PTHrP-Indian hedgehog (Ihh) feedback loop.[39]

The PTH/PTHrP receptor (PPR) is G-protein-coupled receptor with seven transmembrane spanning domains. PTHrP-PPR signals are conveyed through two subtypes of heterotrimeric G-proteins: GαS and Gαq11. GαS activates the adenylate cyclase (AC)/cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) cascades and Gαq11 activates the phospholipase C (PLC)/inositol trisphosphate (IP3)/diacylglycerol (DAG)/intracellular calcium/protein kinase C (PKC) cascades, respectively.[40]

The loss-of-function mutations in the PPR gene in humans cause Blomstrand chondrodysplasia (BOCD), which is characterized by lethal dwarfism accompanied by severe defects of endochondral bone formation. These patients also show severely abnormal tooth form.[41]

In tooth development, PTHrP is expressed in the enamel organ, specifically in the inner and outer epithelium during crown morphogenesis.[42] During subsequent root morphogenesis, PTHrP is expressed predominantly in the dental follicle in a pattern surrounding teeth, especially immediately outside HERS.[43]

PTHrP is a crucial factor for tooth eruption in mice.[44] PTHrP knockout mice die at birth from a chondrodystrophic phenotype characterized by premature chondrocyte differentiation and accelerated bone formation. To investigate the role of PTHrP in tooth development, Col-II-PTHrP transgenic mice were crossed with PTHrP null heterozygous mice and the obtained rescued mice showed approximately normal skeletal phenotype. However, tooth root formation and eruption were inhibited in the rescued mice. On the other hand, K14-PTHrP/Col-II-PTHrP double transgenic mice showed normally-scheduled tooth root formation and eruption both in incisors and molars. These results strongly suggest that PTHrP is a crucial factor for tooth eruption.

PTHrP also is associated with osteoclast formation in terms of tooth eruption.[45] The stellate reticulum and outer enamel epithelium express abundant amounts of PTHrP mRNA, whereas the surrounding bone, dental papilla and dental follicle express PPR mRNA. *In vitro* osteoclast formation can be inducted by co-culture of stellate reticulum cells and dental follicle cells without adding osteoclast precursors and induc-

tion factors (e.g., vitamin 1,25 [OH]2). Additionally, bone resorption activity was upregulated by applying the conditioned medium from dental follicle cells, suggesting that dental follicle cells may be the central target of PTHrP to activate osteoclast formation during root eruption.

PRR signaling is involved in both odontoblastic and ameloblastic differentiation.[46] The transgenic mice that have a constitutively active PPR in odontoblastic cells interrupt the normal odontoblastic and ameloblastic differentiation. The transgenic mice displayed large incisors and molars and their root formation was delayed dramatically, suggesting that PPR signaling in odontoblasts affects their differentiation directly and ameloblasts differentiation indirectly.

Primary Failure of Tooth Eruption (PFE)

PPR signaling is associated with tooth eruption in humans. Primary failure of tooth eruption (PFE) is a non-syndromic disorder characterized by partial or complete eruption failure of permanent teeth. This disorder can be caused by mutations in the PPR gene and, in many cases, this clinical condition occurs on a familial basis. The treatments of choice for these affected patients are surgical and/or orthodontic therapy. However, patients usually cannot obtain favorable treatment outcomes because the teeth become ankylosed as soon as orthodontic force is applied.[47] BOCD is known as a genetic disorder characterized by advanced endochondral bone maturation and increased bone density; along with these symptoms, BOCD patients also exhibit severely abnormal tooth shape and impacted teeth.[41] Analysis of PPR cDNA from BOCD patients revealed that patient was heterozygous for a point mutation that cause the deletion of the amino acid.[48] Thus far, variants of PPR have been reported in connection with PFE and almost of them are heterozygous loss-of-function mutations in PPR.[49-52] These mutations in the PPR gene cause the disturbed amino array and prevent PTHrP from binding to PPR. A novel homozygous PPR variant has been identified recently in PFE in a consanguineous family in Saudi Arabia.[53]

PTHrP Signaling in Dental Mesenchyme During Root Formation and Eruption

We recently reported the role of PTHrP signaling in Osx-expressing mesenchymal progenitor in root morphogenesis.[43] In this study, we used a tamoxifen-inducible Osx-creER and R26R-tomato

reporter system. Osx-creER;R26R-tomato mice received tamoxifen at P3 when root morphogenesis began and only cells actively expressing Osx at P3 (Osx-P3 cell) underwent recombination in the presence of tamoxifen and produced tomato protein permanently. Until P25, Osx-P3 cells had participated actively in root formation by differentiating into a majority of the odontoblasts, dental pulp cells, cementoblasts and some PDL cells, indicating that Osx-P3 cells can differentiate into all kinds of periodontium. We also investigated a PTHrP expression pattern during root morphogenesis by analysis of PTHrP-LacZ knock-in mouse. PTHrP-expressing blue cells were found primarily in the dental follicle in a pattern surrounding the tooth, particularly immediately outside the HERS and beyond between P3 to P7. Fluorescent immunostaining of PRR revealed that the PPR was expressed in odontoblasts, dental pulp cells and dental follicle cells. Next, to investigate the role of PPR in Osx-expressing root forming cells, we conditionally deleted the PPR using Osx-creER and the PPR-floxed allele. At P18, Osx-PPR conditional knockout (Osx-cre;PPRfl/fl) showed a significantly truncated root form compared with the control (PPRfl/fl,fl/+) and conditional heterozygous group (Het; Osx-cre;PPRfl/+) and it did not erupt into the oral cavity like PFE. Our data demonstrate that the PPR signaling in dental mesenchymal progenitor is essential for tooth root formation and eruption.

CONCLUSIONS

In the last decade, studies of tooth root development and eruption have evolved. The tooth root formation is achieved by the epithelial and mesenchymal interaction as other organs do in early development. Thanks to the recent progress in mouse genetics, beneficial *in vivo* study models have been established which can be helpful tools to figure out the mechanisms of tooth root development. This chapter provided an overview of current understanding of root development and highlights the developmental biology of the tooth root; however, we have not obtained full knowledge of this field yet.

For better understanding of the detailed mechanism of tooth root formation and eruption, we need to acquire more specific genetic tools that can mark the dental stem cells responsible for tooth root development. The hope and expectation is to collaborate with other researchers in this field to design better strategies that will be beneficial for the use of stem cells for tissue engineering purposes.

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A. Takahashi and W. Ono contributed to the chapter's conception, design, data acquisition, analysis and interpretation, and drafted the manuscript. N. Ono contributed to the chapter's conception and critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work.

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PRE-SURGICAL ORTHOPEDICS IN NEWBORNS WITH CLEFT LIP AND PALATE OR PIERRE ROBIN SEQUENCE

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ABSTRACT

Pre-surgical infant orthopedics (PSIO) is a treatment procedure that frequently is performed at the German Cleft Palate Centers (Rostock and Tuebingen, Germany) for newborns with cleft lip and palate (CLP) or Pierre Robin Sequence (PRS). It is an integral part of the guidelines for cleft care that have been established at the University Hospitals in Rostock and Tuebingen. However, since its introduction in the 1950s, there has been an ongoing debate about the efficiency and outcomes of the PSIO treatment in patients with craniofacial malformations.

Therefore, the aim of the first part of this chapter is to provide an overview of current knowledge on the positive and negative effects of PSIO treatment in children with CLP, as well as to summarize available scientific data on this topic. Furthermore, a recently developed method to analyze the efficiency of PSIO treatment by using 3D model analysis will be introduced. In addition, the results of a pilot study in thirteen non-syndromic newborns with unilateral CLP will be reported.

The aim of the second part of the chapter is to present a non-invasive treatment concept for infants with PRS, which is characterized by micro-retrognathia, glossoptosis and respiratory distress; in approximately 50% of the cases, a cleft palate may be present. The prevalence of PRS in Germany is 12.4 out of 100,000 births, placing PRS in the category of rare diseases. The main clinical problems include upper airway obstruction (UAO), as well as feeding difficulties and failure to thrive. Various treatment modalities for infants with PRS consist of invasive procedures (e.g., mandibular distraction osteogenesis, tongue-lip adhesion, mandibular traction, tracheostomy, use of a nasopharyngeal airway, continuous positive airway pressure [CPAP]), or by recommending the prone position. In contrast to these procedures, we present a treatment concept that utilizes the TuebingenPalatal Plate (TPP) in combination with Manual Orofacial Regulation Therapy according to Castillo Morales® and appropriate feeding training. The TPP is a palatal plate with a velar extension which shifts the tongue to a more ventral and horizontal position, thereby widening the obstructed airway. The TPP may act like a functional orthodontic appliance in that it may induce at least partial catch-up growth of the hypoplastic mandible. This treatment concept has been evaluated successfully in infants with isolated and syndromic PRS. It has

been shown to improve respiration and weight gain in a significant manner. Therefore, it can be regarded as an effective, causal, non-invasive and safe treatment modality for infants with PRS.

KEY WORDS: pre-surgical infant orthopedics (PSIO), cleft lip and palate (CLP), Pierre Robin sequence (PRS)

PART I: TREATMENT OF UNI- AND BILATERAL CLEFT LIP AND PALATE (CLP) WITH PALATAL PLATE

INTRODUCTION

Clefts of lip, alveolus and palate are among the most frequent congenital malformations in humans. A cleft lip and palate (CLP) incidence rate of one in 600 individuals has been reported.[1] Complete unilateral CLP, as a subtype, occurs less frequently and has a syndromic background in one out of three cases.[2] Medical care for CLP patients requires an interdisciplinary approach for diagnosis and therapeutic interventions (Table 1).[3,4]

Non-invasive pre-surgical infant orthopedics (PSIO)—with or without naso-alveolar molding involving the insertion of a passive plate—

Table 1. Special need for interdisciplinary diagnostics and therapy in patients with CLP.

SEVERAL PROBLEMS	SPECIALTIES
Nutrition problem	Neonatology, pediatrics, phoniatrics, logopedics, orthodontics
Cleft lip, alveolus and palate	Craniomaxillofacial surgery, radiology
Hearing, ENT problems	ENT medicine, pedaudiology
Speech disorders	Phoniatrics/logopedics
Disturbances in craniofacial growth, malocclusion	Orthodontics, craniomaxillofacial surgery, pediatric dentistry, prosthetics, restorative dentistry, radiology
Facial esthetics	Craniomaxillofacial surgery, orthodontics, pediatric dentistry, prosthetics, restorative dentistry, ENT, radiology
Psychological problems	Psychology

has been incorporated into the guidelines of cleft care established at the University Hospital in Rostock, Germany (Table 2).

The German Cleft Palate Center was founded in 1956 by Dr. Armin Andrae, who, at that time, was the head of the Department of Maxillofacial and Plastic Surgery. Since then, the interdisciplinary treatment protocol used for patients with CLP has been modified. While more invasive treatment procedures (e.g., active lip retraction, Latham procedure) were advocated for newborns with CLP in the beginning, treatment philosophy shifted to application of PSIO treatment starting in the 1960s. This influence came from a young orthodontist, Dr. Rosemarie Grabowski, who was involved in the cleft care of newborns at that time and later became the chair of the Department of Orthodontics at the University Hospital in Rostock. Her clinical work with cleft patients was influenced profoundly by Dr. Rudolf Hotz in Zurich, Switzerland, an advocate of non-invasive PSIO treatment at that time (Fig. 1).[5,6] Her clinical practice and experience of more than 50 years had a major impact on establishing guidelines for interdisciplinary therapy at the cleft center at Rostock's University Hospital and on the development of orthodontic treatment strategies from birth until adulthood for cleft care patients.[7,8]

The four main orthodontic treatment goals in cleft care at the University Hospital in Rostock are:

Table 2. Orthodontic treatment strategies for patients with CLP at the University Hospital in Rostock, Germany.

TX GOALS	ORTHODONTIC MEASURES
Enhancement of craniofacial growth in the midfacial region	Non-invasive pre-surgical infant orthopedics in combination with naso-alveolar molding
Functional orthopedics during craniofacial growth period	Removable and fixed functional appliances, especially Functional Regulator Type III orthopedic appliances (e.g., face mask, rapid maxillary expansion [RME])
Establishing occlusion in adolescents	Orthodontics with fixed appliances, skeletal anchorage devices
Improving orofacial esthetics in adults	Orthodontics with fixed appliances in order to improve prosthetic or surgical interventions

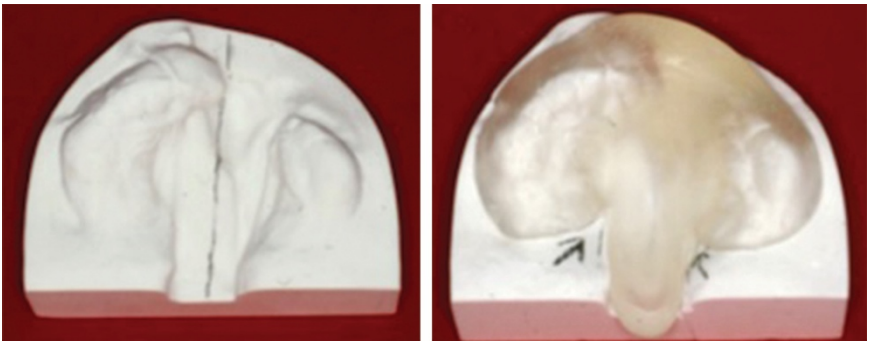

Figure 1. Passive Hotz plate used for PSIO in a newborn with unilateral CLP.

- Enhancement of craniofacial growth in the midfacial region;
- Functional orthopedics during the craniofacial growth period;
- Establishing exact occlusion in adolescents; and
- Improving orofacial esthetics in adults.

These goals fit well with the overall multi-disciplinary treatment concept for CLP patients that is provided by several medical and dental disciplines at the Cleft Center. The specialist team is comprised of maxillofacial surgeons, ENT specialists, speech therapists and orthodontists, and meets weekly to see CLP patients and coordinate diagnostic measures, as well as treatment procedures.

PSIO IN NEWBORNS WITH CLP: AN ONGOING CONTROVERSY

According to Dr. Hotz's theory, an acrylic plate that covers the cleft defect in the maxillary arch is adjusted in a specific way so that cleft width is reduced by the natural growth of the two maxillary segments.[5,6] This type of appliance is called the "passive Hotz plate" or the "drinking plate" as no active force is used to bring cleft segments together to narrow cleft width prior to lip surgery. At the University Hospital in Rostock, the procedure is performed mainly in newborns with complete unilateral (Fig. 2) or bilateral CLP (Fig. 3), or in newborns with isolated cleft palate. It often is combined with naso-alveolar molding as described by Cutting and Grayson.[9] Parents are instructed how to insert and hand-

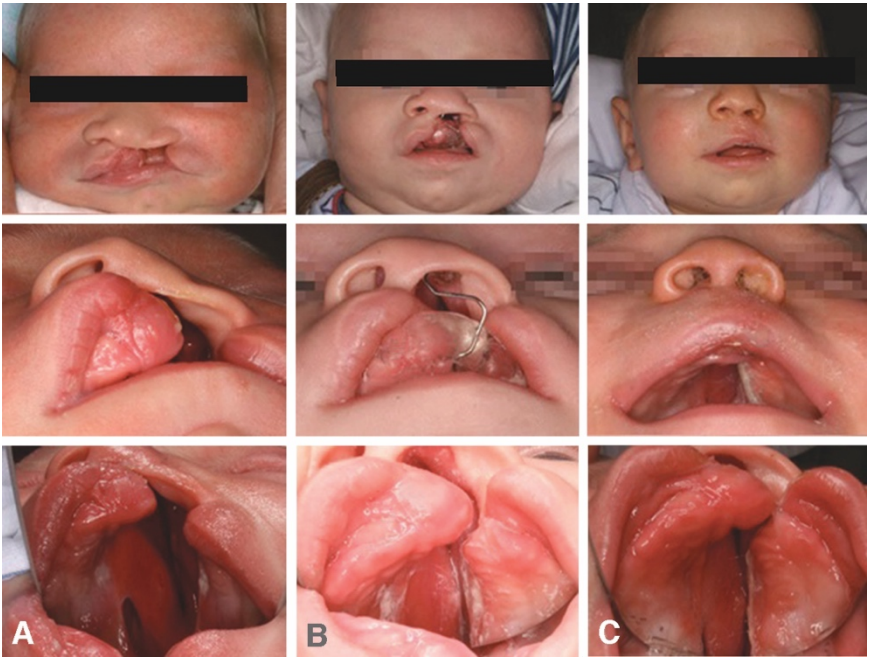

Figure 2. PSIO treatment in combination with naso-alveolar molding in a newborn with unilateral CLP. *Column A:* Prior to PSIO treatment. *Column B:* During PSIO treatment in combination with naso-alveolar molding. *Column C:* Upper arch after PSIO treatment of six months and after primary lip surgery. Photographs used with parental permission.

le the plate and patients are seen every two to three weeks for consultations. PSIO continues until surgical lip closure is performed. Within this time period of approximately six months, two plates typically have to be fabricated in order to accommodate the dimensional changes in the maxilla. No plate is worn after lip closure at the cleft center in Rostock.

