Review

Alveolar Bone Architecture: A Systematic Review and Meta-Analysis

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Background: There is a need for studying bone characteristics systematically for a better understanding of planning (i.e., timing of placement and loading) and outcomes of implant therapy. Therefore, the aim of the present review is to evaluate alveolar bone microarchitecture and its modifiers.

Methods: Two independent reviewers conducted electronic and manual literature searches in several databases, including MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane Oral Health Group Trials Register, for articles published up to February 2015 reporting alveolar bone microstructure. The random-effect model was applied to calculate the weighted mean (WM) of total bone volume (TBV), which has a range from 0 to 1. TBV was stratified by anatomic locations, atrophic status, and types of specimens. Correlations between TBV and other bone-related parameters were also analyzed.

Results: A total of 800 articles were initially identified. After abstract/full-text review, 24 articles were included in the systematic review, of which 23 were also included in the quantitative analysis. The WM TBV was 0.365 (95% confidence interval = 0.278 to 0.452), higher in the maxillary/mandibular anterior sites than the maxillary/mandibular posterior sites. However, great variations existed within each anatomic location. Additionally, WM TBV was lower in atrophic sites than non-atrophic sites. TBV was correlated negatively with trabecular spacing (R^2 = 0.11).

Conclusions: The present systematic review suggests that the TBV might not be different between the defined anatomic locations. However, the atrophy status might influence TBV. *J Periodontol 2015;86:1231-1248.*

KEY WORDS

Alveolar bone grafting; bone and bones; dental implantation, endosseous; dental implants; evidence-based dentistry.

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Alveolar bone constitutes the most labile structure of the periodontium subject to continuous remodeling process because of its high sensitivity to external mechanical stimuli.[1] As such, in the presence or absence of forces generated, the natural dentition potentially influences bone "quantity"[2-4] and "quality."[5] Accordingly, after tooth extraction, a series of events trigger cellular and morphologic changes in alveolar bone architectural characteristics and dimensions. Amler et al.[6] showed that 8 to 12 weeks after extraction, there is a mix of mature bone and osteogenic tissue that reaches its complete fill after 100 days in undisturbed sockets. Although mineralized tissue eventually repopulates the extraction socket, the healed socket changes in bone trabecular composition and orientation. It has been demonstrated that the alveolar socket is formed mostly by woven and "necrotic" bone, with numerous empty bone lacunae.[7] Furthermore, 35% of the spontaneously healed sockets analyzed were considered "non-vital" empty lacunae that displayed as reduced osteoblastic activity, increased osteoclastic activity, and the presence of polymorphonuclear neutrophils.[8] Bone grafting materials used for socket augmentation have influenced bone quality as well.[9] Changes in bone quality and quantity have a significant influence on performance of implant therapy.[10]

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As a matter of fact, bone characteristics may vary among different anatomic locations.[5] It has been shown that a link exists between bone resorption rate and initial bone density before tooth extraction.[5] It was evidenced that atrophy-related remodeling processes commence earlier and progress farther in posterior regions than in anterior and premolar sites.[5] Furthermore, it has been shown after remodeling that trabecular organization was more haphazard in the posterior maxillary area compared to other sites.[11] Hence, it seems logical that bone resorption may not occur equally in all regions; location may potentially influence bone characteristics. Misch[12] proposed a bone density classification related to implant therapy based on the composition and measurable density reading from computed tomography (CT). According to this classification, D3–D4 bone, characterized by a porous thin layer of cortical bone and fine trabecular bone, is found primarily in the posterior maxilla, whereas D1–D2 bone represents a denser bone located commonly in the anterior and posterior mandibular ridges.[12] Trisi and Rao[13] validated the Misch classification with histomorphometric data. Interestingly, they failed to distinguish between D2 and D3 bone densities (66.78 ± 15% and 59.61 ± 19%, respectively, without statistical significance). Moreover, these types can be found randomly in the maxilla and mandible. Indeed, it seems that there is agreement regarding the influence of ridge (maxilla versus mandible) on bone density and composition,[14-17] but little is known about the influence of location and anatomic characteristics on the resorptive process of alveolar bone after extraction.

