The psychobiological links between chronic stress-related diseases, periodontal/peri-implant diseases, and wound healing

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Abstract

Chronic stress is a relevant disease to the periodontal practice, encompassing 25-28% of the American population [1]. While it is well-established that chronic psychological stress can have significant deleterious systemic effects, only in recent decades have we begun to explore the biochemical, microbial, and physiological impacts of chronic stress diseases on oral tissues. Currently, chronic stress is classified as a 'risk indicator' for periodontal disease. However, as the evidence in this field matures with additional clinically-controlled trials, more homogeneous data collection methods, and a better grasp of the biological underpinnings of stress-mediated dysbiosis, emerging evidence suggests that chronic stress and related diseases (depression, anxiety) may be significant contributing factors in periodontal/peri-implant disease progression and inconsistent wound healing following periodontal-related therapeutics. Ideal solutions for these patients include classification of the disease process and de-escalation of chronic stress conditions through coping strategies. This manuscript also summarizes periodontal/implant-related therapeutic approaches to ensure predictable results for this specific patient subpopulation.

Introduction

The first observation between stress and oral disease was reported in the 1970s, when mucous membrane lesions from viruses (i.e. Coxsackie, Rhinovirus) developed more rapidly and severely under conditions of psychosocial stress. Since these observations, there has been steadily increased effort to understand the molecular mechanisms involved between psychosocial stress and oral inflammatory diseases such as periodontal/peri-implant diseases and wound healing. Several recent systematic reviews of the current literature that have pointed to an increasing platform linking chronic psychosocial stress/disorders with diseases of the periodontium/periosteum [2-4] due to dynamics in the immune system, oral microbiome shifts/biofilm formation, enzymatic-mediated protein/collagen turnover ratios, and local/systemic disease progression[5]. Towards this end, there are three possible interactions between the periodontium/periosteum and stress: stress→periodontium/periosteum, periodontium/periosteum←stress, stress↔periodontium/periosteum [6]. These three interactions will be explored throughout this manuscript to assess the psychobiological links between chronic stress-related diseases and the periodontal/peri-implant diseases.

Section 1: Periodontal and Peri-Implant Tissues

The gingival tissues and peri-implant mucosa that surround natural teeth and dental implants share many common soft tissue characteristics. Namely, tissue phenotype/thickness

and presence of keratinized tissue/mucosa, bony coverage on the buccal surface are all local factors involved in maintaining a healthy homeostatic and stable situation [7, 8]. However, fundamental differences between periodontal and peri-implant tissues lie in the connection of the tooth and/or implant to the alveolus. To this end, natural teeth are suspended in the socket and connected to the alveolar bone in a perpendicular orientation by the periodontal ligament, whereas an endosseous implant is directly connected to the bone through osseointegration[9].

In the case of disease onset in situations of periodontitis and peri-implantitis, bacterial aggregation in contact with gingival and peri-implant mucosa leads to inflammation and increased probing depth [10]. In both clinical situations, pathology progresses in an apical direction that invades the alveolar bone compartment and subsequently manifests clinically as infrabony or furcation pockets/defects [11, 12]. Histological evaluations of biopsies from periodontal disease lesions reveals dysbiotic microbiotas with higher numbers of motile organisms and less coccoid/straight rod cells in established gingivitis and advanced periodontal disease samples compared to healthy gingiva controls [13]. From an immunological perspective, cellular infiltrate of established gingivitis and advanced disease showed increased quantities of plasma cells and relative decrease in fibroblasts and lymphocytes compared to healthy controls [13].

Furthermore, like inflammatory lesions in periodontitis, peri-implantitis also progresses apically, invading the alveolar bone compartment and causes infrabony (intraosseous) pockets [11]. However, important nuances have been reported in human biopsy material that the apical extension of inflammatory cell infiltrate is more pronounced in peri-implantitis compared to periodontitis [12]. In experimental studies, differences between disease progression of periodontitis and peri-implantitis were also noted. Following ligature removal, a “self-limiting” process may occur in gingival tissues surrounding teeth due to a reactive connective tissue capsule formation that separated the inflammatory infiltrate from bone, while in peri-implant tissues histological sections showed significant inflammatory infiltrate extending all the way to the bone crest [12]. Also, histological data collected from failing implants in humans, showed large areas of connective tissue (~64%) containing inflammatory infiltrates consisting of plasma cells, lymphocytes, and leukocytes [14].

The core principles of periodontal/peri-implant therapeutics remain centered on controlling the microbial challenge and host factors that contribute to microbial dysbiosis, exacerbated inflammatory infiltrate, and subsequent tissue destruction [15]. Some patients present on a more aggressive disease path that doesn’t necessarily correlate with the typical tenets discussed above, suggesting that other contributing factors are present [16]. Recent

evidence highlights that diseases related to the periodontium are a positively reinforced and self-sustained loop of inflammation and microbial dysbiosis that drive tissue destruction and disease progression [17]. This loop is further perpetuated and reinforced by systemic contributing/risk factors [18].

Systemic risk factors for periodontal disease include poorly controlled diabetes, tobacco smoking, and immunodeficiency states such as neutropenia and AIDS/HIV infection, with significant longitudinal evidence of effects on disease progression [19]. However, compounding evidence suggests that there are additional contributing systemic factors in periodontal/peri-implant disease progression and response to therapeutic strategies, including psychological stress [19]. Psychobiological connections between stress and systemic health/immunological dysregulation/microbial dysbiosis are emerging, as more evidence is presented. To achieve control of disease progression in aggressively progressing cases, timely assessment of both host- and microbe-centric perspectives must be incorporated to achieve long-term clinical success for these patients.

Section Two: Stress and the Body's Biological Response

Notably, the physiological stress response is an evolutionarily conserved biological mechanism that connects an organism to the surrounding environment. Stressor cues can take on both physical and/or psychological forms in modern times. Physical cues of stress activation include trauma-, infection-, or tumor-associated. Psychological or emotional cues include life events, such as financial deficits, caregiving, and loss of a spouse; or ongoing disorders such as Post Traumatic Stress Disorder (PTSD) and depression. For example, psychological or emotional stress might interfere with normal immune function and increase certain levels of hormones that could affect the periodontium or peri-implant surrounding tissues. The effects of these factors can be significantly exacerbated to the point of disease presentation in the context of poor coping strategies.