As mentioned previously, PSIO treatment in newborns with CLP has been part of the multi-disciplinary treatment procedure offered for cleft care patients at Rostock for many years. Although members of the cleft team have changed over the years and study results on the effectiveness of PSIO treatment have been mixed and remain controversial, Rostock's strategy of using PSIO for CLP care has been maintained. The reasons for this are due to good clinical results with regard to maxillary growth resulting in few orthognathic cases in young adults with CLP.[8] The positive clinical experience over more than 50 years at the Cleft Cen-

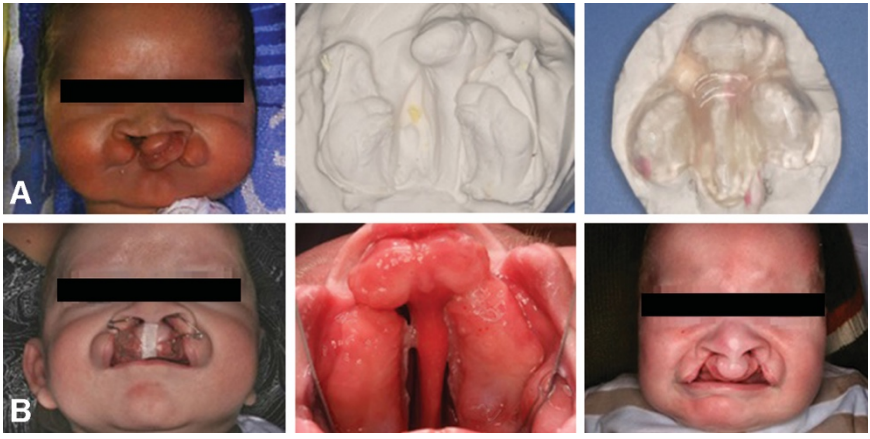

Figure 3. PSIO treatment in combination with naso-alveolar molding in a patient with bilateral CLP. *A:* Status prior to PSIO treatment and fabricated passive Hotz plate. *B:* Status during PSIO treatment in combination with naso-alveolar molding and status prior to primary lip surgery. Photographs used with parental permission.

ter in Rostock is reinforced by some of the positive effects of PSIO treatment that have been reported in the literature.

The reported advantages of PSIO are:

- Facilitating intra-oral feeding (feeding plate);[10]
- Achieving physiological tongue position (help to initiate sucking reflex);[11,12]
- Reducing cleft size through guided and non-restricted growth of the cleft and nasolabial segments;[6,13,14]
- Facilitating primary surgeries (lip, alveolus, palate);[15-18]
- Reducing nasal deformity;[9] and
- Improving midfacial and craniofacial growth.[19]

There is an ongoing debate, however, about the efficiency and patient outcomes after PSIO treatment.[15-18] While older studies mainly focused on the treatment effects of surgical interventions, more recent studies have analyzed treatment outcomes regarding dental arch and speech parameters.[6,13,20-24] Unfortunately, most of the studies published on the effects of pre-surgical orthopedic appliances in the past are compromised by deficiencies in their study design. Often, they did not

use controls, only retrospective data was analyzed, or important parameters were not considered.[21,25,26] Literature reviews on this topic criticize the small number of eligible trials, the heterogeneity of treatment protocols, results with risk of bias and the poor quality of the available evidence.[27-29] So far, only one randomized controlled trial (RCT) has been published on this topic in the literature.[21] When summarizing the results of the recently published literature reviews on this topic, it must be stated that the positive long-term treatment effects of PSIO cannot be confirmed and still are debatable.

Statements from current literature reviews and meta-analyses of PSIO treatment include:[27-31]

- It is not necessary for feeding or orthodontic reasons;
- It does not improve general body growth;
- It is not cost effective;
- There are no beneficial effects on maxillary arch dimension or dental arch relationship; and/or
- It influences speech negatively due to delayed palate closure.

They all conclude that more well-designed RCTs with long-term follow-ups are needed in order to answer specific questions more precisely.

FUTURE RESEARCH STRATEGIES IN THIS FIELD

Taking all of the previous studies into consideration, it has to be stated that the scientific evidence on short- or long-term PSIO treatment effects in line with evidence-based standards needs to be improved. But are RCTs the only way to answer questions that have been asked for decades in this field? Some authors have suggested that the use of RCTs in orthodontics is questionable for several reasons, including high cost, ethical problems, parental informed consent and problems recruiting sufficiently large study sample—all of which make it difficult to conduct RCTs in newborns with CLP.[32,33] However, there are alternatives that can be considered when planning projects in the future.[32]

The Department of Orthodontics at the University Dental Hospital in Rostock has initiated a national project called GERMAN CLEFT NETWORK STUDY. This prospective clinical trial aims to enhance sample size

by including cleft patients from eleven university cleft centers in Germany. In most centers, the Hotz plate procedure is used in PSIO treatment. The overall aim of this study is to compare short- and long-term treatment results across different cleft palate centers and, ultimately, draw conclusions about different treatment protocols for cleft palate patients in Germany.

We started this project with a pilot study that aimed to analyze the efficiency of pre-surgical orthopedic treatment by means of 3D model analysis. The efficiency of PSIO treatment was measured by the development of cleft size and other edentulous arch parameters in newborns with non-syndromic unilateral CLP.[34] In this pilot study, upper arch models of thirteen newborns with unilateral CLP were fabricated immediately after birth (T1) and prior to surgical lip closure (T2). Between T1 and T2, PSIO treatment with the Hotz plate was conducted for six months. Digital models from T1 and T2 were gained by means of a 3D model scanner (Elaboro Scanpoint 75T, Schwerin, Germany). Single scans then were assembled into one model using CAD software (Geomagic® Studio® 12, 3D Systems, Rock Hill, SC). This was part of the doctoral thesis by author MS, which aimed to develop a new software for measuring cleft volume in newborns with unilateral CLP. The newly developed software was called CLEFT DYNAMIC (Rostock, Germany).[34]

Volumetric evaluations of edentulous jaw models in cleft patients have been described rarely in the past.[35-39] CLEFT DYNAMIC enables three-dimensional (3D) volumetric evaluation of changes in the alveolar segments in cleft patients. This enables us to describe the cleft area more precisely and to analyze changes in cleft volume during PSIO treatment for the first time. The upper jaw is divided into different areas radiating from the constructed center of the model in order to analyze different alveolar regions. Segmentation of the alveolar ridge is based on reproducible mucosal points.[40-42] 3D development of alveolar segments next to the cleft area are of special interest for orthodontists practicing PSIO treatment (Fig. 4). By the superimposition of model scans at T1 and T2, a direct comparison of volumetric changes in that space (size of alveolar cleft) is possible. A measuring sector for calculation of cleft volume before and after PSIO treatment was defined (yellow sector). It can be divided into three separate subspaces of volume (V1, V2 and V3; Fig. 5). Volume 1 (V1) represents alveolar cleft volume at T1 and T2. Volumes 2 and 3 (V2, V3) represent alveolar ridge volume next to the cleft

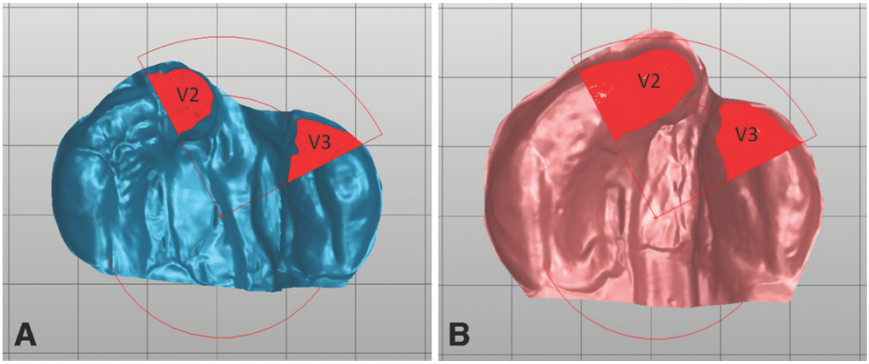

Figure 4. Illustration of V2 and V3 represent alveolar ridge volume next to the alveolar cleft area by using cleft dynamic in cleft patient. *A:* Upper model scan of cleft patient before PSIO treatment (T1). *B:* Upper model scan of the same cleft patient treated with PSIO for six months (T2).

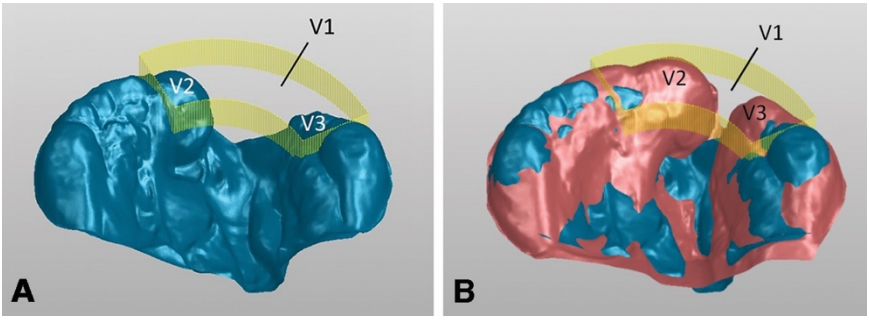

Figure 5. Definition of a measuring sector (yellow sector) for calculation of cleft volume before and after PSIO treatment by using cleft dynamic. *A:* Three separate subspaces (V1, V2 and V3) form total volume of the cleft area before PSIO treatment. *B:* Superimposition of upper model scans at T1 and T2 displays increase in V2 and V3 and decrease in V1 (cleft size) during PSIO treatment.

area at the same observation time points. An increase in V2 and V3 during PSIO treatment consequently would lead to a decrease in V1 (cleft size; Fig. 5).

Preliminary results of this pilot study showed that the greatest increments of volume were detected in alveolar ridge segments neighboring the alveolar cleft (V2, V3). This led to a reduction of alveolar cleft size of 50% within six months of PSIO treatment. There was good reproducibility for measurements of volumetric changes in the alveolar cleft area in patients with unilateral CLP.

PART II: TREATMENT OF PIERRE ROBIN SEQUENCE (PRS) USING PALATAL PLATES

INTRODUCTION

Pierre Robin sequence (PRS) first was described by Fairbairn in 1846 and Shukowski in 1911.[43,44] In 1923, Pierre Robin described infants with a hypoplastic mandible and glossoptosis resulting in upper airway obstruction (UAO) and a U-shaped cleft palate in about 50% of the cases.[45] In 1934, Robin investigated this disease in a more detailed manner and he became the eponym for this condition.[46] The incidence of PRS ranges from 1:8500 to 1:14500 live births and, therefore, is considered a rare disease.[47,48] A recent survey determined a birth prevalence of 12.4 per 100,000 live births in Germany.[49] Prenatal diagnosis of PRS is possible by ultrasound examination during pregnancy, by assessing the size of the fetal mandible and calculation of the jaw index. It also can be diagnosed by facial profile analysis, as the growth process of the mandible is impaired primarily in the sagittal plane.[50,51] In 2016, recommendations for the initial evaluation of PRS and clinical descriptors were published in a consensus report.[52]

PRS may occur as an isolated entity (isolated PRS), as a part of a syndrome (syndromic PRS), or in association with other malformations (associated PRS).[53] Currently, more than 50 syndromes have been described in association with PRS, the most common being Stickler syndrome, Treacher Collins syndrome and 22q11 deletion syndrome (velocardiofacial syndrome).[54] Approximately 40% of patients have isolated PRS and 60% of patients have additional syndromic features.[55]

CLINICAL PRESENTATON OF PATIENTS WITH ISOLATED PIERRE ROBIN SEQUENCE

PRS is characterized by micrognathia, retrognathia and glossoptosis (Figs. 6 and 7*A*) and presents clinically with UAO, feeding difficulties and failure to thrive. Cleft palate is present in approximately 50% of the cases which typically is broad and U-shaped. Glossoptosis appears as an erected tongue in the pharynx, which may be in a vertical position, or as a tongue that is retracted into the oropharynx and is barely visible. Glossoptosis is the primary cause of UAO and respiratory problems in PRS. Upper airway dysfunction is characterized during sleep by snoring, noisy

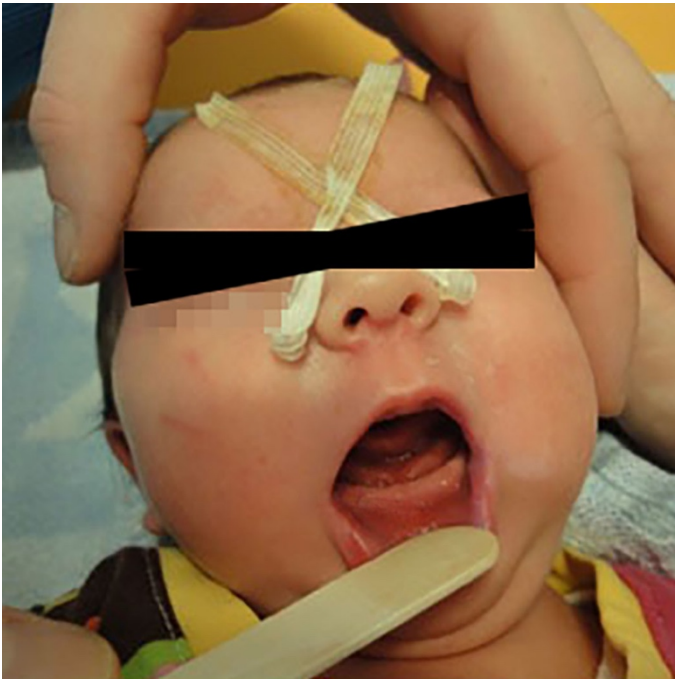

Figure 6. Neonate with PRS: glossoptosis. Photograph used with parental permission.

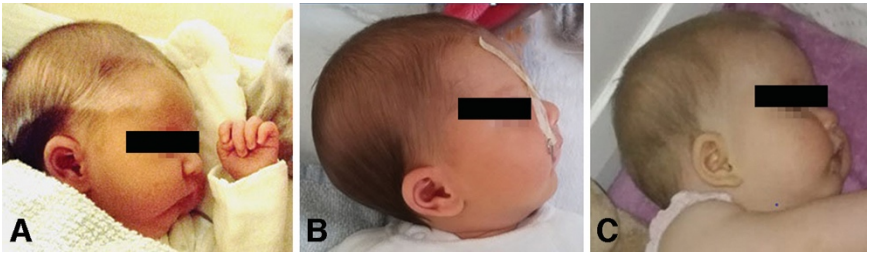

Figure 7. Patient with PRS. *A:* Neonate with micro- and retrognathia and severe UAO, mixed-obstructive apnea index (MOAI) 25 and severe obstructive sleep apnea (OSA). *B:* Five days later with TPP *in situ*, chin is in a more ventral position (MOAI with TPP 3.5). *C:* Patient is six months old, no more need for TPP (MOAI 0.8, no more OSA). Photographs used with parental permission.

breathing, intercostal or jugular retractions, witnessed apneas or increased respiratory effort due to an increased upper airway resistance and pharyngeal collapsibility. This may develop over time during the first weeks of life. In general, UAO worsens in the supine position, while asleep and during feeding.