Since commencement of implant therapy, bone quality has gained attention because it was thought to be related directly to implant success.[13] Early studies demonstrated statistically significantly lower survival rates for implants placed in the posterior maxilla compared to other regions.[18,19] However, this does not represent the current reality because of improvements in implant designs and the enriched knowledge in implant biomechanics.[20] Nevertheless, bone characteristics strongly influence the degree of primary stability that can be achieved. How much primary stability is necessary? Evidence suggests that excessive primary stability may be harmful to bone homeostasis.[21] Higher torque, an indicator of high primary stability, has been shown to be associated with a zone of dead and dying osteocytes, along with microfractures that lead to greater peri-implant bone resorption.[21] In other words, is bone with low density truly poorer in terms of quality?[22] Certainly, primary stability is provided by a proportion of the mineralized bone tissue component, which has been traditionally confused with the cortical bone thickness; notwithstanding, in a lower proportion of bone marrow, a lower proportion of mesenchymal progenitor cells, mononuclear precursors, and endothelial cells and vessels needed for adequate biologic stability are expected.[23] It is also important to keep in mind that reparation after trauma, such as implant insertion, is guided by these biologic components that are mainly located in the non-mineralized bone component. Therefore, poor mechanical quality may represent a high potential for faster biologic integration.[22]

Bone characteristics and their determinant factors should be studied comprehensively to better understand their effect on implant therapy planning (i.e., placing and loading) and its outcomes. As such, the current systematic review aims to evaluate bone microarchitecture at the different regions of the human oral cavity and the anatomic/intrinsic factors that could influence them.

MATERIALS AND METHODS

Information Sources

Electronic and manual literature searches were conducted by two independent reviewers (AM and BE) in several databases, such as MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane Oral Health Group Trials Register, for articles published up to February 2015 without language or year restriction.

Focused Modified PICO Question and Outcome Measures

P: problem/patient. Complete or partially edentulous healthy individuals (i.e., no presence of systemic infectious diseases at the moment of implant insertion and no presence of serious diseases or conditions known to alter bone metabolism, such as osteoporosis, renal disease, oncologic disease, or disturbance of the calcium metabolism) with non-atrophic/atrophic maxillary/mandibular pristine ridges were included.

I: intervention. No real interventions were evaluated for ethical issues. However, the types of analysis to study bone characteristics were considered as the interventions: direct bone microstructure assessment (i.e., histomorphometric analysis, micro-CT, dual-photon absorptiometry, or back-scattered electron microscopy) in living individuals or human cadavers.

C: comparison. Different location and anatomic considerations in the edentulous sites were compared: 1) anterior versus posterior; 2) maxillary versus mandibular; and 3) atrophic versus non-atrophic.

O: outcome. The primary outcome was total bone volume (TBV), which is the total amount of bone present in relation to the analyzed bone volume. It is a parameter used widely in pathologies that alter

bone turnover because it perfectly reflects bone gain/loss. It indicates the fraction of a given volume of interest occupied by mineralized tissue. Therefore, implant anchoring at implant placement will rely primarily on this parameter.

Secondary outcomes included both direct metric parameters and non-direct parameters. The direct metric parameters were as follows. 1) Trabecular thickness (Tb.Th) is used to analyze the bone fill and to determine the mean thickness of the osseous structures. 2) Trabecular spacing (Tb.Sp) is used to detect the marrow spaces and thus should be correlated to TBV: the more TBV, the less Tb.Sp.[24] Therefore, this parameter inversely determines bone density. 3) Trabecular number (Tb.N) implies the number of times the trabeculae are crossed by means of length in a randomly selected way across the bone volume analyzed. 4) Trabecular pattern (Tb.Pf) quantitatively describes trabecular connectivity.[25] It is an inverse connectivity index. Therefore, concavity of the trabecular surfaces implies connectivity, whereas convexity means isolated and misconnected structures.

Non-direct parameters were as follows. 1) The structural model index (SMI) determines the relative presence of either plate- or rod-like trabeculae. It is defined in a range of 0 to 3, in which 0 corresponds to an ideal plate and 3 to an ideal cylinder.[26] Normally, plate-like trabeculae are associated with a higher osseous stiffness. 2) Degree of anisotropy (DA) measures the presence or absence of structures lined in a specific direction. Thus, biopsies analyzed with a high DA indicate that the trabeculae are oriented in the same direction. Mechanical anisotropy means that the mechanical properties are different for measuring different directions in the same sample.[27] Therefore, DA is probably the most important determinant of biomechanical strength.[28] 3) Bone mineral density (BMD) compares the attenuation coefficients of two hydroxyapatite patterns of known density (250 and 750 mg/cm^3). This is an area density and not a true volume density because it has a dependency on bone size.[29] 4) Microscopic bone composition includes lamellar bone, containing parallel, spirally arranged collagen fibers, and woven bone, which has a haphazard collagen organization.