Stimulus duration is also an important consideration to assess clinical downstream effects (**Figure 1**). Acute stressors (infection, surgical procedure) often present with upregulation of innate immune mechanisms but suppression of cellular immunity [20]. Conversely, chronic stress often presents with suppression of both the cellular and innate immune responses [21, 22]. The notable paradigm in this field suggests that stressors with the temporal parameters of the acute/fight-or-flight situations in their evolutionary roots elicit beneficial changes allowing the body to recover from injury quickly if necessary [20]. For example, in following acute trauma experienced in periodontal/peri-implant surgery, the innate surveillance mechanism is

heightened to promote clearance of debris and facilitate resolution and healing of wounds. On the other hand, the more these stressors deviate from these biologically preserved parameters (i.e. chronic stress), the more the immune system is detrimentally affected [20]. For example, periodontal/peri-implant surgery under conditions of chronic stress, there might be a decreased debris clearance response with sustained low-grade inflammation that delays wound healing and creates a less favorable regenerative milieu.

The exact point at which stressors move from acute to chronic in nature is currently an intense area of research [23]. However, the guiding mechanisms that create these systemic alterations include the hypothalamic-pituitary-adrenal axis that generates glucocorticoids and the adrenergic nerve signaling axis that generates norepinephrine, adenosine triphosphate, and neuropeptide Y. A myriad of other chemicals are released within the stress response cascade of both the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, but in depth discussion of these additional chemokines reside outside the scope of this manuscript.

A. Glucocorticoids

The effects of hypothalamic-pituitary-adrenal axis glucocorticoids act in catabolic, lipogenic, anti-reproductive, and immunosuppressive circuits resulting in mobilization of energy stores, mild chronic inflammation, intra-abdominal accumulation of visceral fat, increased sodium retention, hypertension, insulin resistance and inability to fight bacterial infection [24-27]. Periodontal tissues specifically have glucocorticoid receptors that respond to the chronic release of hypothalamic-pituitary-adrenal axis glucocorticoids. In addition, keratinocytes are unique mediators of the stress cycle and also create an autocrine stress mileu, producing cortisol and neurotrophins [28]. Both systemic and local balance of glucocorticoid levels are needed to achieve soft tissue homeostasis. These excess glucocorticoid levels reduce keratinocyte expression of growth factors and cytokines necessary for re-epithelialization following injury, delaying wound healing. This may result in poor clinical outcomes due to open wound, infection, and abscess formation that often lead to compromised healing events. In addition, these excess glucocorticoid levels also lead to anti-inflammatory actions that lend the periodontal area susceptible to infection [29].

Importantly, most of the individuals experiencing stress-related adrenal insufficiency may still receive routine dental care or minor surgical procedures, including periodontal surgery, without the need of having supplemental glucocorticoids unless previously diagnosed with primary adrenal insufficiency [30]. If patients have been previously diagnosed with primary adrenal insufficiency, discussion regarding a “stress dose” (an administration of increased

hydrocortisone coverage during major stress events to avoid a life-threatening adrenal crisis) is necessary with the patient's endocrinologist for any surgical interventions [31].

B. Norepinephrine

The effects of adrenergic nerve signaling cascade molecules norepinephrine, adenosine triphosphate, and neuropeptide Y directly affect the vasculature of post-synaptic smooth muscles. Vascular tension affects many pertinent organ systems in the periodontium. Vascular flow decreases to connective tissue plexuses limit cellular and nutrient diffusion through adventitia or collagenous fibrils, causing poor adaptive immune responses and restricted repair reactions in periodontal and periosteal (bone) tissues [32-34]. Adrenergic nerve fiber synaptic effects also limit vascular perfusion at primary/secondary lymphoid tissues, resulting in host-wide immunodysregulation [32, 35]. Immunodysregulation in any form can have system-wide effects, especially noted in marginal alveolar bone loss and periodontal disease progression [36, 37].

C. Neurological Alterations Affecting Behavior

In addition to these hard-wired peripheral and central system responses, stress duration can also initiate physically adaptive changes in the form of cognition and behavior (feeding/hunger, vigilance, alertness). In fact, functional imaging studies have shown that morphological changes in the brain, the hippocampus in particular, occur with psychosocial stress and related disorders [38-40]. In a post-mortem study of chronically depressed patients, distinct patterns in protein expression changes were noted in scaffolding proteins and ion channels within the hippocampal sub-regions [41]. These data are further in line with other studies that report epigenetic changes in hippocampal sub-regions in rodent chronic stress studies [42, 43]. Overall, hippocampal morphology changes might play a role in the behavior modifications (lethargy, anxiety, lack of organization/motivation, difficulty in keeping appointments, hygiene practice, and compliance to treatment) seen in situations of chronic stress and depression.

Section Three: Psychobiological Effects on Periodontal/Peri-Implant Structures and their Wound Healing Capacity

Both physical and psychological stimuli can affect a biological system at an organ system level, cellular level, and molecular level through mechanisms of the hypothalamic-pituitary-adrenal axis, adrenergic nerve signaling axis, and behavior modification (**Figure 2**). Periodontal structures including mucosal tissues/keratinocytes/periodontal extracellular matrix,

periosteum/bony tissue, and the microbiological/periodontal microenvironment are most susceptible to stress-related dysbiosis. The following sections will discuss periodontium/periosteum specific responses and adaptations under conditions of chronic stress.