Failure to thrive and feeding problems may be secondary to respiratory problems (i.e., an increased effort to breathe due to UAO), leading to a higher energy expenditure and also may be caused by swallowing dysfunction and an abnormal sucking pattern, which leads to a low calorie intake. If left untreated, severe consequences (e.g., neurodevelopmental delay, failure to thrive, behavioral difficulties, pulmonary hypertension, congestive heart failure and even sudden death) may occur.[56-59] It is described in the literature that the cognitive and psychosocial development of children with isolated PRS who were treated for UAO was within the reference range.[60]

Endoscopical Evaluation of UAO

Four types of UAO can be differentiated endoscopically.[61] Type 1 obstruction consists of the posterior movement (true glossoptosis) of the dorsum of the tongue to the posterior pharyngeal wall so that the majority of the airway constriction is anteroposterior (Fig. 8*A*). Type 1 obstruction is found in 90% of patients with isolated PRS, but in as few as 44% of patients with syndromic PRS.[62]

Etiopathology

PRS is not a syndrome in itself, but a sequence in which a single primary anomaly leads to multiple secondary anomalies. The primary structural anomaly in the sequence seems to be the deficient outgrowth

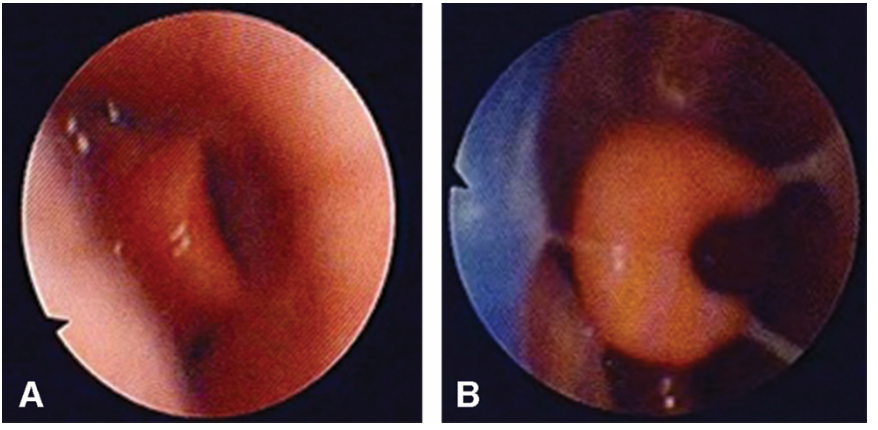

Figure 8. Endoscopic view of the epiglottis. *A:* Obstruction due to glossoptosis. *B:* TPP *in situ*, the velar extension pushes the tongue in a more anterior position and, thereby, widens the airway.

of the mandible before the embryological age of nine weeks, which reduces the oropharyngeal space. It is deemed that the restricted mandibular growth inhibits the downward and forward movement of the tongue, thereby impeding the fusion of the palatal shelves. Therefore, glossoptosis and cleft palate are secondary defects.[63,64] The other hypothesized model includes a muscular defect with failure of tongue descent and dysfunction of the oropharyngeal muscular function.[65] The SOX9 gene, a chondrogenic regulator, has been linked to isolated RS.[66]

Treatment Modalities

Presently, there is no consensus on the ideal treatment of patients with PRS, but predominantly PRS is managed internationally by: rather invasive procedures (e.g., mandibular distraction osteogenesis, tongue lip adhesion or mandibular traction); bridging the narrow airway through a tracheostomy; use of a nasopharyngeal airway; airway stenting by continuous positive airway pressure (CPAP) or high-flow nasal cannula; or by recommending the prone position, which may lead to increased risk of sudden infant death.[67]

In Tuebingen and Rostock, an oral appliance—the Tuebingen Palatal Plate (TPP; Fig. 9), in combination with Manual Orofacial Regulation Therapy according to Castillo-Morales® and appropriate feeding techniques—is used as the first line of treatment for infants with PRS and UAO.[68] This treatment concept has been evaluated successfully in Tue-

Figure 9. The Tuebingen palatal plate (TPP).

bingen in infants with isolated and syndromic PRS, as well in children with syndromic craniosynostosis.[69-74]

The TPP

Palatal plates with a dorsal extension first were reported in 1967 by Pielou, but received little attention.[75] The pharyngeal extension was intended to move the base of the tongue forward, thereby correcting the glossoptosis.

In Tuebingen, these palatal plates with velar extension have been in use for infants with PRS for more than 20 years. The TPP consists of a palatal plate with a velar extension (Fig. 9) that shifts the tongue into a more anterior and horizontal position, thereby widening the airway and releasing UAO (immediate effect; Fig. 8*B*). The second goal of the plate is to facilitate feeding by normalizing tongue position. We assume that the TPP acts like a functional orthodontic appliance not only because it shifts the tongue, but also because it shifts the mandible to a more anterior position (Fig. 7*A*-*C*). This new anterior mandibular position may stimulate condylar growth, which enables skeletal adaptation to the new mandibular position. This at least may result in a partial catch-up growth of the mandible (long-term effect). These histological changes in the condylar cartilage of the temporomandibular joint have been described for functional orthodontic appliances.[76]

Manufacturing the TPP

Infants have a maxillary imprint taken (Fig. 10) with a custom-made impression tray using alginate (Tetrachrom-Super-Alginate, ISO 1563, class B, type I, Kaniedenta, Herford, Germany) or a hydrophilic addition silicone (a-silicone; e.g. vinylpolysiloxane; freealgin, Zhermack Dental, Badia Polesine, Italy). An a-silicone is advantageous because there is no risk of impression material tearing off into the cleft, but it takes longer to set than an alginate impression; this may be problematic in infants with severe UAO. The impression procedure is conducted in the presence of a neonatologist in the neonatal intensive care unit (NICU) under cardiorespiratory monitoring without sedation, but with a nasopharyngeal airway in place in order to secure the airway.

From the impression, a plaster cast is produced using high precision dental plaster (Girodur type IV, Synthetic Superhard Stone Plaster for

Figure 10. Fabrication of a prototype I. *A:* Custom-made impression tray. *B:* Imprint.

Sectioned and Master Models DIN EN 26873, white, Girrbach Dental GmbH, Pforzheim, Germany). Using this cast, the cleft is filled completely with dental wax and the approximate shape of the velar extension is modeled from dental wax as a negative and is attached dorsally to the plaster cast. Using this mold, a prototype of the appliance is produced using an acrylic material (autopolymerizing methylmethacrylate, Orthocryl, Dentaurum, Pforzheim, Germany). This prototype consists of a palatal part that covers not only the alveolar ridges, but also the cleft and a velar extension of approximately 3 cm in length. The length and the angle of the velar extension are chosen so that it is adjacent to the dorsum of the tongue. It is always made in a dark color (blue or green) in order to facilitate endoscopic evaluation. After polymerization, this prototype is polished using standard techniques (Fig. 11).

Infants then have a nasopharyngeal endoscopy to assess the type of UAO and to adjust the length and angle of the velar extension. Final adaptation of the spur is done by additive or subtractive methods. Each modification of the velar extension of the prototype is followed by a repeat endoscopy. The tip of the extension has to descend down to the epiglottic vallecula. The angulation of the spur is responsible for anterior shifting of the tongue and the erection of the epiglottis, which opens the airway (Fig. 8*B*). If the airway appears endoscopically and clinically open, the prototype is completed. A security wire is incorporated into the extension to safeguard the device against mechanical failure. Furthermore, extra-oral wires are added to improve retention of the plate and to counteract the force of the tongue (Fig. 9). After that step, the TPP can be delivered to the patient.

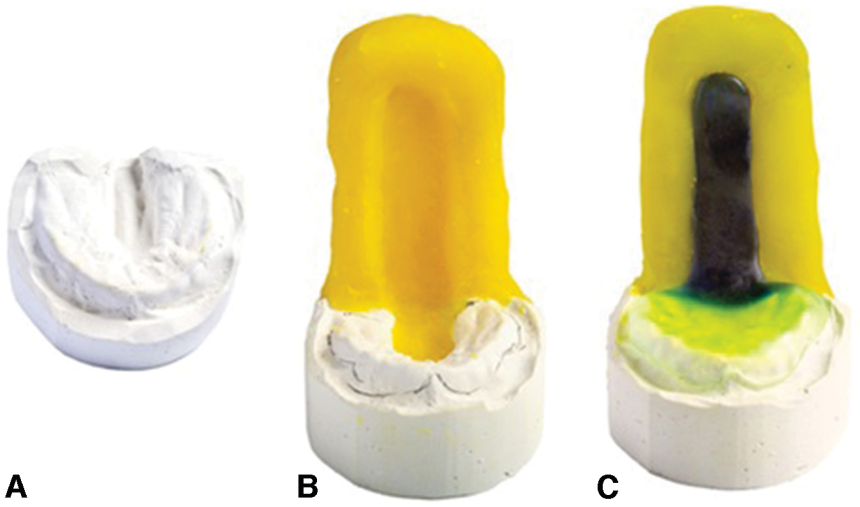

Figure 11. Fabrication of a prototype II. *A:* Plaster cast. *B:* Mold for prototype. *C:* Prototype.

Treatment with TPP

In neonates and during the first three months of treatment, appliances should be worn 24 hours per day and removed only for cleaning purposes. The appliance is held *in situ* by adhesion and suction and with the aid of an adhesion cream (Blend-a-dent Super Haftcreme, Procter & Gamble, Schwalbach, Germany) to improve retention. The extra-oral bows are fixed to the face with adhesive tapes (Steri-Strip and Cavilon-No Sting Barrier Film, Steri-Strip Compound Benzoin Tincture, 3M Health Care, St. Paul, MN). The earlier treatment is started, the easier the plate is accepted by the infant; this means that the ideal start of treatment is during the neonatal period. In general, these plates have to be worn approximately three to six months depending on the results of the polygraphic recordings. In some patients, TPP can be substituted after only three months of treatment with a palatal plate without a spur, but with a stimulation knob for the tongue on the anterior part of the palatal plate.

In most cases, a new plate is necessary after three months during infancy or if a notch appears on the alveolar ridges due to a too-small palatal part of the plate or if respiration deteriorates. After discharge, patients are seen at intervals of six to eight weeks at the orthodontic department in order to control the fit of the plate.

Feeding and Functional Therapy

Treatment with TPP has to be supplemented with an intensive feeding training. In general, the plates are worn during feeds. Feeding is started with “finger feeding” (Fig. 12). If after several days the tongue is in a more ventral position, a nursing bottle that allows control of milk flow during sucking is used (Playtex Drop-Ins, Playtex Products, Edgewell, North Bergen, NY).

Treatment also comprises a Manual Orofacial Regulation Therapy according to Castillo Morales®.[68] This kind of treatment originally was developed for children with Down’s syndrome and involves stimulation of the orofacial musculature. It is delivered by a speech therapist and the parents are taught to do it by themselves. Patients have two of these treatment sessions daily.

Timetable of Treatment

This treatment concept requires an interdisciplinary team consisting of an orthodontist, pediatric sleep specialist, speech therapist familiar Manual Orofacial Regulation Therapy, pediatrician trained in nasopharyngeal endoscopy, maxillofacial surgeon, dental technician and an experienced nursing team.

After admission to the NICU, respiration and feeding are secured. In most cases, a nasopharyngeal airway and a feeding tube are used until the onset of TPP treatment.

First night: infants undergo a baseline sleep study in order to assess the severity of UAO.

Second day: the imprint is taken and the prototype of the TPP is manufactured in the dental laboratory. A nasopharyngeal endoscopy is

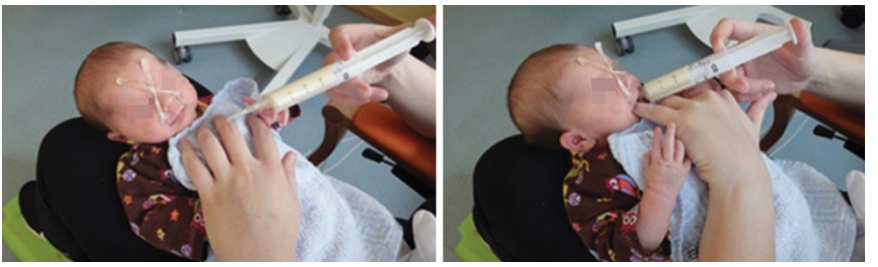

Figure 12. Finger feeding with TPP *in situ*. Photographs used with parental permission.

undertaken in order to assess the type of obstruction according to the Sher classification and, in a second step, the spur of the prototype is adjusted in length and inclination.[61] The prototype is returned to the dental laboratory for completion. In general, the TPP is incorporated in the evening of the same day.

Third day: feeding training is started—first with finger feeding and then with a Playtex bottle some days later—and the Manual Orofacial Regulation Therapy starts as well.

Forty-eight hours after uneventful treatment with the TPP (no impression marks, good tolerance of the plate), a second sleep study is undertaken in order to assess the effectiveness of the plate. If the parameters of the sleep study still indicate OSA, the TPP has to be modified and another mandatory sleep study is performed 48 hours later. Afterward, parents are trained in handling the plate (Fig. 13), applying the

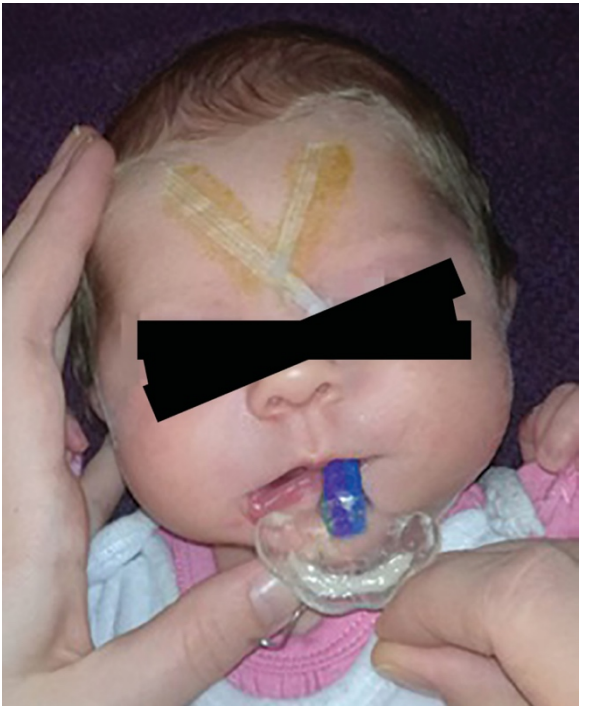

Figure 13. Application of the TPP by a parent. Photograph used with parental permission.

functional treatment and feeding. In general, infants are discharged from the NICU after eight to fifteen days. A control sleep study is undertaken three months after discharge. Cleft palate repair is performed at the end of the first year of life, but only if the sleep study and facial profile are normal.

SCIENTIFIC EVALUATION OF THE TREATMENT CONCEPT

The functional treatment concept presented in this chapter for infants with isolated PRS was evaluated in several studies and its effectiveness and safety are shown.[69-72]

The aim of the first study was to show the effect on UAO of the TPP compared with that of a conventional palatal plate without a velar extension. An RCT with a crossover design and two study groups was conducted. Eleven infants with isolated PRS and OSA were included. Their median age was three days (range 0 to 60 days). Study group 1 received conventional palatal plates first (phase 1) followed by TPP (phase 2); study group 2 received TPP first (phase 1), followed by conventional palatal plates (phase 2). All infants wore each appliance for at least 36 hours before the effect on UAO was assessed with a sleep study. The treatment outcome parameter was MOAI. There was a significant decrease in the MOAI from baseline to the end of the TPP phase in all children ($p = 0.0007$), but no such change was observed for conventional palatal plates in both study groups. With ANOVA, a statistically significant difference in the change of MOAI by treatment modality was found ($p = 0.004$). The relative change (95% CI) in MOAI compared with baseline was 8% for conventional palatal plates and 71% for TPP. Furthermore, no severe side effects were observed.[69] It can be concluded that TPP seems to be safe and effective in reducing UAO in infants with isolated PRS.

In a further prospective, observational study, 15 infants with PRS and OSA were treated with TPP. Sleep studies were undertaken on admission before treatment onset with TPP, at discharge and after three months. Compared with admission, there was a significant decrease in the MOAI at the time of discharge and three months later ($p < 0.0001$). Feeding also was evaluated in this study. Feeding tubes were removed in all children prior to discharge and significant weight gain was observed for both comparisons ($p < 0.001$).[70] No severely adverse effects

occurred. The conclusion was that this treatment modality is safe and treats OSA in infants with isolated PRS.

Additionally, this functional treatment concept—which consists of the TPP, functional treatment according to Castillo-Morales® and feeding training—was evaluated in a longitudinal but single center study with more than 100 infants with isolated PRS over a period of ten years.[71] Sleep studies were conducted before treatment with TPP, after fitting the plate and three months after discharge. Weight gain also was evaluated (z-scores). It was concluded that this functional treatment approach improves respiration ($p < 0.001$) and weight gain ($p = 0.02$) significantly. Furthermore, feeding improved and a decrease of infants requiring nasogastric tube feeding—66% at admission to 8% at discharge—was observed. None of the infants included in the study required tracheostomy and no severe adverse events (e.g., bleeding, systemic infection or aspiration) were observed. All infants tolerated the therapeutic procedures well.

This treatment concept has proven its effectiveness for airway obstruction and feeding problems in infants with isolated PRS in a prospective multi-center cohort study in Germany.[72]

CONCLUSIONS

The TPP in conjunction with a Manual Orofacial Regulation Therapy according to Castillo-Morales®, along with feeding training, improves respiration by reducing the frequency of mixed and obstructive apneas during sleep. Furthermore, this treatment concept normalizes tongue position and function, and facilitates bottle feeding, thereby improving weight gain.

This treatment concept appears to induce at least a partial catch-up growth of the mandible and, therefore, can be considered as a causal treatment of UAO in these patients in contrast to CPAP and tracheostomy. The treatment concept presented here can be considered as a non-invasive, causal and effective option for infants with isolated PRS, which may help to avoid more invasive treatments.