Screening Process

For the PubMed library, combinations of controlled terms (MeSH and EMTREE) and key words were used when possible. Other terms not indexed as MeSH and filters were applied also. As such, the key terms used included the following: (((((((maxilla [MeSH Terms]) OR maxillae [MeSH Terms]) OR mandible [MeSH Terms]) OR alveolar bone [Title/Abstract]) OR density [Title/Abstract]) OR quality [Title/Abstract]) OR architecture [MeSH Terms]) OR trabecular [Title/Abstract]) AND histology [MeSH Terms]) OR micro computed tomography, x ray [MeSH Terms]). This preliminary screening was limited to 'humans' and 'clinical trials.' A second broader screening was conducted due to the small number of articles found indexed with the preliminary screening strategy: (((((((alveolar [Title/Abstract]) AND maxilla [Title/Abstract]) OR mandible [Title/Abstract]) AND pristine [Title/Abstract]) OR native [Title/Abstract]) AND bone [Title/Abstract]) OR process [Title/Abstract]) AND histomorphometric [Title/Abstract]) OR histomorphometry [Title/Abstract]) OR micro computed tomography [Title/Abstract]) OR microCT [Title/Abstract]) OR histology [Title/Abstract]). Again, "humans" and "clinical trials" were applied as restricted studies.

For the EMBASE and Cochrane libraries, the key terms used were (Title, Abstract, Keywords): bone architecture AND maxilla OR bone architecture AND mandible OR bone density AND maxilla OR bone density AND mandible OR bone quality AND maxilla OR bone quality AND mandible OR total bone volume AND maxilla OR total bone volume AND mandible. The screening in such databases were limited to "clinical trials" AND "humans." An electronic screening of the "gray literature" at the New York Academy of Medicine Gray Literature Report was conducted as recommended by high standards for systematic reviews (Assessment of Multiple Systematic Reviews guidelines).[30]

Additionally, a manual search of periodontics-related/implant-related journals, including *Journal of Periodontology*, *Clinical Implant Dentistry and Related Research*, *Clinical Oral Implants Research*, *Implant Dentistry*, *Journal of Clinical Periodontology*, *Journal of Dental Research*, *Journal of Oral and Maxillofacial Implants*, and *The International Journal of Periodontics & Restorative Dentistry,* from January 2000 to February 2015, was also performed to ensure a thorough screening process. Furthermore, references of included articles were screened to check all available articles.

Eligibility Criteria

Articles are included in this systematic review if they met the following criteria: randomized controlled prospective or retrospective, cohort or case series studies involving human participants aimed at showing bone microstructure by means of TBV in the different locations of the oral cavity. Articles in which the location could not be extracted clearly were included in the qualitative but not in the quantitative analysis (meta-analysis). Accordingly, several factors were retrieved from the studies: 1) study design; 2) number of examinations (biopsies); 3) specimen; 4)

Table 1.