A. Mucosal Tissues/Keratinocytes/Extracellular Matrix

Stress-related psychobiological changes in endocrine, autocrine, and paracrine signaling systems affect oral soft tissue kinetics during homeostasis and during wound healing responses. Increased glucocorticoid production following a punch biopsy was associated with greater perceived stress and delayed dermal healing [44]. Spatial or temporal summation of these psychobiological effects also interplay, resulting in the delayed healing phenotype. Congruently, catecholamine production (the other major biochemical player within the biological stress response as discussed above) in soft tissue can also delay soft tissue wound healing responses [45]. Hence, caution is needed when performing periodontal/implant surgery in a highly stressed patient or in an individual in a high stress environment, and special considerations and issues include: primary wound closure, longer healing time, antibiotic coverage, minimize extensive and long surgical procedure or even postpone the surgery to a time when there is less stress in the patient's life. Without expedient soft tissue closure, injury or infection of these susceptible oral tissues and underlying structures can be persistently problematic both short- and long-term.

Oral tissues are constantly under a state of general maintenance and assault from homeostatic forces, microbiome changes, or occlusion [46]. Oral soft tissue wound healing follows a well-established trajectory that is comprised of four categories: (1) Hemostasis/Inflammation, (2) Migration, (3) Proliferation, (4) Remodeling (Decker 2018). It appears that the psychobiological effects of stress may affect all stages of wound healing in some capacity.

During the initial, mid, and late phases of wound healing phases, a variety of stress models report observations in cytokine/immune crosstalk dysregulation, hypoxia, dysregulation of cellular mobility and metabolomic kinetics, and matrix metalloprotease activity.

Immunological Effects

A human study that evaluated the association of chronic caregiving stress and distribution of T cell phenotypes reported important changes in relative proportions of T cell subpopulations consistent with immunological aging [47]. These T cell subpopulations appear to include those involved in periodontal disease progression;

however, more research is needed in this area due to the complexity of subpopulation characterization [48].

Cytokine Alterations

In multiple human blister study model trials, monitoring of local cytokine production showed that increased levels of perceived stress was associated with a delay in the initial phase of wound healing with lower interleukin-1α, interleukin-8, interleukin-1B, interleukin-6, tumor necrosis factor-α cytokine levels [49, 50]. Additionally, exogenous glucocorticoid administration can also transiently depress skin and mucosal cytokine signaling through suppression of interleukin-1β, tumor necrosis factor-α and platelet derived growth factor production [49]. Furthermore, in an animal model of experimental periodontitis that applied chronic stress conditions, authors reported elevated inflammatory mediators, interleukin-1β and tumor necrosis factor-α, and decreased expression of regenerative factors, such as basic fibroblast growth factor [51]. These data suggest that in situations of chronic stress, the local periodontal environment appears to be in a pro-inflammatory and anti-regenerative state. Care should be taken to avoid these consequences; it is often recommended to prescribe antibiotics to prevent potential infection.

Hypoxia

A well oxygenated environment is essential to maintain homeostasis and achieve regeneration or repair following injury in the periodontal apparatus. Through use of a stress-induced animal model, several papers reported that chronic stress could increase wound hypoxia measured via nitric oxide synthase levels (a common indicator of wound hypoxia) [52-55]. Furthermore, some have also reported reversal of these stress-induced impairments and nitric oxide synthase levels by implementing hyperbaric oxygen therapy [54].

Mechanisms of hypoxia in chronic stress are currently an intense area of investigation. In a series of studies, osteoblasts exposed to chronic glucocorticoid dosing downregulated hypoxia-inducible factor 1-alpha and vascular endothelial growth factor [56, 57]. These hypoxic effects of chronic glucocorticoid exposure could contribute to a local clinical state that is ill-primed for periodontal regeneration or repair.

Cellular Migration and Proliferation

Chronic stress associated delays in soft tissue wound repair has also previously been mechanistically ascribed to early/mid phase wound healing delays in cellular migration and proliferation [58-61]. Elevated cortisol levels, mimicked results with administration of corticosteroids showing delayed epithelial wound healing via diminished cellular migration and proliferation. Furthermore, inhibition of glucocorticoid synthesis can reverse, stress-induced skin abnormalities in healing or barrier function [58-61]. In addition, glucocorticoids inhibit proliferation and suppress essential Wnt-signaling pathways (a group of signal transduction pathways which begin with proteins that pass signals into a cell through cell surface receptors) in periodontal ligament stem cells, suggesting that their regenerative capacity becomes limited under conditions of chronic stress [62]. These deleterious observations could be compounded further with addition of concomitant stress-related catecholamine production locally in the periodontal tissues, which express an abundance of adrenergic signaling receptors [63]. Furthermore, catecholamine production in soft tissue impairs initial stages of wound healing through reduction of keratinocyte motility and migration [45].

Matrix Metalloprotease Activity

Mid and Later stages of oral wound healing also appear to be affected by the psychobiological changes induced in conditions of chronic stress by alterations in matrix metalloprotease activity. Matrix metalloproteases are essential enzymatic proteins that breakdown damaged protein/collagen or turnover existing protein/collagen at a periodontal injury site [64, 65]. Specifically, activity of collagenases matrix metalloprotease-1 and matrix metalloprotease-13 as well as gelatinases matrix metalloprotease-2 and matrix metalloprotease-9 appear to be important in wounded oral tissue healing [66]. In human surveys of stress and surgical outcomes, there was a negative correlation between increased stress levels and amounts of local matrix metalloprotease-9 [64]. When hydrocortisone was applied to gingival fibroblasts, an increased production of matrix metalloprotease-1, -2, -7, and -11 was noted [67]. This implies that under conditions of chronic stress or increased cortisol concentrations, periodontal destruction might occur at a higher rate [67].

Interestingly, a negative correlation between plasma cortisol levels and matrix metalloprotease-2 protein levels was reported in human blister wounds [65]. These findings were confirmed in a murine stress model - indicating that stress can also

downregulate matrix metalloprotease production at the wound site in both human and murine models [68].