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ORTHODONTIC CARE FOR PATIENTS WITH CRANIOSYNOSTOSIS: GENERAL GUIDANCE AND A CASE REPORT

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ABSTRACT

The functional and structural complexities accompanying craniosynostosis make dental and orthodontic care for these patients particularly challenging. Optimal diagnosis, treatment and management can be accomplished only by a multi-disciplinary specialty team that provides comprehensive interdisciplinary care. The first multi-disciplinary effort to develop parameters for caring patients with craniosynostosis was made in 2010; the first clinical guidance was published in 2011. In this guidance, medical focus and a brief description of interventions are listed and all the key interventions relevant to each of the disciplines are grouped and described precisely based on the age of child with craniosynostosis. Subsequently, the dentofacial working group published an article in 2012 titled, *Parameters of Care for Craniosynostosis: Dental and Orthodontic Perspectives.* Timing and types of dental and orthodontic interventions were recommended. It is essential for dentists and orthodontists to understand dentofacial deformities and problems of the patients with craniosynostosis: hypoplastic maxillary in sagittal, vertical and transverse dimensions; severe crowding on maxillary arch; delayed eruption; periodontal problems; and abnormal dental anatomy. We report a case of multi-disciplinary intervention for a seventeen-year-old male with a history of craniosynostosis and multiple comorbidities, presently undergoing growth hormone therapy, who sought comprehensive orthodontic treatment. The patient was diagnosed with an Angle Class III anterior open-bite malocclusion secondary to bi-maxillary skeletal discrepancy and was treated successfully with comprehensive orthodontics in conjunction with multiple orthognathic surgical procedures. Providing optimal patient care for patients often requires collaboration among multiple specialties in medicine and dentistry.

KEY WORDS: craniosynostosis, multi-disciplinary care, orthodontics, orthognathic surgery, parameters for care

INTRODUCTION

Craniosynostosis is a medical condition in which one or multiple cranial sutures fuses prematurely in an infant skull. Normal cranial sutures separate the skull bone plates and enable rapid growth of the skull, which is dictated largely by growth of the brain.[1-5] Therefore, craniosynostosis can be a critical problem for infants as the brain grows rapidly for the first two years of life. If a suture is fused prematurely, normal skull growth is inhibited perpendicular to the affected suture and compensatory excessive growth occurs parallel to the affected suture. If not treated properly in a timely manner, this medical condition can lead to multiple medical complications including elevated intracranial pressure, craniofacial anomalies, obstructive sleep apnea (OSA), neurobehavioral impairment and delayed development.[6,7] Craniosynostosis can be classified as syndromic or non-syndromic; non-syndromic also is referred to as "isolated." Approximately 40% of all craniosynostosis is syndromic and 60% is non-syndromic (isolated). Of the syndrome types, Crouzon and Pfeiffer are the most common, followed by Mueunke and Apert syndromes.[8] Although 60% of the patients diagnosed with craniosynostosis are non-syndromic, this condition can occur in association with more than 200 different syndromes.[9] Physical findings in craniosynostosis may include a brachycephalic skull shape, circumorbital retrusion, midface hypoplasia, malocclusion and developmental delay.[10]

The incidence of this developmental anomaly is estimated to be one in 2,000 to 2,500 live births worldwide.[8,11] Previous investigations have discovered more than 100 mutations in the genes encoding fibroblast growth factor receptors 1, 2 and 3 (FGFR 1-3), muscle segment homebox 2 (MSX2) and TWIST, which have been implicated in the etiopathogenesis of craniosynostosis.[1,12] Craniosynostosis can be caused by epigenetic factors as well.[13] Constraint inside the womb during pregnancy is known to be associated with regulatory gene expressions in bone development. C57B1/6 mice underwent cervical cerclage for fetal constraint. In this animal study, it was claimed that constraint-induced suture fusion was associated with decreased expression of Indian Hedgehog (Ihh) and Noggin, which play important regulatory roles in constraint-induced craniosynostosis.[13] Multiple research groups have found evidence that smoking is responsible for an increased risk of craniosynostosis, whereas drinking alcohol has no association with de-

velopment of craniosynostosis.[14-17] Hyperthyroidism also can be another cause, as high levels of thyroid hormone leads to faster skeletal maturation resulting in hormone-mediated premature closure of sutures.[18]

CLINICAL GUIDANCE DEVELOPED FOR CARE OF PATIENTS WITH CRANIOSYNOSTOSIS

The first multi-disciplinary effort to develop parameters for caring for patients with craniosynostosis was made in Atlanta, GA from March 4-6, 2010. The National Foundation for Facial Reconstruction hosted the meeting for the craniosynostosis working group. This multidisciplinary meeting was called *Craniosynostosis: Developing Parameters for Diagnosis, Treatment and Management.*[8] Fifty-two conference attendees from sixteen different medical/dental specialties reviewed the current state of knowledge based on the literature or their clinical experiences. The specialty fields of the attendees included anesthesiology, craniofacial surgery, dentistry, orthodontics, genetics, hand surgery, neurosurgery, nursing, ophthalmology, oral and maxillofacial surgery, otolaryngology, pediatrics, psychology, public health, radiology and speech/ language pathology. During this meeting, the attendees reviewed the current state of knowledge in craniosynostosis; draft recommendations were presented by each of the attending disciplinary groups. After discussion among the sub-group participants and incorporating the feedback into the draft recommendations in an iterative manner, the edited draft documents were reviewed by all the participants. Subsequent revisions were made by the committee in response to each of the specialty society reviewers' feedback and the final draft document was ratified by the participants. One year after this meeting, the craniofacial working group published the article titled *Parameters of Care for Craniosynostosis* in the Cleft Palate Craniofacial Journal.[8] This article consists of two parts: "Overview of Key Interventions by Age" and "Evaluation and Treatment Parameters." An ideal management of craniosynostosis requires early intervention from the perinatal stage and coordinated care in a timely manner is essential. In "Overview of Key Interventions by Age," the medical focus and brief description of interventions are listed on the following period of time: prenatal period, birth to three months, four months to three years, four to eight years, nine to twelve years, thirteen to seventeen years and eighteen years to adulthood. In "Evaluation and Treatment

Parameters," all the key interventions relevant to each of the disciplines are grouped and described precisely, though the authors emphasize that all the procedures are not necessarily required for every patient, as each patient's care needs to be planned individually according to his/her medical, dental and psychosocial conditions. This consensus clinical manual provides detailed clinical guidance in these conditions of the patients with craniosynostosis and recommends state-of-the-art, interdisciplinary team assessments and interventions.

Patients with craniosynostosis typically have unique oral health conditions and abnormal craniofacial growth problems. It is important, therefore, to have dental and orthodontic considerations for comprehensive, multi-disciplinary and long-term care. Two years after the first multidisciplinary conference (2010), the dentofacial working group published an article titled *Parameters of Care for Craniosynostosis: Dental and Orthodontic Perspectives.*[10] General recommendations by the child's age were suggested as follows. From birth to six years, no direct orthodontic intervention may be needed; rather, anticipatory monitoring is recommended on the patient's craniofacial growth and dental development. It is noteworthy that no direct orthodontic intervention is deemed necessary at this stage, whereas patients with cleft lip and palate typically need surgical repair of cleft lip and/or palate at this early stage. During mixed dentition stage, phase I orthodontic treatment can be indicated (e.g., active eruption guidance and space maintenance). Once phase I treatment is completed, proper retention needs to be planned until phase II treatment initiates. If indicated, dentists and orthodontists should start communicating with the surgeon for any potential surgical treatment required. Once the patient is in the permanent dentition stage, orthodontists need to communicate with multiple dental specialists including the pediatric dentist, periodontist, prosthodontist and oral surgeon. Long-term follow-up is recommended for retention. We advocate that timing and type of interventions may vary, as clinical decisions need to be made on an individual basis.

Dentofacial Deformities of Patients with Craniosynostosis

Normal maxillary growth takes place by sutural growth around the maxilla including the median suture. This leads to downward and forward displacement of the maxilla, which is called "primary displacement of the maxilla." Additionally, growth of the cranial base contributes to

downward and forward displacement of the maxilla, which is called "secondary displacement of the maxilla." Dentofacial anomalies associated with syndromic craniosynostosis are related to premature fusion of the sutures resulting in the maxillary hypoplasia in sagittal, vertical and transverse dimensions.[19,20] Therefore, in many cases, the orthognathic surgical intervention should be planned in conjunction with the orthodontic treatment. Maxillary hypoplasia also can lead to skeletal discrepancy between the maxilla and mandible, delayed eruption and severe crowding in the maxillary arch.[19-22] Constricted maxillary growth and the associated upper airway restriction may lead to mouth breathing, dry mouth, gingival inflammation and possibly excessive open bite.[19,22,23] Compared to normal individuals, craniosynostosis patients' dental development is delayed by at least one year, which often results in delayed eruption and abnormal eruption pattern of permanent teeth.[21] Multiple dentofacial findings described above (e.g., dental malocclusion, skeletal discrepancy, crowding and gingival swelling) tend to worsen during growth and adequate orthodontic treatment could reduce the worsening.[22] Abnormal dental anatomy and tooth size also were reported.[19,20]

Diagnosis, treatment and management of craniosynostosis can be challenging; therefore, optimal care can be accomplished only by a team of dental and medical specialists including general/pediatric dentistry, orthodontics, oral and maxillofacial surgery, neurosurgery, plastic surgery, anesthesiology, otolaryngology, ophthalmology, endocrinology, pediatrics, genetics, social work and speech/language pathology.[8]

CASE REPORT

We present a case of multi-disciplinary intervention for a patient who was diagnosed with craniosynostosis involving multiple cranial sutures and comorbidities.

Medical and Dental History

A seventeen-year-old Asian male presented to the Department of Orthodontics, College of Dentistry & Dental Clinics at the University of Iowa with a chief complaint of "my teeth don't touch in the front." The patient's past medical history included craniosynostosis with multiple cranial sutures prematurely fused, Albright's hereditary osteodystrophy

(AHO), amblyopia, hypothyroidism, ventricular septal defect (VSD) and developmental delay. His elder sister, who passed away eight month after birth due to post-surgical complications, also had been diagnosed with craniosynostosis, VSD and hypothyroidism. The patient reported no history of allergies or reactions to any medications and had no symptomatic temporomandibular joint (TMJ) problem. Since infancy, he had received comprehensive care with the Cleft Palate Craniofacial Anomalies Team at the University of Iowa Hospitals & Clinics and the College of Dentistry & Dental Clinics. The patient's family established his dental home at the Department of Pediatric Dentistry where he received all aspects of primary and comprehensive preventive and therapeutic oral health in a continuously accessible, coordinated and family-centered manner. Due to poor oral hygiene and high-caries risk, the patient's individualized preventive oral care during his teenage years consisted of patient education, motivation for daily oral hygiene, diet control, three-month recalls with 5% sodium fluoride varnish applications at each visit, sealants of pits and fissures, and brushing twice daily with 5,000 ppm fluoride toothpaste.

Clinical Evaluation

At seventeen years of age, the patient was in need of complete facial balancing to treat the facial sequelae of this craniosynostosis and Albright osteodystrophy. A multi-disciplinary approach was used to treat his upper face, midface and both jaws.

Facial analysis indicated a flattened and irregular forehead due to partial resorption of the frontal bone that underwent multiple operations. His ocular protection was adequate, but he had a flat brow, an asymmetric midface with asymmetric alar groove on nose, malar deficiency, a straight profile with long lower anterior facial height, lip strain on closing mouth (i.e., interlabial gap at rest), maxillary cant and inadequate incisal display on smile (Fig. 1).

The dental diagnosis was Angle Class III malocclusion secondary to maxillary skeletal hypoplasia and mandibular skeletal hyperplasia, anterior open bite to molars, anterior cross bite with negative overjet and bilateral posterior cross bite (Fig. 2). Mandibular incisors were retroclined due to dental compensation (Fig. 2). Upper dental midline was deviated to left of facial midline by 2 to 3 mm (Fig. 1). The maxillary arch had 2 mm space and the mandibular arch had 1 mm crowding. Maxillary lateral in-

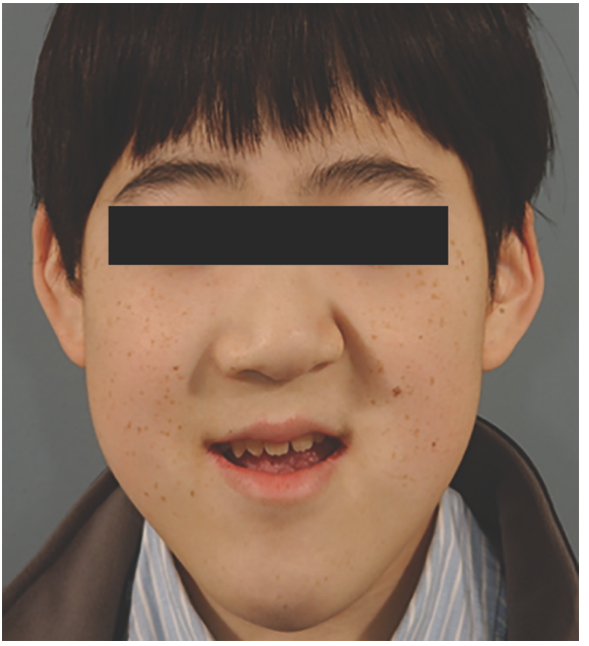

Figure 1. Initial extra-oral photo on facial front smiling.

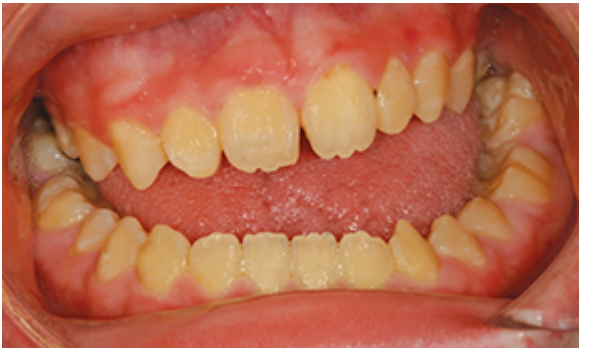

Figure 2. Initial intra-oral photo on dental front at maximum intercuspation.

cisors were smaller in size compared to the normal ones (Fig. 2). All 3rd molars were missing and the maxillary left 2nd molar (#15) was impacted. Lateral cephalometric radiograph indicated maxillary skeletal hypoplasia and mandibular skeletal hyperplasia, steep mandibular plane and long lower anterior facial height.

Treatment Objectives

Treatment objectives were to achieve normal orthognathic profile and ideal dental occlusion with normal overjet, normal overbite, Angle Class I molar relationship and Angle Class I canine relationship.

Treatment Plan and Sequence

To increase the width of maxillary arch, a rapid maxillary expander (RME) was bonded. After activating the RME appliance by 8 mm (0.25 mm/day for one month), maxillary intermolar width was increased by 3 to 4 mm without splitting the midpalatal suture. All dentition was bonded with Edgewise orthodontic appliances (0.022" x 0.028"). Maxillary and mandibular arches were leveled and aligned. Impacted maxillary left second molar (#15) was extruded gradually using elastic thread and leveled to the rest of the maxillary dentitions. One year after orthodontic treatment, the progress radiograph revealed that the patient's mandibular prognathism became larger due to the growth hormone treatment (Fig. 3). After discussion with the patient's endocrinologist and oral surgeon, growth hormone therapy was ceased twelve months prior to the orthognathic surgeries.

Multiple orthognathic surgeries were performed to correct his skeletal discrepancies. Maxillary distraction osteogenesis was performed for the correction of maxillary retrognathism. The maxilla was downfractured with a standard LeFort I osteotomy. Then, internal maxillary distractors were placed bilaterally to the zygomaticomaxillary buttress. The distractors were activated and the maxilla was distracted incrementally toward an anterior direction for four weeks (Fig. 4*A*). Seven weeks after the completion of the maxillary distraction, the previous osteotomy sites were noted to be healing without signs of non-union and the maxillary internal distractors were removed. On the same operation date, two surgical procedures were performed on the mandible: bilateral sagittal split osteotomy (BSSO) for a mandibular setback of 6 mm and genioplasty for vertical reduction of 4 mm. One year after the mandibular BSSO, maxillary repositioning surgery was done (Fig. 4*B*). The maxilla was downfractured carefully and appropriate bone was removed to allow anterior repositioning of 3 mm and a differential impaction to close a residual open bite and obtain coincident dental midlines (Fig. 4*B*). Malar implants were placed bilaterally to augment and balance his asymmetric midface (Fig.

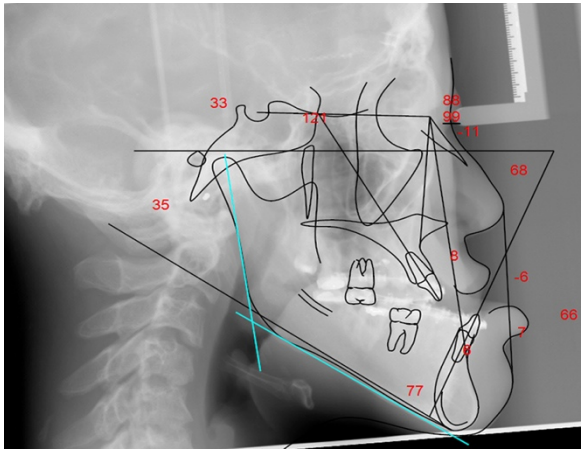

Figure 3. Pre-surgical progress; lateral cephalometric x-ray with tracing.