Characteristics of Studies Included in the Qualitative Assessment

Reference (methodology)	Specimen	Objective	N (age [years])	Location	Atrophic	TBV	Direct Metric Parameters				Non-Direct Parameters		BMD	Conclusion
							Tb.Th	Tb.Sp	Tb.N	Tb.Pf	SMI	DA		
Aksoy et al., 2009[33] (Histomorphometry)	Living (whites)	To determine the relationship between radiologic bone density, tactile sense, primary stability, and histo-morphometric evaluation	12 (42.2)	Maxilla	No	38.20 ± 9.65	NR	NR	NR	NR	NR	NR	NR	Hundsfield units determined by CT are reliable to distinguish different bone densities. resonance frequency analysis and tactile sense must be studied further
			10	Mandible	No	44.08 ± 14.97	NR	NR	NR	NR	NR	NR	NR	
Bertl et al., 2014[35] (Histomorphometry)	Cadavers (whites)	To study the position and configuration of the mandibular canal	50 (74.3)	Mandible (posterior)	No	19.5 ± 8.82	122.24 ± 37.97	NR	NR	NR	NR	NR	NR	Bone surrounding alveolar nerve and vessels is associated with the quality of adjacent trabecular bone. Thus, the mandibular canal seems to be trabecular, not cortical, origin and to lack typical canal structure
Bertl et al., 2015[34] (Histomorphometry)	Cadavers (whites)	To describe the characteristics of cortical and trabecular bone in the atrophic edentulous mandible	185 (78.2)	Mandible (incisor)	Yes	24.98 ± 2.7	160 ± 20	NR	NR	NR	NR	NR	NR	Cortical bone remains mainly stable with increasing residual ridge resorption. The amount of cortical bone increased in evaluations of the complete mandibular area, and this was shown to be attributable to loss of mandibular height at the expense of trabecular bone area and not to a real increase in cortical bone.
			185	Mandible (premolar)	Yes	22.25 ± 3.6	150 ± 28	NR	NR	NR	NR	NR	NR	
			185	Mandible (molar)	Yes	18.6 ± 4.9	140 ± 20	NR	NR	NR	NR	NR	NR	
Blok et al., 2013[15] (Micro-CT)	Cadavers (NR)	To compare the microarchitecture and mineralization of trabecular bone in the anterior and posterior areas in mandible and maxilla	10 (73.7)	Maxilla	No	24 ± 13	20 ± 5	69 ± 24	157 ± 56	598 ± 394	NR	165 ± 29	886.6 ± 50.5	There are significant differences in microarchitecture between the maxillary and mandibular jawbones. This fact can influence the implant primary stability
			10	Mandible	No	37 ± 18	29 ± 11	71 ± 25	150 ± 42	506 ± 405	NR	164 ± 35	914.4 ± 77.7	

Table 1. (continued)

Characteristics of Studies Included in the Qualitative Assessment

Reference (methodology)	Specimen	Objective	N (age [years])	Location	Atrophic	TBV	Direct Metric Parameters				Non-Direct Parameters		BMD	Conclusion
							Tb.Th	Tb.Sp	Tb.N	Tb.Pf	SMI	DA		
Fanuscu et al., 2004[36] (Micro-CT)	Cadaver (NR)	To analyze maxillary and mandibular moderately resorbed bone in a human cadaver	1 (72)	Maxilla (anterior)	Yes	29	130	31	230	1,530	0.42	NR	NR	Bone mass and microarchitecture differ regarding the area analyzed. Higher bone density and connectivity are found in the anterior mandible.
			2	Maxilla (posterior)	Yes	16	105 ± 5	52.5 ± 2.5	159 ± 7	1,030 ± 50	0.96 ± 0.2	NR	NR	
			1	Mandible (anterior)	Yes	26	120	34	217	1,784	0.29	NR	NR	
			2	Mandible (posterior)	Yes	15 ± 3	100 ± 10	61 ± 10	142.5 ± 17.5	930 ± 170	1 ± 0.29	NR	NR	
Galindo-Moreno et al., 2010[37] (Histomorphometry)	Living (whites)	To compare the maxillar pristine bone with composite graft of anorganic bovine bone mixed with autologous bone 6 months after sinus augmentation procedure	10 (48.3)	Maxilla (posterior)	Yes	45.73 ± 7.98	NR	NR	NR	NR	NR	NR	NR	In higher proportion of residual anorganic bovine bone, less vertical bone resorption of graft occurs. Furthermore, its mixture with autologous bone enhances histologic behavior of biomaterial for sinus augmentation.
de Oliveira et al., 2012[38] (Micro-CT)	Living	To describe clinical parameters at dental implant bone sites with characteristics of bone tissue microarchitecture	46 (42)	Maxilla and mandible	No	35.5 ± 14.3	10 ± 7	35 ± 10	455 ± 210	–946 ± 697	–11.2 ± 14.5	NR	NR	Bone architecture, density, bulk, and spacing can be used for bone quality evaluation for implant treatment planning.
González-Garcia el al., 2013[39] (Micro-CT)	Living (whites)	To compare to conventional histomorphometry as the gold standard to study bone microarchitecture	39 (51.6)	Maxilla and mandible	No	48.7 ± 17.85	20 ± 7	30 ± 10	220 ± 72	–140 ± 744	0.4 ± 1.78	270 ± 145	NR	Micro-CT represents a reliable method to study bone microarchitecture providing less invasiveness compared to conventional histomorphometry.
Kim et al., 2015[16] (Micro-CT)	Cadavers (NR)	To compare correlation between microarchitecture through micro-CT and bone density in jaws of human cadavers	18 (NR)	Maxilla	Yes	14.59 ± 7.68	10 ± 2	63 ± 18	207 ± 80	NR	0.98 ± 1.87	NR	214.15 ± 95.04	Quality of trabecular bone has direct relation with micro architecture parameters. Bone volume fraction and BMD have direct relation with bone quality.
			16	Mandible	Yes	27.28 ± 10.19	9 ± 2	42 ± 18	376 ± 199	NR	–3.23 ± 0.09	NR	382.41 ± 118.46	