B. Periosteum/Bone Homeostasis and Hard Tissue Wound Healing

Stress-related psychobiological changes in endocrine, autocrine, and paracrine signaling systems affect oral bony tissue kinetics during homeostasis and during wound healing responses. Chronic stress disorders, including post-traumatic stress disorder (PTSD) and depression, and stress-related adrenergic signaling are associated with poor alveolar bone growth [69], osteoporosis [70-73], and short stature if affected as a child [74, 75]. The underlying mechanisms for these stress-induced, bone-associated phenotypes include poor maintenance of osteoid competence. Care should be taken to minimize the risk of adverse outcomes in these patients.

Maintenance of bony tissue requires a balance between resorption and formation that is mediated by osteoclastic and osteoblastic mechanics, respectively. Resorptive phases are characterized by higher levels of Receptor Activator of Nuclear Factor-κB Ligand (RANKL), whereas formative phases are characterized by higher levels of Osteoprotegerin (OPG). Healing of alveolar bone following periodontal disease, injury, or surgical intervention, including implant placement, requires a shift in the balance of the osteoid cycle towards increased bony lineage commitment and concomitant decreased bone resorptive activity. Interestingly, chronic stress can cause a shift in this ever-important osteoid cycle, affecting osteoid competence through alterations in the balance between additive or resorptive lineage committing cells within the bone.

Osteoid Metabolomics Cycle

Accumulating evidence suggests that chronic stress is associated with alterations in skeletal status/fragility [76, 77]. However, specific dysregulated bone metabolic mechanisms have recently been investigated. Chronic elevated exposure to glucocorticoids can reduce bone mass altogether by shunting mesenchymal stem cell differentiation from an osteoblastic lineage towards an adipogenic lineage, thereby increasing expression of Wnt signaling inhibitors [78, 79]. Furthermore, osteoblasts and osteocytes respond to increased Receptor Activator of Nuclear Factor-κB Ligand/ Osteoprotegerin (RANKL/OPG) ratios with higher rates of apoptosis and autophagy [80, 81]. Interestingly, one group reported that chronic stress from social isolation in rats did not affect sclerostin expression, a marker of bone formation, but bone resorption

markers were significantly altered, showing a decrease in cathepsin K and increase in C-terminal telopeptide-I [82]. These data suggest that while alterations in bony phenotypes are observed as a result of chronic stress, the complex nature of psychological and biological mechanisms involved require more *in vivo* and *in vitro* studies to determine pharmaceutical target adjuncts that would be circumferentially effective in the local periodontal space.

In an attempt to isolate the effects of the sympathetic arm of chronic stress on alveolar bone metabolic regulation, investigators have also used systemic adrenergic receptor blockers. In an animal ligature model of periodontal disease, an adrenergic signaling blocker, propranolol, was delivered at three different concentrations. At low doses of propranolol, alveolar bone resorption was suppressed through inhibition of Receptor Activator of Nuclear Factor-κB Ligand (RANKL)-mediated osteoclastogenesis. In addition, propranolol also reduced osteoclastic activity through depressed tartrate-resistant acid phosphate (TRAP), cathepsin K, and matrix metalloprotease-9 expression [83]. These data suggest that the destructive effects of chronic stress seen in periodontitis or peri-implant diseases might be targeted through one arm of the chronic-stress pathway via administration of sympathetic receptor blocking pharmaceuticals. *However, in discussing use of sympathetic blocking pharmaceuticals, it is important to acknowledge that their significant systemic effects require research in coordination with cardiovascular experts to ensure these drugs are thoroughly and appropriately vetted before moving forward.*

C. Microbial-Periodontal Microenvironment

Research in the field of chronic stress pertaining to the microbial-periodontal interface is limited; however, insights from other studies provide helpful directions for the field of periodontology. Multiple human and animal studies highlight the role of stress in shaping microbial profiles and colonization in favor of microbial dysbiosis, disease, and related immunological changes [84]. For example, pre- and post-natal stress impact neonatal microbial colonization [85, 86]. Additionally, mice subjected to social-related stressors demonstrate microbial dysbiosis in the gut and a concomitant increase in levels of circulating cytokines [87]. Acute and chronic stress can affect intestinal secretory immunoglobin A [88]. Chronic caregiver-related stress in humans has additionally been shown to affect the distribution of T cell phenotypes; changes that are consistent with periodontal disease progression [47, 48]. Increased perceived stress levels are also

accompanied by delayed initial-phase wound healing in humans, with lower interleukin(IL)-1α, IL-8, IL-1B, IL-6, and tumor necrosis factor(TNF)-α cytokine levels [50, 59]. In humans, prolonged stressors result in changes in glucocorticoid physiology that, in turn, interfere with appropriate regulation of inflammation, implicating the role of stress in health and disease [27].

Furthermore, in the context of periodontitis, chronic stress elevates inflammatory mediators, such as IL-1β and TNF-α, and decreases expression of regenerative factors, including basic fibroblast growth factor [51]. Such data cumulatively suggests that, in situations of chronic stress, the local periodontal environment shifts toward a state of pro-inflammation and anti-regeneration. Importantly, the stress hormone cortisol directly induces shifts in the oral microbiome and its gene expression profiles *in vitro*, which reproduces results found in the expression profiles of periodontal disease and its progression [89]. These studies and others have important implications for understanding stress-mediated oral dysbiosis, periodontal disease pathogenesis, and related oral immune responses.

Stress additionally has major implications for periodontal disease pathogenesis in the context of increased susceptibility to wound infection and delayed wound healing. For example, increased levels of the opportunistic pathogen *Staphylococcus aureus* were observed in a murine model subjected to stress conditions by 2 to 5 logs compared to control conditions, and stressed mice moreover demonstrated bacterial counts predictive of infection (87.5%) compared to controls (27.4%) [90]. Furthermore, mice subjected to insomnia or crowding-related stress revealed more severe infection outcomes following intradermal injection of *Streptococcus pyogenes* compared to control conditions [91]. Notably, this effect was mimicked with glucocorticoid administration and reversed with a glucocorticoid receptor antagonist [91]. Infections/inflammation also trigger stress [92]; stress and the immune response have a bidirectional relationship that may include microbial dysbiosis. Chronic stress-associated delays in soft tissue wound repair are mechanistically ascribed to delays in cellular migration and proliferation [59, 60, 93, 94]. Furthermore, gingival fibroblasts subjected to hydrocortisone treatment display increased production of tissue destructive matrix metalloprotease(MMP)-1, -2, -7, and -11 [67], suggesting that chronic stress or increased cortisol concentrations may compromise periodontal wound healing by promoting a tissue destructive phenotype [67]. Stress-related changes in endocrine, autocrine, and paracrine signaling systems also affect oral