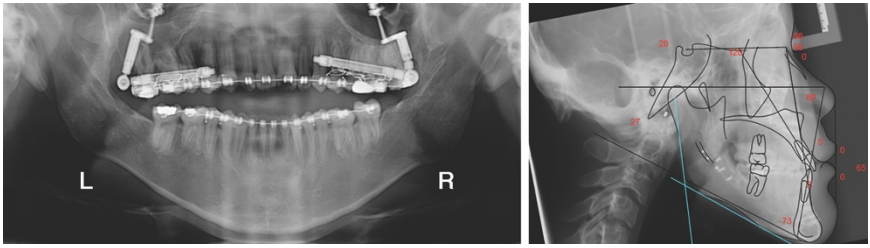

Figure 4. *A:* Post-surgical pantomograph that shows internal distractor. *B:* Post-surgical lateral cephalometric x-ray with tracing.

4*B*). After detailing occlusion with finishing bends on the orthodontic fixed appliances, the case was debanded and fixed retainers were bonded on maxillary and mandibular anterior teeth.

Treatment Outcome

Following orthodontic treatment in conjunction with orthognathic surgery, an Angle Class I canine/Class I molar relationship, an ideal overjet and overbite were achieved (Fig. 5). Buccal overjet of posterior teeth was within a normal range. Alveolar bones of the maxilla and the mandible were coordinated well in all three dimensions. The soft tissue profile remained straight and long, but was improved significantly after the treatment. Nasal dorsum remained diminished on the left side; however, maxillary retrognathism and mandibular prognathism were improved significantly (Fig. 6). Upper and lower lips were closed at rest with-

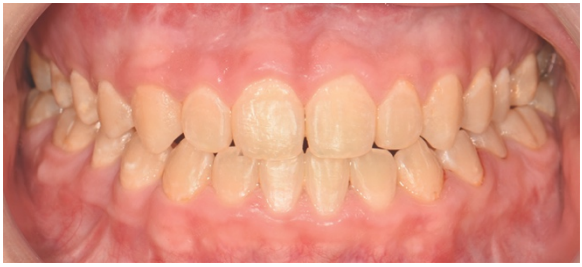

Figure 5. Final intra-oral photo on dental front at maximum intercuspation.

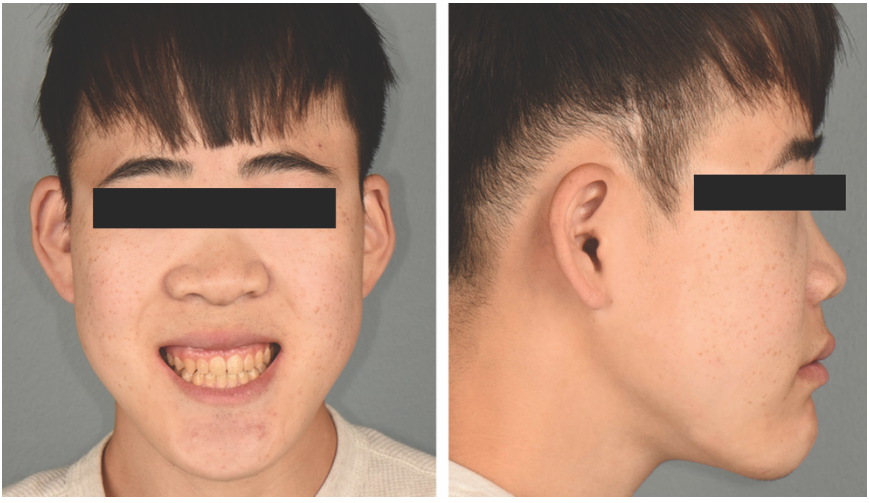

Figure 6. *A:* Final extra-oral photo on facial front smiling. *B:* Final extra-oral photo on profile.

out an interlabial gap (Fig. 6*B*). Asymmetry of the midface decreased and both soft tissue and skeletal chin projections changed to within a normal range.

At age 21, the patient transitioned to a general dentist who was knowledgeable and comfortable in managing the patient's specific disabilities and oral healthcare needs. The patient and his family considered future plastic surgeries for improving his midface and forehead.

DISCUSSION

Due to the complexity of functional and structural abnormalities, care for patients with craniosynostosis can be complicated. Optimal

diagnosis, treatment and management can be accomplished only by a multi-disciplinary specialty team providing comprehensive interdisciplinary care.[4,8,11] In this chapter, we reported an example case of a patient with craniosynostosis who had been treated by a multi-disciplinary team for a long period of time. For more than 20 years, the Cleft Palate and Craniofacial Anomalies Team at the University of Iowa has been dedicated to providing comprehensive dental and medical care for this patient. The patient in Figure 5 received his first cranial vault expansion surgery at age of three months and completed his comprehensive orthodontic treatment at 22 years of age. Clear communication among clinicians from other specialties was crucial during this long-term, multidisciplinary care.

Pediatric and/or general dentists who are part of the multi-disciplinary team of patients with special healthcare needs have to be aware of the patients' increased risk of developing dental caries and periodontal diseases, as well as the need to provide appropriate preventive and therapeutic dental care in a timely manner.[3] The patient in this case report presented with severe malocclusion, which became worse with condylar growth stimulated by growth hormone therapy. Due to this severe malocclusion, he suffered from chewing difficulties and mouth breathing, which led to reduced salivary flow and dry mouth. This patient did not manifest maxillary marginal gingivitis, in spite of mouth breathing, nor any periodontal issues at any point during this treatment as he maintained optimal oral hygiene and was compliant with his periodontal maintenance appointments in the Pediatric Dentistry Department at the University of Iowa. The general dentist or pediatric dentist, as a part of the multi-disciplinary team, needs to be aware of the patient's high risk of oral diseases and provide appropriate primary dental care or referral in a timely manner.

In general, the team for patients with craniosynostosis should embrace a patient-centered care approach. Consensus documents with parameters of care were published by craniosynostosis working groups, in which they detailed the multiple physical, functional and developmental characteristics, as well as the management needs of patients with craniosynostosis.[4,8,10] However, they did not mandate timing or a specific type of any dental/medical procedure due to variations in each patient's conditions, as well as different treatment protocols of various interdisciplinary teams. Therefore, it is essential for the interdisciplinary team to

take the patient's specific conditions into account and also accept the family as an equal partner in making patient-centered, personalized treatment decisions.[5,24,25] For example, we understood that the patient and his family were willing to continue receiving growth hormone therapy for his stature growth improvement. Timing of orthodontics/orthognathic treatment was coordinated accordingly so that the patient could benefit from the growth hormone therapy. It also was anticipated that hormone therapy would affect condylar growth and resulted in increased dental and skeletal Class III relationships. Maxillary distraction osteogenesis was performed rather than a LeFort I osteotomy so that the large maxilla-mandibular discrepancy could be corrected.[26,27] This case demonstrates that timing and type of procedures can be tailored to assure the satisfaction of the patient/family, as well as quality of the care.

CONCLUSIONS

In this chapter, craniosynostosis and clinical guidance developed for the care of patients with craniosynostosis was reviewed. In addition, successful care for a patient with craniosynostosis and multiple comorbidities was reported. Resultant improvement in appearance and function of the patient's craniofacial and dental structures, along with his emotional confidence, attests to the importance of multi-disciplinary team care for patients with multiple medical and dental complications.

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FACTORS TO MAXIMIZE FACIAL PROFILE IMPROVEMENTS IN HYPERDIVERGENT PATIENTS USING MICRO-IMPLANTS

Hyo-Sang Park

ABSTRACT

In the treatment of severely hyperdivergent patients, the counter-clockwise auto-rotation of the mandible after intrusion of the posterior teeth has an essential role in improving the facial profile. The many factors that affect facial profile changes include intrusion of the upper posterior teeth, anteroposterior cant of the occlusal plane, bodily retraction of the upper incisors, intrusion of the upper incisors, intrusion of the lower posterior teeth, vertical position of the lower incisors and, most importantly, coordination of movement at the upper and lower posterior teeth and the upper and lower incisors. This chapter discusses the considerations to maximize facial profile changes and demonstrates treatment of a case with profound facial profile improvement after intrusion of the upper and lower molars, bodily retraction and intrusion of the upper incisors, and retraction and intrusion of the lower incisors using micro-implants.

KEY WORDS: micro-implants, hyperdivergent patients, profile changes

INTRODUCTION

The development and use of micro-implants have brought about significant changes in orthodontic treatment. The first important change is that the tooth movement is possible in all three dimensions without adverse side effects on anchorage or reactive components. Another important aspect is that tooth movement can be controlled precisely and teeth can be moved to a specific target goal using skeletal anchorage.

The first experience in my career using skeletal anchorage was distalization of the entire maxillary dentition after space closure of extraction sites; this introduced the concept that a micro-implant could provide anchorage for anterior teeth retraction without anchorage loss

at the molars.[1] The micro-implant has been used mainly for anchorage for retraction of anterior teeth in bialveolar protrusion treatment requiring maximum retraction of the anterior teeth.[2,3] The micro-implant also has been used for distal retraction of the entire arch, intrusion of a tooth or teeth and in openbite treatment after intrusion of the posterior teeth.[4-10] In addition, the micro-implant was used more efficiently in correction of mesially tipped molar, impacted canine and scissor bite.[11-13]

With conventional orthodontic treatment, intrusion of the posterior teeth is considered difficult, if not impractical. However, with the use of micro-implants, intrusion of posterior teeth has become a more common and predictable treatment option often with significant increase in the amount of tooth movement achieved. There have been many case reports and studies to evaluate treatment effects after the intrusion of the posterior teeth.[14-16] Even after intrusion of the posterior teeth in either the maxillary or mandibular arches, the facial profile changes occasionally were less than desirable. An alternative treatment option for hyperdivergent patients is orthognathic surgery including maxillary surgical impaction and mandibular advancement with or without genioplasty. The intrusion of the posterior teeth in both arches produces auto-rotation or counter-clockwise rotation of the mandible, which can result in profound change of the facial profile potentially eliminating the need for maxillary impaction surgery.

In this chapter, factors that affect facial profile changes will be discussed using data from analysis of hyperdivergent and long face patients treated with micro-implants and intrusion mechanics. In addition, a case with profound changes in facial profile after retraction of the anterior teeth and intrusion of the posterior teeth will be illustrated.

SKELETAL AND DENTAL CHARACTERISTICS OF HYPERDIVERGENT PATIENTS

The skeletal characteristics of severe hyperdivergent patients include high mandibular plane angle, retropositioned mandible, upcanted palatal plane and long lower anterior facial height. The dental characteristics are mesially tipped molars, long anterior alveolar height and divergent upper and lower functional occlusal planes. Therefore, the treatment of hyperdivergent Class II patients should include coun-

ter-clockwise rotation of the mandible to move the chin forward after intrusion of the posterior teeth, as well as retraction of the anterior teeth.

Facial Profile Changes

Regarding improvement of the facial profile, the two areas of concern are maxillary and mandibular changes. Distal movement of A point can be obtained by bodily retraction of the upper anterior teeth.[17] Even though the upper anterior teeth are retracted, A point would not move distally with tipping movement of the upper incisors. Mandibular changes are more important in improving facial profile than changes in the maxilla. The patient in Figure 1 did not show much change in the upper lip position even with distalization of the upper incisors; however, changes in the lower lip and soft-tissue menton was more pronounced, which profoundly influenced the patient's profile. Therefore, changes in lower lip and menton might be more important than the maxillary changes when facial profile is considered.

If patients have a significant interlabial gap at rest, they typically need to use the mentalis muscle when closing their lips. This strain at the mentalis muscle produces a poor-looking appearance. The key to improving the facial profile in hyperdivergent patients is to release this muscle activity by reducing the vertical distance at the level of the hard tissue (Fig. 2). This reduction can be performed in two ways: retraction of the anterior teeth and reduction of the vertical dimension. Both methods can reduce distance of the hard tissue (Fig. 3), but the reduction of the vertical dimension may produce more profile changes by decreasing the vertical dimension. The profile can be improved dramatically when the hyperactivity of mentalis muscle is eliminated by decreasing in vertical distance with counter-clockwise movement of the mandible.

Factors Affecting Profile Changes

The first factor to consider in decreasing the vertical dimension is with the intrusion of the maxillary posterior teeth, which results in counter-clockwise rotation of the mandible and forward movement of chin. Even after intrusion of the maxillary posterior teeth, however, some patients did not show profile changes and a decrease in vertical dimension. With clinical experience and after treating many patients, other factors that affect the rotation of the mandible and subsequent pro-

Figure 1. In hyperdivergent Class II patients, profound profile changes can be obtained not by upper lip changes, but by soft-tissue changes on the mandible.

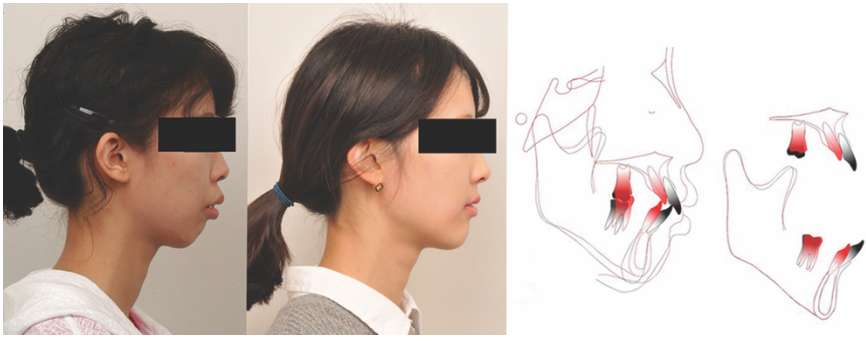

Figure 2. Facial profile changes by eliminating mentalis hyperactivity after retraction of anterior teeth and reduction of vertical dimension. Black line = pre-treatment; red line = post-treatment.

file changes in severely hyperdivergent patients are presented.[18,19] Factors to consider are:

1. *Extrusion of the lower posterior teeth should be prevented.* Although the intrusion of the upper posterior teeth is the first consideration for counter-clockwise rotation of the mandible, extrusion of the posterior teeth can occur occasionally during intrusion of the upper posterior teeth, which may result in no change of the vertical dimension. Therefore, extrusion of the lower posterior teeth should be monitored and mandibular posterior micro-implants

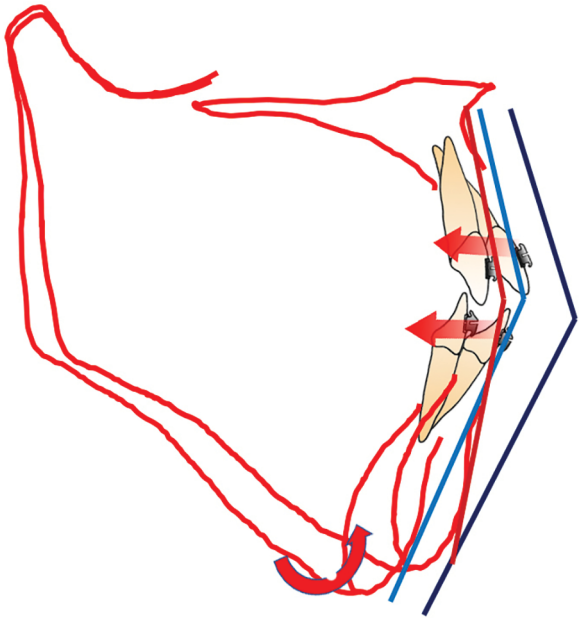

Figure 3. Two methods to reduce hard-tissue distance: retraction of the anterior teeth and reduction of vertical dimension.

should be used to hold the vertical position of the lower posterior teeth.

2. *The anteroposterior cant of the occlusal plane should be minimized.* The large amount of intrusion of the upper posterior teeth with subsequent lingual tipping of the upper anterior teeth can make the occlusal plane steep. Steepness of the occlusal plane restricts the amount of counter-clockwise auto-rotation of the mandible. In order to prevent this, intrusion of the upper anterior teeth needs to be considered when large intrusion of the upper posterior teeth is required. Even in patients with anterior openbites, the upper anterior teeth need to be intruded when a large intrusion of the upper posterior teeth is required in order to correct the steep occlusal plane. The counter-clockwise rotation of the mandible after intrusion of the posterior teeth will not produce contacts at the upper and lower incisors

in openbite patients, but may cause contacts at the incisors in normal overbite patients. These contacts restrict the counter-clockwise rotation of the mandible. Therefore, in order to provide space for auto-rotation of the mandible, the intrusion of the upper anterior teeth needs to be considered.

3. *The upper anterior teeth should be retracted bodily.* The lingual tipping of the upper incisors may move the roots forward and prevent bone remodeling at A point.[17] If the upper incisors are tipped lingually during retraction, the incisal tip of the upper anterior teeth is brought down, which causes contact between incisal tips of the upper and lower incisors, decreasing the closure of the mandibular plane angle or even opening the mandibular plane angle (Fig. 4). This reduces counter-clockwise auto-rotation of the mandible and reduces profile changes. Although slight lingual tipping of the upper anterior teeth can be allowed in cases where the upper incisors are initially in labioversion, the incisal tip of the upper incisors should not be extruded during retraction. In other words, the roots of the upper incisors should be intruded during retraction in order to minimize downward movement of the incisal tip of the upper incisors. Conclusively, bodily retraction is the most suitable movement for the upper incisors.
4. *The lower anterior teeth need to be retracted and intruded to provide space for auto-rotation of the mandible.* The lower incisors are retracted with lingual tipping, which will cause upward movement of incisal tip of the lower incisors and cause incisal contacts. Therefore, the intrusion of the lower incisors can be required to avoid incisal contacts.
5. *In severely hyperdivergent cases, the lower posterior teeth need to be intruded.* As discussed earlier, the amount of intrusion of the upper posterior teeth can be limited because of the antero-posterior occlusal cant and intrusion of the anterior teeth may not be

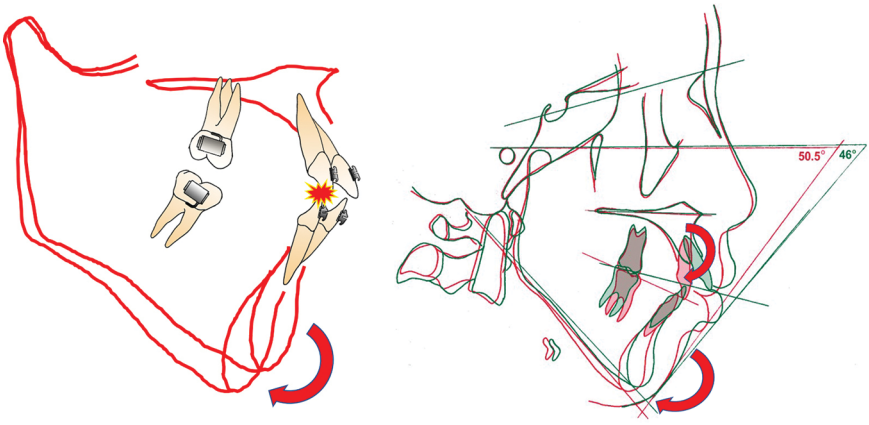

Figure 4. Incisal contacts restrict counter-clockwise rotation of the mandible even after intrusion of molars. Lingual tipping of upper incisors can produce opening of mandibular plane angle due to incisal contacts.

possible due to upper incisor display at rest. In cases where intrusion of the upper teeth is limited, intrusion of the lower posterior teeth should be performed for auto-rotation of the mandible and profile improvement.

6. *The upper and lower posterior teeth and incisor movements must be coordinated.* If the retraction of the upper anterior teeth moves too quickly, this causes incisal contacts and blocks the counter-clockwise rotation of the mandible. The speed of movement at the incisal edge is fast when the upper incisors are retracted with lingual tipping; this also will cause incisal contacts (Fig. 4). The intrusion of the posterior teeth should be coordinated with retraction of the upper and lower anterior teeth and intrusion of the anterior teeth in order to minimize premature tooth contact. The counter-clockwise rotation of the mandible can be obtained at the moment that all four areas of the dentition are moved simultaneously to provide space for this rotation. If at anytime a tooth has premature occlusal contact, auto-rotation of the mandible will not occur in hy-

perdivergent patients. Therefore, the coordination of the movement is of utmost importance.

7. *In the mandibular arch, the extraction of the lower second premolars is better in terms of profile improvement than first premolar extraction (Fig. 5) because protraction of the lower posterior teeth is helpful in reducing vertical dimension by moving the fulcrum forward.*[20] For this response, the mandibular molars should be protracted bodily or with root movement, not with tipping.
8. *The position of micro-implants in the mandibular arch can influence auto-rotation of the mandible.* The micro-implants placed between the first and second molars can produce the counter-clockwise rotation of the lower occlusal plane and the resultant auto-rotation of the mandible can be followed. When profound profile changes are desired, micro-implants need to be placed between the lower second premolars and first molars in order to generate intrusion of the entire lower dentition. This will produce much greater auto-rotation of the mandible and bring about significant changes in the facial profile.

Treatment Mechanics and Procedure

After extraction of the upper first premolars, 0.022" slot straight wire brackets can be bonded. The upper first molars need to be banded in order to insert the removable transpalatal arch (TPA).

Upper micro-implants need to be placed between the upper second premolars and first molars with the recommended vertical position of the micro-implants of 8 to 10 mm from the bracket slots. Immediately after placement of the micro-implants, less than 50 gm of distal force can be applied from the micro-implants to the canines. This is to prevent forward flaring of canines due to built-in tip on canine brackets. Initial wire is a 0.014" or 0.016" nickel titanium (NiTi) wire. The ligature tie should not be used tightly on rotated teeth on anterior segment of the arches; if this happens, the rotated incisors tip labially and will need to be retracted later during space closure phase. The rotated anterior teeth can be corrected after making a space by distal movement of a canine. The

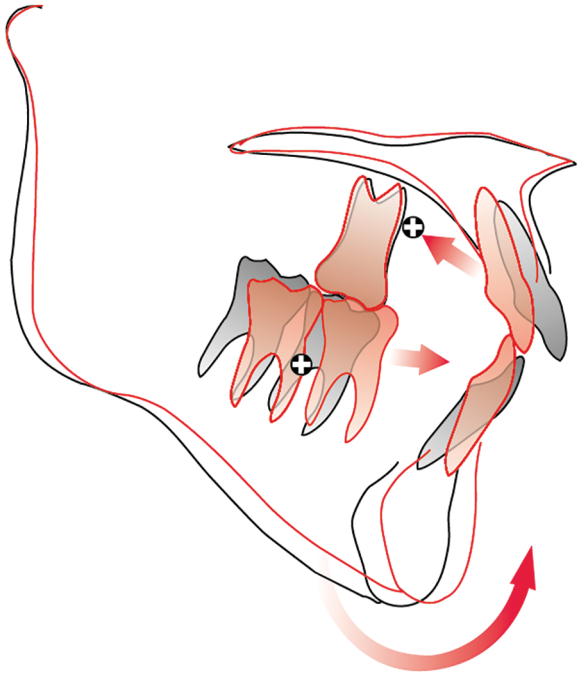

Figure 5. Protraction of the lower molars after extraction of the second premolars can be helpful in closure of the mandibular plane angle.

heavy distal force to canines may produce distal tipping of the canines and resultant vertical bowing. Hence, light force < 50 gm of distal force is sufficient for distal movement of canines with the light NiTi wire.

When fabricating the TPA, space should be given between palatal mucosa and TPA in order to provide space for intrusion of the molars. If the space is too small, frequent adjustment of the TPA is required; if more than 3 mm is given, the TPA can be impinged into the dorsum of tongue. A space of approximately 3 mm and putting acrylic on the loop of the TPA to eliminate tongue impingement and irritation is recommended. With this acrylic button on the TPA, tongue force can act as intrusion force to the molars as well.

The next step in the upper arch is to change the wire to 0.016" x 0.022" TMA wire. Even though incisor alignment is not completed, the wire needs to be switched to TMA wire to prevent side effects, distal tipping of canines and vertical bowing. At this stage, distal force can be applied from the micro-implants to the canines to make space for

alignment of the rotated incisors. For rotation control of the incisors, auxiliary force can be used with square thread or overlay NiTi wire.

Once the anterior teeth are aligned, 0.016" x 0.022" stainless steel (SS) wire can be inserted with hooks crimped between lateral incisors and canines. The length of the hook should be shorter than the vertical height of the micro-implants in order to produce backward and upward force to the anterior teeth. During the retraction of the upper anterior teeth, if there is lingual tipping of the upper incisors, another micro-implant can be placed between upper central incisors to apply intrusion force and prevent lingual tipping of the upper incisors.

In lip protrusion patients with a normodivergent skeletal pattern, the described mechanotherapy and sequence are normal steps for treatment. Hyperdivergent patients, however, require more intrusion of the molars for further improvement of the profile. The intrusion of the upper molars may be interfered by contacts of the molar roots to sinus floor since it is reported that more than 75% of the upper molar roots have contacts with the sinus floor.[21] Therefore, for more intrusion of the upper molars, palatal micro-implants can be placed into the palatal slope between the first and second molars. Because a different amount of intrusion between the right and left molars is not possible with mid-palatal micro-implants, placement of micro-implants into the palatal slope on both sides is preferred. When applying intrusion force to first molars from the palatal micro-implants, the lingual button also needs to be bonded on palatal surface of the upper second molars to apply intrusion force to the second molars.

When intruding the upper molars from palatal micro-implants, the wire needs to be changed to 0.019" x 0.025" SS wire with lingual crown torque on the second premolars. In doing so, buccal and palatal cusps of all upper posterior teeth can be intruded simultaneously and with same amount.

In the mandibular arch, after bonding brackets and leveling, an alignment can be started with 0.014" or 0.016" NiTi wire. The same with the maxillary arch, rotated teeth should be tied lightly so as not to protrude. If lower first premolars are extracted, closing force with square thread needs to be applied between the canines and second premolars. Closing force needs to be applied from the canines to first molars in second premolar extraction cases.

After aligning the lower incisors to the space created by distal movement of canines, 0.017" x 0.025" NiTi and 0.017" x 0.025" TMA wire can be inserted sequentially with hooks crimped between the lateral incisors and canines. Reverse curve of Spee needs to be given to increase distal uprighting or mesial root movement moment on the molars. A power arm needs to be used at the first molars and the force passes the center of resistance of the first molars. Bodily mesial movement of the first molars can move the fulcrum forward, which is helpful to close the mandibular plane angle.

The next wire is 0.017" x 0.025" SS with slight reverse curve of Spee. In the case of severe hyperdivergent patients, micro-implants can be placed between the second premolars and first molars. Distal and intrusion force can be applied to the anterior hooks on the archwire. As the intrusion force can cause buccal tipping of the molars, lingual crown torque needs to be given to the wire on the posterior section. The mandibular micro-implants can be placed between the first and second molars in patients who have less severe hyperdivergency. In order to minimize buccal flaring of the molars and to get a similar amount of intrusion between anterior and posterior teeth, heavy SS wire (e.g., 0.019" x 0.025" SS wire) needs to be used and progressive lingual crown torque should be given on the archwire.

As an example, a hyperdivergent skeletal patient with maximum changes in facial profile after micro-implant treatment is presented.

PATIENT CASE

A 31-year-old female patient with hyperdivergent skeletal pattern with a large mandibular plane angle presented with the chief complaint of protruded lips. She had a severe Class II skeleton with posteriorly positioned mandible. For many, the first option might be orthognathic surgery including maxillary impaction and mandibular advancement with genioplasty; however, treatment with micro-implants was used for this patient.

Extra-oral Findings

Lateral extra-oral photos showed a convex profile with retropositioned mandible. She had long anterior low facial height and showed hyperactivity of mentalis muscle during lip closure (Fig. 6). Upper and low-

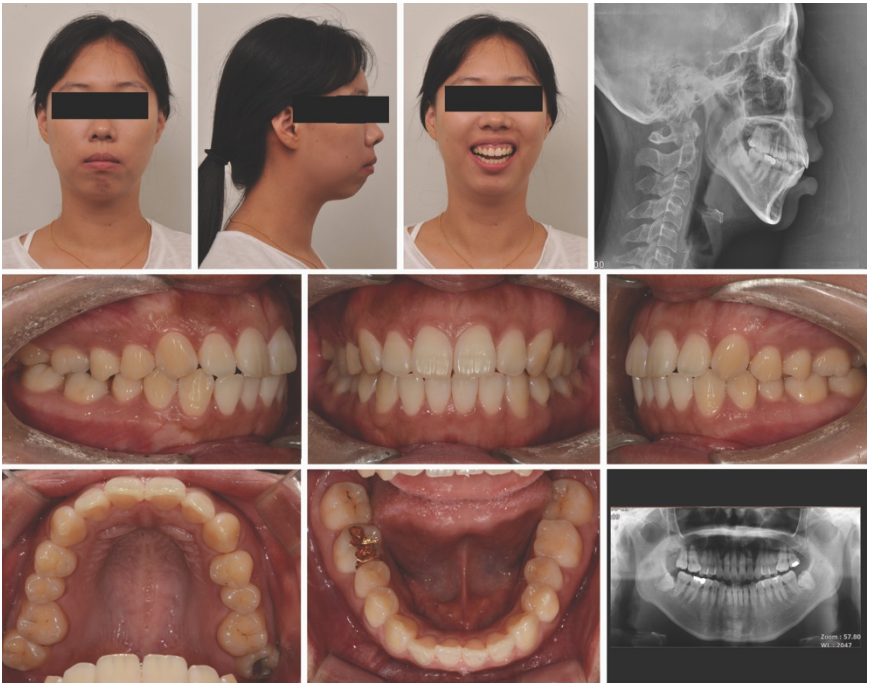

Figure 6. Pre-treatment records of a patient.

er lips were positioned anteriorly from the esthetic line by 4.5 mm and 9 mm, respectively (Table 1).

Cephalometric Analysis and Radiographic Findings

Cephalometric analysis showed that the ANB angle was 8.4° and the FMA angle was 41.2°, demonstrating a dolichofacial pattern with long lower facial height (Table 1). The mandibular anterior teeth were proclined. The patient was diagnosed as having a skeletal Class II malocclusion due to a retropositioned mandible. In a panoramic radiograph, the lower third molars existed and there was no sign of root resorption (Fig. 6).

Intra-oral Findings

The arch length discrepancies were mild, there was -2.0 mm in the maxillary arch, -2.0 mm in the mandibular arch and the curve of Spee

Table 1. Cephalometric measurements.

Measurements	Pre-treatment	12-month treatment	Post-treatment
Skeletal			
SNA	84.2	84	82.8
SNB	75.9	75.1	76.7
ANB	8.4	8.9	6.1
FMA	41.2	40.9	38.5
Dental			
U1 to FH	100.2	102.7	102.8
IMPA	96.5	81	81.7
Soft tissue			
Z-ANGLE	48.7	61.4	68.6
Upper lip to E-line	4.5	2.5	-2.5
Lower lip to E-line	9	3.5	-2.5

was 1 mm. The canine relationships were Class I and molar relationships were Class III on both sides (Fig. 6).

Diagnosis and Treatment Plan

To solve the upper lip protrusion, it was decided to extract the upper first premolars. For maximizing counter-clockwise rotation of the mandible, the lower second premolars were chosen for extraction. Micro-implants were planned for retraction and intrusion of the teeth. Third molars that might interfere with intrusion of the molars were extracted.

Treatment Progress

0.022” straight wire brackets were bonded and the initial alignment was begun. A transpalatal arch was inserted and micro-implants (Absoanchor, SH1312-08; Dentos Co., Daegu, Korea) were placed between the maxillary second premolars and first molars. Immediately after placement of micro-implants, a light 50 gm force was applied to the

hook on archwire or the archwire with Square thread (0.045", Dentos Co., Daegu, Korea). During leveling and alignment with 0.016" NiTi and 0.016" x 0.022" TMA wires in the maxillary arch, a light retraction force was applied from micro-implants to canines or anterior hooks crimped between lateral incisors and canines. One additional micro-implant (Absoanchor, SH1312-07; Dentos Co., Daegu, Korea) was placed between right and left central incisors (Fig. 7); a light intrusion force or vertical holding force was applied from maxillary anterior micro-implant to archwire to minimize lingual tipping of the upper incisors during retraction. After inserting a 0.016" x 0.022" SS wire, 150 gm of retraction force was applied to anterior hooks from micro-implants by Super thread (T-45, RMO, Denver, CO). A 0.019" x 0.025" SS wire was inserted to intrude all maxillary teeth with placement of micro-implants (Absoanchor, SH1413-10; Dentos Co., Daegu, Korea) into palatal alveolar bone between the maxillary first and second molars at eleven months of treatment. To reduce tongue irritation and utilize tongue force as intrusion force, resin was bonded on the transpalatal arch.