bone tissue kinetics during homeostatic conditions and during wound healing responses. Chronic stress disorders, including post-traumatic stress disorder (PTSD) and depression, and stress-related adrenergic signaling are associated with poor alveolar bone growth [69] and osteoporosis [70-73]. These studies highlight that the underlying mechanisms for these stress-induced, bone-associated phenotypes include poor maintenance of osteoid competence, which may be exacerbated in the context of oral dysbiosis, periodontal disease and bone healing around dental implants. Although the effects of stress on the oral microbiome and periodontal wound healing have not been specifically identified, such supporting studies suggest a mechanistic relationship.

D. Health-Impairing Behaviors

In addition to biochemical effects of stress that can cause behavioral changes, stress can promote the adoption of health damaging behaviors, such as tobacco smoking or increased alcohol consumption, inadequate sleep quality, poor diet choices, insufficient hygiene practice, or poor compliance with appointments/post-operative treatment suggestions. Tobacco smoking is well-known to slow healing of surgical wounds [95], increased risk of tooth loss [96], as well as increased risk of periodontal disease relapse [97]. Heavy alcohol consumption can delay cell migration and collagen deposition during healing [98] and is an established predictor of tooth loss [99]. Furthermore, sleep disruption and lack of sleep was recently reported as significantly associated with severe periodontal disease [100] and has been previously shown to diminish skin barrier recovery [101].

Also, inadequate intake of vitamins and minerals through a balanced diet can also impair the wound healing process [102, 103] and has been shown to specifically impact the health and regenerative capacity of periodontal tissues [104]. Relevant to this knowledge, uncontrollable stress changes eating patterns and consumption of hyperpalatable foods, including the ingestion of highly processed carbohydrates and/or fatty foods [105]. Unhealthy diets (i.e. high carbohydrate, processed, fatty foods) are well recognized in promoting states of microbial dysbiosis and are associated with adverse health outcomes, including obesity, high blood pressure, and inflammation [84, 106-109]. However, the role of diet on periodontal disease and peri-implantitis pathogenesis remains minimally explored.

Data from animal models suggest that altered diets mediate changes in oral microbial composition and the local immune response [46, 110, 111]. Consumption of highly processed or fatty foods in the context of stress can further exacerbate changes in the microbiome towards

dysbiosis and disease [84]. In mice, chronic stress in combination with diets high in fat and sugar exacerbates changes in intestinal tight junction proteins and is associated with changes in psychological behaviors and altered inflammatory markers [112]. A direct link between a high-fat diet, the gut microbiota, and behavior has been demonstrated by microbial transfer from high-fat fed donor mice to antibiotic-mediated specific pathogen free (SPF) chow-fed mice [113]. Transfer of the high-fat-related donor microbiota led to increased intestinal permeability and inflammatory markers in the SPF chow-fed recipient mice and was further accompanied by increased anxiety-like behaviors [113]. Interestingly, probiotic treatment in mice was sufficient to prevent the ability of chronic stress to increase intestinal permeability, and to reduce stress-induced sympathetic outflow and hypothalamic pituitary adrenal (HPA) axis activation [114].

Fecal microbial transplantation approaches further demonstrate the causal role of the stress-induced microbiota in behavioral changes. For example, investigators have shown that microbial transplants from stress-exposed conventional mice to germ-free mice results in exaggerated inflammatory responses to bacterial infection [115]. A link between disease related microbiota and behavior has also been demonstrated, in which fecal microbiota transplantation from depressed patients to microbiota-depleted rats increased anxiety-like behaviors [116].

Lastly, chronic stress diseases can also cause behavioral problems such as those associated with poor periodontal treatment compliance and inconsistent periodontal maintenance appointments, which are historically known contributors to disease progression and tooth loss [117].

E. COVID-19 Pandemic, Stress, and Implications for Diseases of the Periodontium

During the current COVID-19 global pandemic the levels of stress are heightened more than normal [118-122]. In support, nearly every major health organization has postings on dealing with stress [123]. In a Harvard University-UNC study of US participants, 55% of individuals reported feeling more stress now during COVID-19 than before, and higher rates of stress were reported for racial and ethnic subgroups (61.1% for Hispanic individuals) [124]. Stress, in and of itself, is not pathognomonic for disease; however, stress can result in aberrant pathophysiology when it is sustained, uncontrollable, and when individuals do not have access to appropriate coping mechanisms. The conditions of the current COVID-19 pandemic foster this type of chronic stress providing the perfect storm of circumstances that remain out of one's control and limited access to appropriate coping strategies (e.g., social support).

Additionally, the concept of *allostasis (*or *allostatic load*), one of the most prominent frameworks in the stress literature, comes to bear. Allostatic load describes the “wear and tear” on the body as a result of chronic stress, and how this contributes to pathology [125, 126]. Thus, allostatic load, especially during the current global pandemic and crisis, may contribute to the breakdown of oral tissues and thereby promote or exacerbate oral diseases, such as periodontal disease.

Pathophysiological stress from COVID-19 is unique, as it activates multiple arms of the stressor mechanisms (i.e. behavioral, adrenergic, and steroid-based signaling) as well as directly affects the immunological infection profile of the respiratory and oral tissues relevant to the periodontal space. These synergistic, positive-feedback, stress-mediated signaling mechanisms have known attributed bacterial co-infections and oral presentations, including necrotizing periodontal disease [127], which appear to be similar to lesions described in COVID-19 patients [128, 129]. When taken in context from work described by Dr. Anthony Fauci, and his group, increased disease severity and mortality among individuals with respiratory viral infections are often attributed to subsequent bacterial co-infections, accounting for approximately 95% of deaths during the 1918 Spanish flu pandemic [130].