The mandibular archwire sequence was: 0.016" NiTi, 0.017" x 0.025" TMA wire, 0.017" x 0.025" SS wire and 0.019" x 0.025" SS wire. At ten months of treatment, the micro-implants were placed between mandibular second premolar and first molar on both sides. Retraction and intrusion force was applied from the micro-implants to the anterior hooks in the lower archwire. In order not to have buccal tipping of the

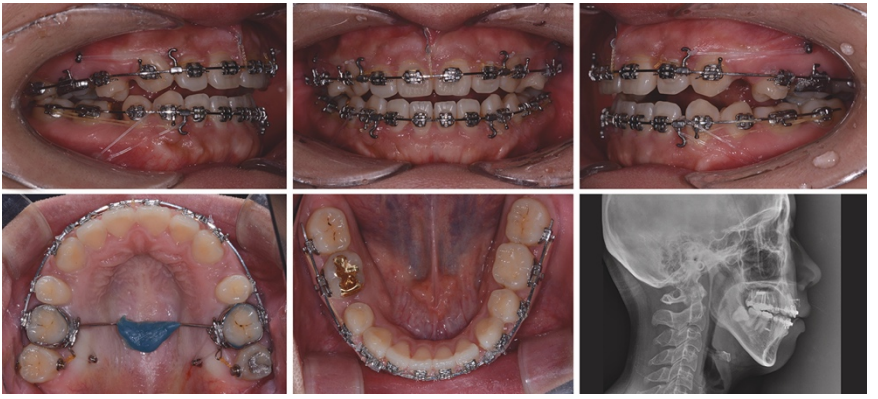

Figure 7. Mid-treatment records at twelve months.

mandibular molars, lingual crown torque was given to the lower archwires.

The necessity for further improvement of the facial profile by counter-clockwise rotation of the mandible justified additional intrusion of the maxillary molar with the micro-implants. At fourteen months of treatment, the micro-implant (Absoanchor, SH1312-10, Dentos Co., Daegu, Korea) was placed into the palatal alveolar bone between the maxillary first and second molars, and intrusion force was applied to the molars from the micro-implants. The intrusion of the posterior teeth rotates the mandible forward. At 20 months of treatment, hypermentalis muscle activity was eliminated at lip closure (Fig. 8).

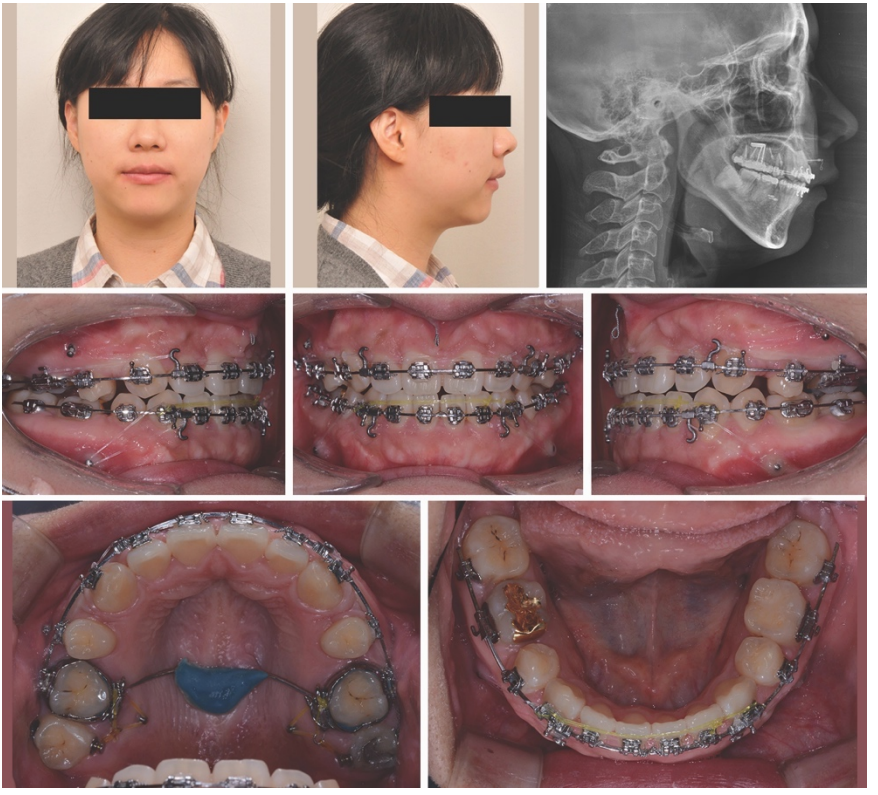

Figure 8. Mid-treatment records at 20 months. Facial profile was improved after retraction and intrusion of anterior teeth and intrusion of the posterior teeth.

Occlusal settling was performed in final detailing procedure. At 31 months of treatment, the treatment was completed with satisfactory facial profile changes (Fig. 9).

Treatment Results

Counter-clockwise rotation of the mandible resulted after intrusion of the maxillary posterior teeth, as well as intrusion and mesial root movement of the mandibular posterior teeth. With these changes, anterior lower facial height was decreased and hyperactivity of mentalis muscle was eliminated and improvement of the facial profile was achieved (Fig. 9). For dental relationships, there was a small residual space left between upper left canine and second premolar because of small maxillary second premolar and Class III molar relationship on the left. In the future, this space needs to be closed with restoration on the second premolar. Coincident maxillary and mandibular midline and favorable arch shape were obtained (Fig. 9).

Panoramic radiograph showed no obvious root resorption, even with a large amount of intrusion and retraction. Cephalometric superimpositions showed that the maxillary and mandibular anterior teeth were retracted and intruded. The amount of distal movement at root was larger than crown movement at the upper incisors (Fig. 10). The maxillary and mandibular molars were intruded by 2 mm and 3 mm, respectively, and counter-clockwise rotation of the mandible was evident. The angle of ANB and FMA decreased by 2.3° and 2.7°, respectively (Table 1).

DISCUSSION

The most common position of mandibular micro-implants is between the first and second molars in micro-implant anchorage (MIA) sliding mechanics and counter-clockwise rotation of the lower occlusal plane is expected with this position. However, because the patient had a long distance between the incisal tip of lower incisors and menton, intrusion of the anterior teeth along with the molar intrusion was necessary for counter-clockwise auto-rotation of the mandible. Therefore, to apply downward and backward force to the mandibular anterior teeth, the micro-implants were placed between the second premolars and first

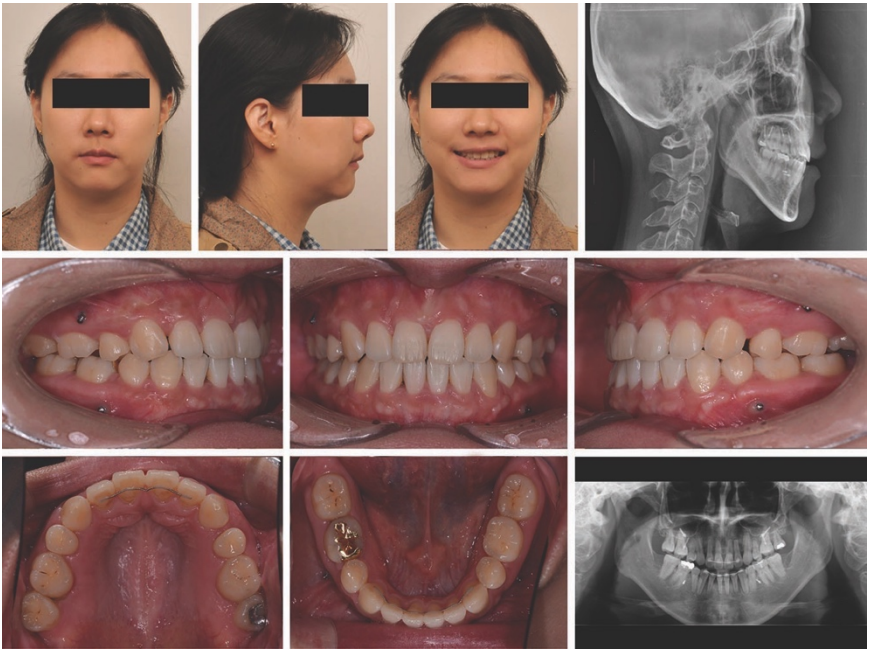

Figure 9. Post-treatment records.

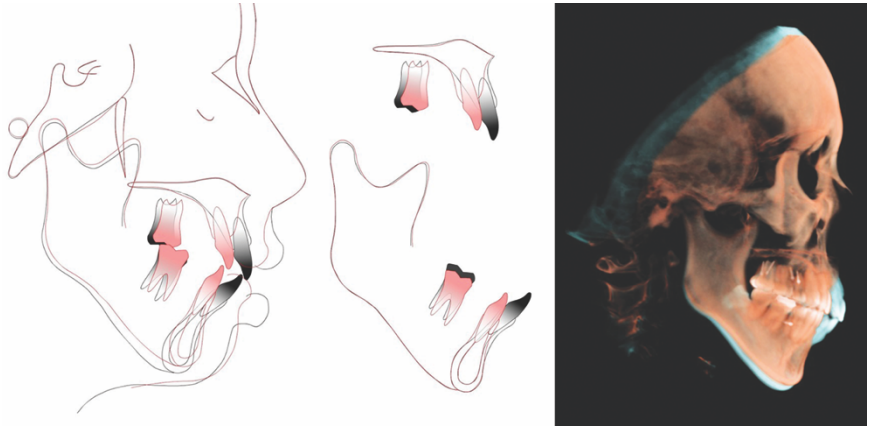

Figure 10. Superimposition of lateral cephalographs and CT. Black line = pre-treatment; red line = post-treatment.

molars. As a result, a large amount of intrusion was obtained on the mandibular molars as well as on the mandibular incisors; counter-clockwise auto-rotation of the mandible was obtained (Fig. 10).

Even though there was a large amount of retraction and intrusion on upper and lower anterior teeth, root resorption was minimal. This is due to light force, a maximum of 150 gm and no jiggling movement.

Basically, the maxillary posterior teeth receive intrusion force when posterosuperior retraction force is applied from the maxillary buccal micro-implants to anterior hooks on the archwire. If more intrusion is required at the maxillary posterior teeth, intrusion force can be added to the archwire from the buccal micro-implant during retraction of the anterior teeth. After extraction space is closed, retraction force from the buccal micro-implant may produce labial tipping of the anterior teeth and may be insufficient to gain the maxillary molar intrusion. Micro-implants can be added into the palatal side between the first and second molars for suitable amount of molar intrusion; this is recommended if the maxillary posterior teeth's roots are close to the maxillary sinus.

Retention is another consideration for this type of treatment. During retention, if there is forward tipping of the lower incisors, there will be opening of mandibular plane angle with increase of the lower anterior facial height. In order to keep tongue position from producing labial flaring of the incisors and strengthening the masticatory muscles, the author instructs the patient to do a "clenching swallowing exercise" during active orthodontic treatment and the retention period, because clenching exercises could produce auto-rotation of the mandible.[22] Lingual bonded retainers on upper and lower incisors are necessary for this type of patient. It also is recommended to keep the lower micro-implants in place and to wear night-time light elastics with clear sheet retainer in the lower arch as a method to improve stability.[23]

CONCLUSIONS

In treatment of severe hyperdivergent patients, the intrusion of the posterior teeth is not enough to improve the facial profile. Therefore, many factors need to be considered so that the amount of counter-clockwise auto-rotation of the mandible is maximized. These factors include: intrusion of the upper posterior teeth; consideration for anteroposterior occlusal plane cant; bodily retraction of the upper incisors;

intrusion of the upper incisors; intrusion of the lower posterior teeth; vertical position of the lower incisors; and most importantly, coordination of movement at the upper and lower posterior teeth and the upper and lower incisors. The extraction of lower second premolars may be helpful to increase amount of auto-rotation of the mandible.

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UNDERSTANDING THE FUNDAMENTALS OF 3D PRINTING

Tung Nguyen and Tate Jackson

ABSTRACT

Additive manufacturing (AM) technologies offer the ability to generate physical models from digital data in a fast and economical way. Initially adopted in the aerospace and automotive industry, this technology is here to stay and is improving continually. The introduction of low-cost 3D desktop printers and increased utilization of intra-oral scanners has improved the digital workflow process in orthodontics. To date, there are over a dozen AM processes, each with its advantages and disadvantages. This chapter will examine the most commonly used printing methods in orthodontics (e.g., stereolithography apparatus [SLA], digital light processing [DLP], fused deposition modeling [FDM], Polyjet and selective laser sintering [SLS]) and will seek to resolve some of the conflicting information regarding accuracy and precision of 3D printing. The significance of xy and y print resolution to the overall accuracy of the printer will be discussed in detail. Lastly, application of 3D printing in orthodontics will be discussed including fabrication of 3D models for diagnosis and appliance fabrication, indirect bonding trays, clear aligners, acrylic/resin functional appliances, metal appliances and bonded retainers.

KEY WORDS: 3D printing, SLA, DLP, Polyjet, accuracy

INTRODUCTION

Three-dimensional (3D) printing, sometimes referred to as additive manufacturing (AM) or rapid prototyping (RP), is a process in which materials such as liquid resins or metal powders are added together and fused to form a 3D object.[1] Chuck Hull of 3D Systems (Rock Hill, SC) introduced and patented a process called stereolithography in 1984 in which ultraviolet lights cures photoreactive resin polymers to form a cross-section of a 3D object.[2] The addictive process stacks, cures and fuses sequential cross sections on top of each other to form the final 3D-

printed object. The 3D-printed model is created either by a computer-aided design (CAD) *via* 3D scanner or digital camera with photogrammetry stitching software. To date, there are over a dozen 3D-printing processes and more are being developed (Fig. 1). 3D printing is used in orthodontics to fabricate models for diagnosis and appliance fabrication, indirect bonding trays, models for clear aligner therapy, acrylic/resin functional appliances, metal appliances and bonded retainers.[3,4]

3D PRINTING MECHANISMS

When flat screen TVs were introduced in the early 2000s, there was much confusion regarding picture quality when comparing LED, LCD and plasma options. The impact of screen resolution and refresh rate on overall picture quality were understood poorly and consumers often were at the mercy of salesmen. The same can be said about 3D printing—understanding its fundamental concepts is important.

In the field of dentistry and orthodontics, commonly used 3D printing methods are stereolithography apparatus (SLA), digital light processing (DLP), fused deposition modeling (FDM), Polyjet and selective laser sintering (SLS).

In SLA printing, a vat of photoreactive liquid resin is exposed selectively to a laser in a specific region. It uses two motors, known as gal-

Figure 1. A list of current 3D printing mechanisms.

vanometers, to direct a laser beam rapidly across the print area in the x and y planes, solidifying resin as it goes along. This process goes point by point along the entire cross section of the 3D object. While highly accurate, the process can be time consuming, especially for larger printed objects.

DLP uses a digital projector to flash a single beam of ultraviolet light in the shape of the desired cross section across the entire platform at once. The process is faster than SLA, however, the cross-sectional image of each layer is composed of square pixels (p), resulting in a layer formed from small rectangular bricks called voxels. Therefore, the surface finish on DLP printers is not smooth or fine compared to those of SLA printers. Since a full high-definition DLP projector has a native resolution size of 1080p, the size of the build platform often is small, especially if high-resolution prints are desired.

FDM and Polyjet use thermoplastic filaments that are melted and extruded from print heads. The extruded materials are laid down onto a high-temperature surface and set in the desired cross-section shape. The machine head repeats the extruding and melting, layer by layer until the part is complete. The Polyjet process is slightly different in that photopolymers are extruded onto the build platform and then cured by a UV light. After a thin layer is created, the process repeats itself by jetting additional layers until the part is formed fully. While the materials and chemical binding processes are different between FDM and Polyjet, the mechanical architecture of the printers, especially the extrusion jets, are nearly identical. The advantage of FDM and Polyjet is that larger build platforms are available for larger print sizes or high-volume printing. However, materials available for 3D printing are more limited compared with SLA and DLP.

SLS 3D printers use a high-power laser to fuse small particles of polymer powders. The process is similar to SLA printing and can produce a wide range of materials, including metals, plastic, glass, ceramics and various composites. Until recently, SLS has been prohibitively expensive and complex, limiting their use to aerospace parts or medical devices.

The advantages and disadvantages of these 3D printing processes are summarized in Figure 2.

Technology	Pros	Cons
SLA	Highly accurate	Slower print speed
	Variety of resins	Expensive sensors
DLP	Highly accurate (less than SLA)	Limited resins due to blue light
	faster than SLA	Smallest build volume
FDM	Largest build volume	Lower accuracy
		Limited resins
SLS	Highly accurate	Expensive
	Stronger materials	Powder is toxic and tech sensitive

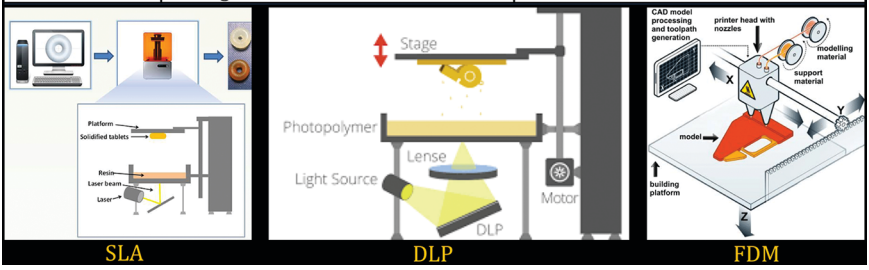

Figure 2. A summary of the advantages and disadvantages of four different 3D printing methods: stereolithography (SLA); digital light projection (DLP); fused deposition modeling (FDM); and selective laser sintering (SLS).