Metagenomic analysis of patients infected with a similar respiratory virus, severe acute respiratory syndrome coronavirus 2, detected extremely elevated reads of *Prevotella intermedia*, in addition to other periodontal pathogenic species including, *Streptococci*, *Fusobacterium*, *Treponema*, and *Veillonella* [131]. A case report was recently published in support of the etiology for necrotizing periodontal disease due to COVID-19 infection with pathogenic bacterial oral infection [132]. In this case, oral lesions achieved resolution with the following regimen of 400mg Metronidazole taken 3 times per day for 5 days and 0.12% chlorhexidine mouthwash twice per day for 10 days [132]. Using case reports and the available literature, these authors predict a spontaneous rise in the prevalence of acute periodontal necrotizing periodontal disease as COVID-19 cases increase [132]. As the pandemic timeline lengthens it is rapidly becoming a long-term, largely uncontrollable stressor, further inciting a need for additional studies on the impact of stress on health and disease outcomes.

Section Four: Classification of Stress for Treatment of the Periodontal/Implant Patient

Chronic stress and related diseases affects each individual differently because the body innately has a buffered reserve capacity to maintain a homeostatic equilibrium of the circulating hormones/chemokines. As individuals take on stressors in the context of predisposing conditions and poor biological/psychological response, these patients may transition to a state

of chronicity, maintaining this state in a continued cycle as resolution and recovery are blocked (**Figure 3**). One of the drawbacks of current chronic stress classifications is the use of diverse and subjective assessment questionnaires without objective evaluation. In the early 2010s, biophysiological distinctions were established between chronic and nonchronic psychological diseases [133]. Moving forward, it may be possible to reliably and objectively stratify the chronic stress population further into a two-tiered system [134-136]. A subclassification of chronic stress disease based on neurological activity, as determined by an electroencephalogram/EEG and novel machine learning algorithms, may be necessary to discern the biological effects of stress on systemic organ systems. This facilitates better understanding of the chronic stress disease process as well as its impact on the periodontium [134-136]. Based on the current body of literature and considering the current accessibility limitations to this neurological testing, we suggest here a two-level classification of chronic psychological stress, as it pertains to periodontal/implant therapeutics, namely low and high tiered categories.

a. Tier One: Low Levels of Chronic Stress

A low level of chronic stress may be defined as a patient exhibiting the clinical diagnosis of chronic stress, but has established coping mechanisms that minimizes biological/systemic effects of the disease process. These patients often present with one of the key chronic stress diseases (i.e. PTSD, depression, psychosis) or life situations (i.e. loss of a spouse, caregiver responsibilities, financial stress), but has identified physical, physiological, community-based management strategies that are effective on a daily basis. For these patients, monitoring availability and consistency of these coping strategies is essential, because over time the needs of the patient, available time, and access to resources will change. Because periodontal therapy is a lengthy process, continued assessment of these patients is essential and reclassification may be needed as the needs of the patient change.

b. Tier Two: High Levels of Chronic Stress

A high level of chronic stress may be defined as a patient exhibiting the clinical diagnosis of chronic stress, but has *not* established coping mechanisms. In these patients, exacerbated biological/systemic effects of the disease process (i.e. elevated cortisol and adrenergics). These patients often display one of the key chronic stress diseases (i.e. post-traumatic stress disorder (PTSD), depression, psychosis, chronic pain or illness) or life situations (i.e. loss of a spouse, caregiver responsibilities, financial stress), but have not identified physical, physiological, community-based management strategies that are effective on a daily basis. For these patients,

it is essential to use mindful treatment strategies and referral opportunities to provide all-encompassing and effective clinical care.

Regarding the tier two population we must also place a superlative emphasis on effective coping strategies. Effective stress coping requires the patient to adjust reactionary emotions and maintain a neutral/positive disposition in responsive to stress-inducing events. Generally, there are many coping strategies which include but are not limited to: asking others/friends for aid, lowering expectations, engaging in problem solving, seeking professional counseling service, maintaining positive attitudes, seeking/maintaining emotionally supportive relationships, distancing yourself from the source of stress, attempting to change the source of stress, and others. Some stress coping may be acute, such as a change in residence or onset of marital problems. Prolonged stressful environments can lead to elevated levels of stress-related hormones and to cause physical breakdown and illness. Some lifestyle change can be a helpful overall approach to coping with stressors. Examples of lifestyle changes include: regular exercise, adequate sleep, quality nutrition, inclusion of a daily meditation routine, avoiding enabling substances such as caffeine and alcohol, among others.

Section Five: Treatment Strategies for Chronic Stress Periodontal/Peri-Implant Patients

a. Preventative Measures

For all chronic stress patients, prevention strategies are the most ideal way to treat periodontal/implant-related diseases. Short periodontal maintenance recalls (both periodontal and peri-implant) have been reported as good strategies to maintain good periodontal/implant health over time [137, 138]. In addition, oral hygiene instruction with emphasis on positive behavior modifications (i.e. consistently keeping appointments, motivation for complete daily plaque removal). Furthermore, psychosocial factors (i.e., anxiety, depression, stress, and well-being) can affect the patients' quality of life on the day of periodontal treatment and the pain experience and medications used after surgical and non-surgical periodontal therapy (4-week period) [139]. Patient-provider communication and informed consent should address the role of these factors in the treatment process [139].

Stress management suggestions are imperative for the high chronic stress patients, as they may be unable to properly identify or manage it effectively without aid. Importantly, coping strategies might be unique to each individual, but as medical providers we can remind patients to continue searching for stress management solutions that fit their needs. The effects of yoga/meditation in the management of periodontal disease with reference to stress has been

examined [140]. While both groups (with and without yoga) exhibited improved periodontal pocket depths and bleeding scores, the group that utilized this stress-management strategy showed accelerated treatment outcomes by combating stress concomitantly with periodontal therapy [140]. Furthermore, the group that utilized the stress-management strategy of yoga exhibited stress scale scores that were significantly reduced [140].