Commercially Available 3D Printers

The desktop 3D printer market has exploded in recent years. While it is nearly impossible to list all of the currently available printers, we highlight the more popular models currently used in orthodontics. A summary of these printers is shown in Table 1. The two most popular printers for orthodontic use are the Form2 (Formlabs, Somerville, MA) and the MoonRay (SprintRay, Los Angeles, CA). The Form2 is an SLA printer which retails for $3,500 USD. The build platform is capable of printing four to five horizontally configured dental arches and eight to ten vertically configured dental arches. The MoonRay is a DLP printer with a smaller build platform that is capable of printing two to four horizontally configured arches and five to seven vertically configured arches. The MoonRay, however, can print in 33% of the time compared with the Form2. For a busy practice, it is recommended that a second printer or a backup plan be in place in case the primary printer fails.

ACCURACY AND PRECISION

When orthodontists are looking to incorporate 3D printing in their practice, questions that are asked most often are:

Table 1. Summary of the most popular 3D printers used in orthodontics. Printer name, print method, build platform size, Z resolution, price and estimated cost to print a non-based model are shown. Note that the price of printer and resin are quoted as of July 2018.

3D printers	Method	Build dimension (mm)	Layer thickness (um)	Unit price	Cost per model
Statasys Objet 30	Polyjet	300 x 200 150	28, 50, 100, 150, 200	$50,000	$15.70
EnvisionTec Vida	DLP	140 x 79 x 100	25, 50, 100, 150	$25,000	$5.20
Park Dental Research Juell 3D-2	DLP	192 x 108 x 230	50, 70, 100	$14,000	$3.10
FormLabs Form2	SLA	145 x 145 x 175	25, 50, 100, 200	$3,500	$3.00
Moonray	DLP	130 x 80 x 200	20, 50, 100	$4,500	$2.10 - $4.00

- Which 3D printer is the most accurate?
- Are accuracy and precision the same thing?
- What does resolution mean in 3D printing?
- Is there a direct correlation between accuracy and resolution?
- Which dimension(s) X, Y or Z matter(s) most for the accuracy of 3D printing?

The answers to these questions are not always simple.

Accuracy and Precision

The accuracy of a 3D-printed model is defined by its "trueness" in shape and dimension to the 3D virtual model (i.e., does the 3D resin printed cast match up to the exact shape and size of the intra-oral scan of the dentition?). In the literature, accuracy is measured by laser scanning the printed part and digitally superimposing it over the CAD model. The accuracy of the printed model often is reported as a percentage of the CAD model volume.

Precision refers to the "reproducibility" of a 3D printer to manufacture the exact same dimension and shape consistently time after time. While precision is more important for automotive and aerospace manufacturing, in orthodontics, it has an impact on when multiple models are printed for clear aligner therapy.

3D printed casts can be accurate within 20-110 µm depending on the resolution and mechanism of the printer.[5-8] However, studies examining which printing mechanism is more accurate or precise have been conflicting. Deitrich and associates found that Polyjet produced more accurate models, but with less precision compared with SLA.[6] Kim and colleagues reported the overall trueness of Polyjet and DLP prints were better than SLA; however, SLA prints were more accurate when occlusion (cusp tips and crown) were evaluated.[7] It is important to note that while these findings were significant statistically, the differences in accuracy were only 20-50 µm, which are insignificant clinically for most orthodontic applications. In addition, the diameters of the SLA laser used in the above studies are larger than current industry standards, which further confound the results.

X, Y and Z Resolution

Many factors are involved in the accuracy/trueness of a 3D printer beyond print mechanism and resolution. There are three dimensions to consider for printing resolution: the two planar 2D dimensions (X and Y) and the Z dimension (layer thickness). Since the XY and Z dimensions generally are controlled *via* very different mechanisms, their resolutions will be different and need to be treated separately. As a result, there is a lot of confusion about what the term "resolution" means in 3D printing and what level of print quality to expect. It is recommended that the XY resolution be a minimum of 100 µm for orthodontic use, 75 µm for dental applications and less than 50 µm for restorative work. In SLA printing, the XY resolution is determined by the diameter of the laser. The finer the beam of the laser, the higher the XY resolution of the print. With DLP printing, the resolution size is fixed by the number of pixels displayed by the projector. For example, a high definition DLP projector has a fixed resolution of 1900 x 1200. This means there are 2.3 million pixels available through the entire build platform to cure the resin. If the build platform is small (e.g., 140 x 80 x 100 mm), the resulting pixel size is 70 µm. If the build platform is larger or the resolution of the projector is smaller, the resulting pixel will be larger and the print will be less accurate. This is analogous to projecting a flashlight onto a wall. The closer the flashlight is to the wall, the finer the edges of the beam will be, but the total surface area of the beam is reduced. This is why the build platforms for DLP printers are smaller compared to SLA or Polyjet. In addition, light at the edges

of a DLP often is diffused compared to those at the center of the beam. This means that DLP prints at the center of the build platform tend to be more accurate than those at the periphery.

In theory, SLA has better XY resolution compared to FDM or Polyjet. Unlike FDM or Polyjet printers, the minimum resolution size in the XY plane on SLA printers is not limited by melted plastic flow dynamics, but rather optics and polymerization kinetics (e.g., the size of the laser beam). Polyjet is more accurate compared to FDM in the XY plane, but its resolution still has a limited flow dynamic of the resin and clearance of the extruder nozzle.

The Z resolution is the dimension that often gets the most attention when reading 3D printer spec sheets, but how important is it to the overall print accuracy? Z resolution refers to the height/thickness of the layer printed. For most 3D printers, this is controlled mechanically by how much the platform rises after each pass. Early machines struggled to break the 1 mm barrier, but now layer heights on FDM printers can be below 100 µm, while SLA and DLP machines reach resolution below 25 µm. The Z resolution also is influenced by resin dimensional stability and flow characteristics. Acrylonitrile Butadiene Styrene (ABS), which sometimes is used for surgical splints, requires thicker Z dimension (0.75 to 1.2 mm) for the individual layers to have dimensional stability. In reality, Z layer thickness has a bigger impact on surface finish rather than overall dimensional accuracy. In the early days of Invisalign, models used for the thermoplastic aligners were printed at 200 µm in the Z dimension. One can see the horizontal striations/lines in the trays clearly, yet this had little impact on the fit of the trays. While smoothness of the surface finish makes for more comfortable dental appliances in the mouth, it is not the best indicator of final dimensional accuracy once it is below 100 µm. Testing done by Ortho Cosmo showed that prints at 50 µm had the same dimensional accuracy compared to those printed at 100 µm.[9] Our in-house study found that 3D models printed at 25 µm Z resolution actually had the worst overall accuracy compared to those at 100 µm. While there are several potential reasons for this discrepancy, it could be that finer Z resolution means more exposure layers, four times as many in this case. That, in turn, requires more repositioning of the build plate in the Z axis during the build process and, therefore, more opportunities for motion control and repositioning errors. A thinner layer equals longer print time and could lead to more artifacts and errors.

There are instances in which thinner Z resolution is beneficial to the overall accuracy. Curvy objects with steep diagonal transitions or those that end with a sharp point clearly benefit from thinner Z resolution. To date, no study has evaluated whether thinner Z layers increases accuracy for proclined teeth, with severe undercuts at the CEJ, and adult patients with bone loss and furcation involvement.

Other Factors That Impact Accuracy

There are other factors that affect the overall accuracy of the print. As briefly discussed above, the reliability of the platform to rise perfectly parallel is essential for creating uniform Z layer thickness. If one side of the platform rises even slightly more than the other, the cumulative effect is distortion and skewing of the printed models. Some printers utilize sophisticated servomotors, while others incorporate a dual rail system to ensure a parallel rise of the platform. Regardless of the mechanism, 3D printers need to be calibrated on a routine basis to ensure reliable and accurate prints. Most manufacturers recommend calibration every three to four months or after a certain volume of prints.

The orientation of the prints also impacts accuracy. In general, horizontal prints tend to be more accurate than vertical prints. This is not just a byproduct of the mechanical rise of the platform, but is caused by shrinkage and warping of unsupported structures. Currently, printer software automatically adds support struts to prevent shape distortion.

The material property of the resin also can affect accuracy. Flexible resins (e.g., those used for indirect bonding trays) tend to be less stable dimensionally compared to standard rigid SLA resins. The viscosity of the resin is another important factor. If the resin does not flow well or is older, the cured layers will not be uniform. The color of the resin can affect curing (i.e., laser and DLP light), can pass through transparent resins and can cure undesired regions, producing artifacts.

CLINICAL APPLICATIONS OF 3D PRINTING

The increased popularity of intra-oral scanning has led to a digital workflow revolution in dentistry and orthodontics. Advantages of the digital flow include: higher volume production (hundreds of casts can be printed simultaneously, rather than being poured individually); better product durability; decreased need for physical storage; and decreased

transit time. Multiple studies have validated the use of digital models for orthodontic diagnosis and treatment planning, yet printing of resin casts continues to be the primary application for 3D printing since the orthodontic appliance fabrication processes still require a physical cast. [10-12] Other clinical applications for 3D printing include: fabrication of indirect bonding trays; functional appliances; metal appliances (e.g., expanders); clear aligners; and retainers.[3,4,13]

Indirect Bonding

The intra-oral scan (STL format) is imported in commercial software such as OrthoAnalyzer (3Shape, Copenhagen, Denmark) where the virtual models are cleaned and oriented to a set plane. Early versions of digital indirect bonding software automatically placed the brackets at the center of the tooth and left it to the clinician to adjust them as needed. With newer software, the teeth are digitized and a virtual setup is performed to give the clinician an indication of the 3D outcomes with the teeth aligned and leveled. The brackets are positioned automatically to a "straight-wire" setup to obtain the virtual alignment. The clinician can change the virtual bracket position as desired on the aligned teeth. The bracket position relative to the tooth is transferred back to the initial malalignment. The indirect bonding trays can be fabricated by two methods: 3D printing the dental model with the brackets; or 3D printing the indirect bonding tray (Fig. 3). If the choice is to print the model with brackets, most software automatically will block out any undercuts from the tie wings and hooks. The indirect bonding tray can be fabricated with the clinician's material of choice; once this happens, an assistant can insert the brackets into the indirect bonding tray prior to the bonding appointment. The advantage of this method is that it can be used with any currently available indirect bonding material (e.g., silicon-based, thermoplastic, or dual materials with different flexibility).

The second method is to print the indirect bonding tray directly. Unlike traditional indirect bonding methods, the 3D-printed methods described above lack a custom base and can produce excess composite flash around the brackets. We have used pre-pasted brackets containing high viscosity composite (e.g., Clarity Flash-Free [3M ESPE, St. Paul, MN]) with good success. Currently, there are a limited number of companies that manufacture a biocompatible transparent resin to allow light curing, while offering some flexibility to facilitate tray removal without debond-

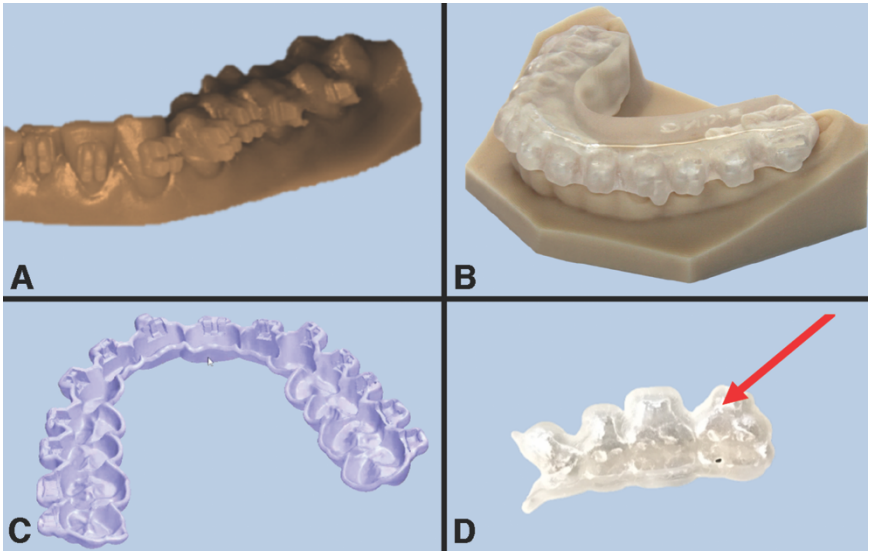

Figure 3. Indirect bonding trays can be made by printing the model with bracket (*A*) and then fabricating the tray with a material of choice (*B*) or directly printing the tray using a specialized resin (*C*). Once the trays are made or printed, the brackets are inserted into the slots by an assistant before the bonding appointment (*D*).

ing the brackets. Unfortunately, most resins are not interchangeable between different printer manufacturers. Research data still lacks the accuracy and precision of these 3D-printed indirect bonding systems.

Clear Aligners

The increased accessibility and affordability of 3D printers, combined with the development of commercial software to align teeth and generate sequential models for tooth movement, has made it possible for a practice to fabricate their own "in-house" aligners. A scan of the dentition is obtained and imported into commercial software such as Orchestrate3D (Orchestrate Orthodontic Technologies, Rialto, CA), OrthoAnalyzer (3Shape, Copenhagen, Denmark), or OnyxCeph (Image Instruments, Chemnitz, Germany; Fig. 4). The models are cleaned, oriented and based. The teeth are segmented and aligned to the desired position virtually. The software automatically calculates the numbers of trays/models needed based on pre-set algorithms of tooth velocity movement. Some software automatically places attachments for difficult movements. The clinician can overcorrect and change attachments as desired.

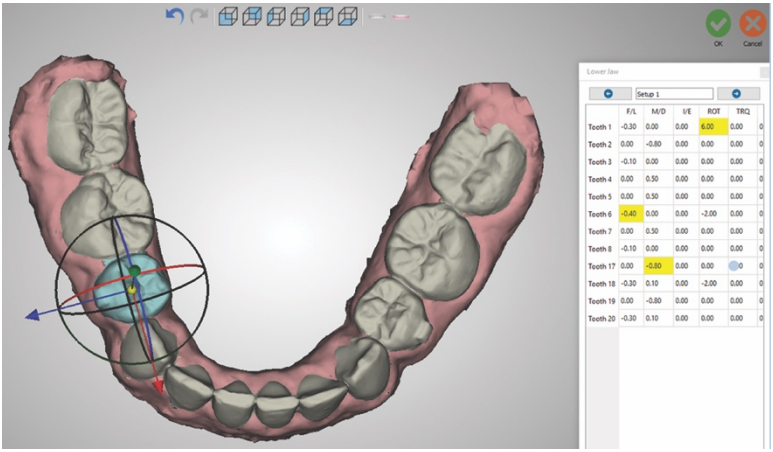

Figure 4. An example of software used to fabricate in-house aligners. The software reports the degree of movement for each tooth and calculates the total number of trays needed for the movement based on pre-set movement velocities.

Alternatively, online services (e.g., ARCAD, AccuSmile or ArchForm) can perform the setup and send the STL files of the sequential tooth movement for a fee. The development of Artificial Intelligence and Deep Learning software will automate the entire process one day, making the digital workflow quicker and easier for clinicians. In addition, some companies such as EnvisionTec (Dearborn, MI) are developing resins (E-Ortholign) to print clear thermoform aligners directly.[14] This will reduce the number of steps in the manufacturing process dramatically and ultimately lower the cost to fabricate “in-house” aligners.

Metal Appliance Fabrication

One of the more exciting developments in 3D printing is SLS, which currently can print 316 stainless steel, cobalt chromium, T64 titanium, porcelain, plastics and glass. The prints often have high strength and stiffness, but early SLS prints exhibited porous surface texture and post-sintering shrinkage. Recent improvement in post-sintering shrinkage has made it possible to print metal orthodontic appliances (e.g., lingual holding arches, skeletal anchorage attachments, rapid palatal expanders [RPEs] and brackets with high precision).[4] Fabrication of complex multi-piece mechanical parts is still in the early stages of develop-

ment, so current printing of orthodontic appliances often is a two-step process. Bands, lingual pads and support arms are printed separately and then laser welded to the commercially-made expansion screw to complete the RPE appliance. While 3D printing saves chairside time of fitting bands and can achieve a better fit, data is lacking on whether or not this process reduces cost, improves workflow or clinical outcomes. As SLS technology continues to improve and production cost decreases, fabrication of complex parts for appliances like Herbst and RPE can be printed completely in one step and assembled.

CONCLUSIONS

Advances in 3D printing technology will improve the digital workflow in clinical orthodontics. Next generation 3D printers will have larger build platform, faster speed, increased precision and print a variety of materials.

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