In addition to suggestions of stress management options, providers must also understand that chronic stress can negatively influence decision making by individuals [141-143] resulting in negative coping behaviors. In these situations, clinicians should consistently update records pertaining to lapses in destructive behavior (i.e. depression, smoking, unhealthy diets), continue communication with the primary physician regarding systemic areas of decline/concern, and refer patients to counseling/medical services (i.e. smoking cessation, nutritional counseling, sleep specialists, etc.) when detrimental behavior modifications surface. While all detrimental behaviors need to be fastidiously managed, one example with well-established importance to the success of periodontal treatment is smoking cessation. Smoking cessation remains a significant factor in tooth retention for periodontal/implant patients and should be discussed and considered in all periodontal treatment plans, especially in the context of periodontal patients with chronic stress [144].

b. Therapeutic measures

If patients with chronic psychosocial stress present for periodontal treatment it is important to identify and remove the etiology, be resourceful in strategies to manage the patient, and utilize conservative treatment techniques. The most important therapeutic strategy is to identify and remove the etiology of the disease to address the onset and progression of the disease. Once the treatment plan is established, adjunctive therapies can help cultivate success and maintain therapeutic outcomes in patients with chronic psychosocial stress. Some adjunctive considerations are scheduling early morning appointments to help minimize waiting anxiety that might build with additional interactions throughout the day.

In addition, prophylactic antibiotics might be considered in immunocompromised individuals. Administration of low-dose doxycycline might also be an adjunct to consider during initial phases of treatment to help mitigate tissue destruction processes during the inflammatory phases of healing. Lastly, during therapeutic phases of treatment conservative surgical techniques are important to minimize the inflammatory phases of healing. As such flap management strategies remain essential [145, 146]. Furthermore, the use of antimicrobial oral

rinses, such as chlorohexidine 0.2% mouthwash post-operatively, should be considered to manage site healing during periods where oral hygiene cannot be maintained [147].

Section Six: Drawbacks of Current Models

The classification of psychosocial stress can be very heterogeneous. Some classification systems include major life events, chronic stressors (i.e. financial, care takers of individuals with chronic diseases), post-traumatic stress disorder, or even depression. Heterogeneity in classification can contribute to differences in reported values of serum/salivary concentrations of biomarkers and skew correlations with disease presentation. Furthermore, individual coping strategies can modify the outcomes of reported biomarkers. Among individuals in similar stressor groups, coping strategies could lend different physiological responses to the stressor stimulus. Importantly in chronic situations, coping strategies could inherently improve or deteriorate over time. Controlling these factors may be imperative to evaluating the psychobiological mechanisms affecting the interplay between psychosocial stress and periodontal-related diseases.

Questionnaires are often used in these studies to address these shortcomings, but there is not a consensus on this tool either. Use of more or less variables on “stress scales” to homogenize stress-inducing life events can also result in different outcomes [44, 64, 148]. It appears that detailed questions that allow investigators to discern between types of stressors, demographic information, acute vs. chronic stress, coping effectiveness may all be necessary [18, 149, 150]. Towards this point, one investigation that used a 6-point questionnaire found no significant differences in measured periodontal parameters [18]. Conversely, another investigation used a more comprehensive questionnaire and reported significantly impaired healing of chronic wounds [151].

Section Seven: Conclusion

Chronic stress is a relevant disease to the periodontal/implant practice, encompassing 25-28% of the American population [1]. Ideal solutions for these patients include de-escalation of chronic stress conditions, but sometimes this isn’t possible (i.e. care for family member with Alzheimer’s disease if unable to receive external help). As such, we must take measures as clinicians to incorporate knowledge of this systemic contributing factor and how it contributes to disease so that we can adjust our therapeutic approaches to ensure that periodontal or peri-implant diseases can be effectively mitigated or predictably treated.

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Figure Legends:

Figure 1: Psychobiological differences in acute versus chronic stress. Acute stressors (infection, trauma, surgical procedure) often present with upregulation of innate immune mechanisms but suppression of cellular immunity. This bodily response is evolutionarily preserved to allow quick recovery if necessary in dire situations. Conversely, chronic stress (Depression, post-traumatic stress disorder (PTSD), Caregiving responsibilities) is phenomenon that has less evolutionary-bearing and often presents with suppression of both the cellular and innate immune responses.

Figure 2: The effects of chronic stress axes on the periodontium and wound healing. The three axes involved in chronic stress include the Hypothalamic-Pituitary-Adrenal Axis (HPA), Behavioral Axis, and Adrenergic Axis (Neurovascular). Concomitant aberrance to homeostasis via these three mechanisms result in diminished wound healing capacity and susceptibility to progressive periodontal/peri-implant disease.

Figure 3: The stairway to chronic stress and context for a two-tiered classification. As individuals take on stressors in the context of predisposing conditions and poor biological/psychological response, these patients may transition to a state of chronicity. The tier1 population has excellent coping strategies and positive biological/psychological response to stressors with minimal compounding systemic diseases, and large systemic reserve capacity to resolve and restore homeostasis. The tier2 population falls into a perpetual cycle or relapse and chronic disease with systemic/periodontal complications as resolution and recovery pathways are blocked.

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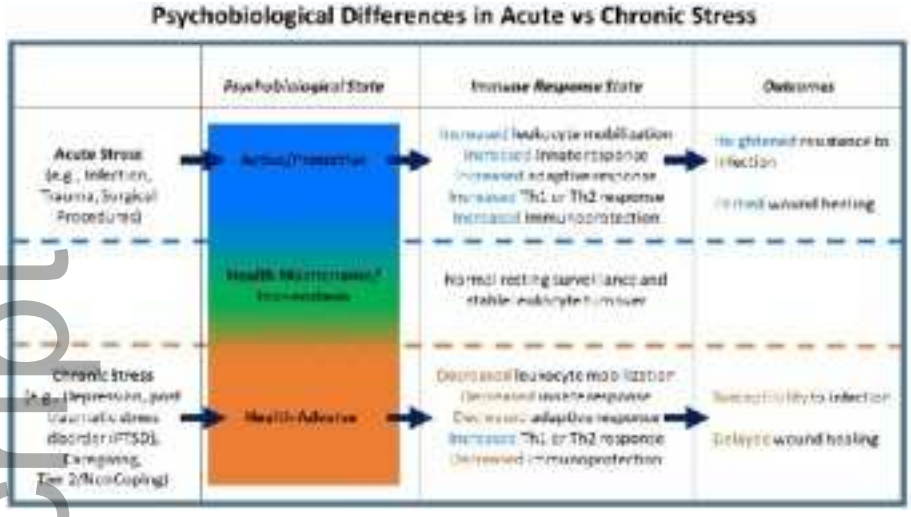

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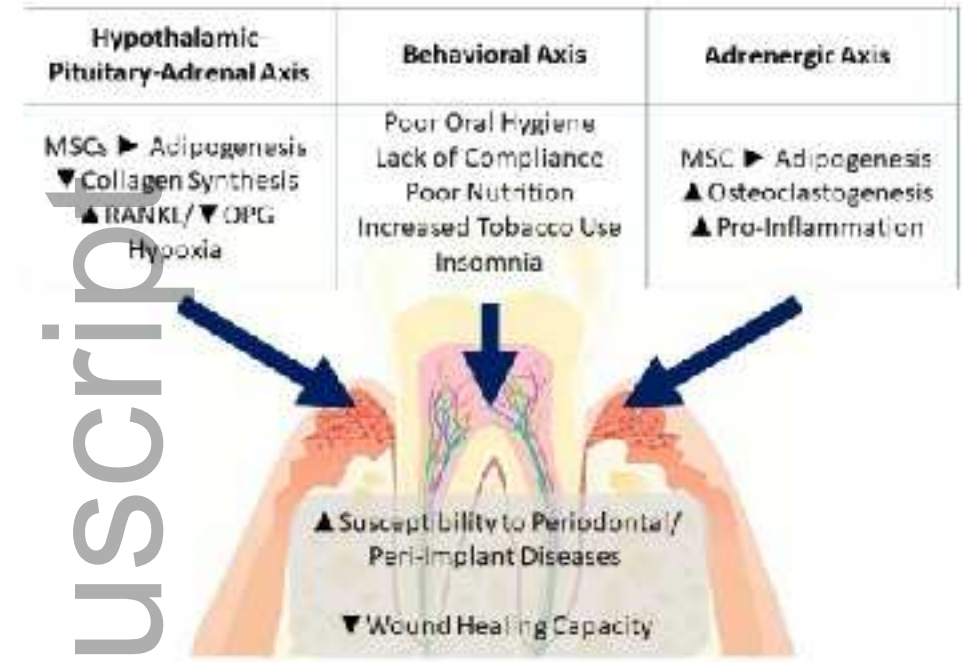
Effects of Chronic Stress Axes on the Periodontium and Wound Healing



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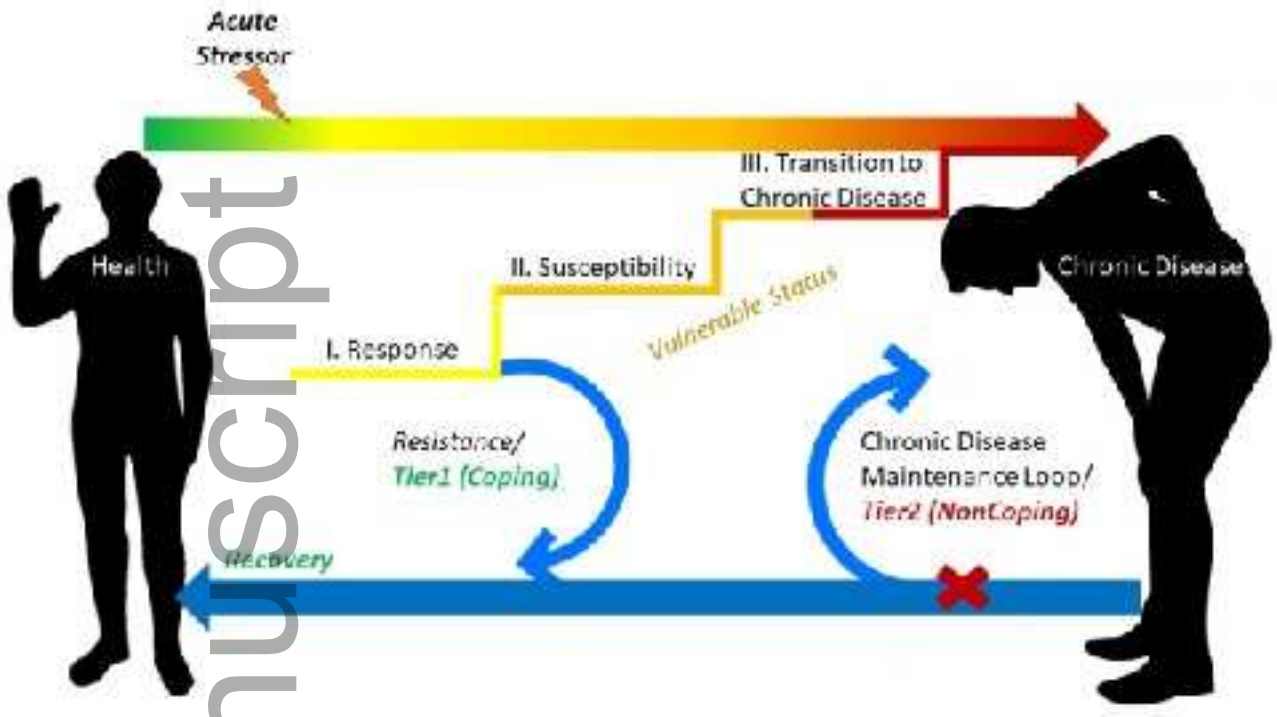
The "Stairway" to Chronic Stress and Context for Tiered Classification



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