Table 1. (continued)

Characteristics of Studies Included in the Qualitative Assessment

Reference (methodology)	Specimen	Objective	N (age [years])	Location	Atrophic	TBV	Direct Metric Parameters				Non-Direct Parameters		BMD	Conclusion
							Tb.Th	Tb.Sp	Tb.N	Tb.Pf	SMI	DA		
Lindhe et al., 2013[17] (Histomorphometry)	Living (whites)	To observe composition of tissue in partially edentulous patients in different parts of mandible and maxilla	19 (NR)	Maxilla (anterior)	No	44.3 ± 3.6	NR	NR	NR	NR	NR	NR	NR	There are differences in terms of composition between maxilla and mandible. The cortical crest seems to be wider in the symphysis area, exhibiting less bone marrow compared to maxilla. The maxillary anterior region is poor in lamellar bone but rich in bone marrow.
			45 (NR)	Maxilla (posterior)	No	55.5 ± 1.8	NR	NR	NR	NR	NR	NR	NR	
			26 (NR)	Mandible (anterior)	No	70.5 ± 3.3	NR	NR	NR	NR	NR	NR	NR	
			33 (NR)	Mandible (posterior)	No	61.5 ± 2.2	NR	NR	NR	NR	NR	NR	NR	
Lindhe et al., 2012[11] (Histomorphometry)	Living (whites)	To compare bone structure in posterior edentulous maxilla in healthy individuals or with history or periodontal disease	36 (NR)	Maxilla (posterior)	No	55.2 ± 19.1	NR	NR	NR	NR	NR	NR	NR	Trabecular bone has frequently random orientation. The direction of the trabeculae might be the reason why bone in the posterior maxilla may provide limited instrumentation resistance. In addition, no significant differences were found between smokers versus non-smokers and periodontitis versus healthy individuals.
Makary et al., 2012[40] (Histomorphometry)	Living (NR)	To study correlation between insertion torque and bone density by means of TBV	6 (48.8)	NR	No	D1, 79.28 ± 10.19	NR	NR	NR	NR	NR	NR	NR	Tactile feedback during osteotomy preparation is predictable to discriminate soft and hard bone quality. Nonetheless, it does not seem reliable in discriminating intermediate bone types (D2–D3).
			12		No	D2, 43.68 ± 9.57	NR	NR	NR	NR	NR	NR	NR	
			13		No	D3, 39.96 ± 10.16	NR	NR	NR	NR	NR	NR	NR	
			9		No	D4, 28.57 ± 7.24	NR	NR	NR	NR	NR	NR	NR	

Table 1. (continued)

Characteristics of Studies Included in the Qualitative Assessment

Reference (methodology)	Specimen	Objective	N (age [years])	Location	Atrophic	TBV	Direct Metric Parameters				Non-Direct Parameters		BMD	Conclusion
							Tb.Th	Tb.Sp	Tb.N	Tb.Pf	SMI	DA		
Monje et al., 2015[41] (Micro-CT)	Living (whites)	To investigate bone-related characteristics of posterior atrophic maxilla and influence of its height on bone parameters	27 (56 ± 11.4)	Maxilla (posterior)	Yes	31.42 ± 10.12	16 ± 41	31 ± 87	180 ± 46	539 ± 345	1.48 ± 0.64	125 ± 94	432.47 ± 147.50	Bone volumetric fraction is influenced by bone height in posterior atrophic maxilla. As such, the lesser the remaining bone height, the lesser density is present.
Monje et al., 2015[14] (Micro-CT)	Living (whites)	To compare microarchitecture of different parts in non-atrophic maxilla	17 (50.4 ± 9.2)	Maxilla (anterior)	No	51.90 ± 28.42	28 ± 3	26 ± 10	430 ± 220	890 ± 320	–1.01 ± 1.7	NR	NR	Bone microarchitecture in non-atrophic maxilla is not dependent on location. Moreover, it is a direct association between TBV and Tb.N and TBV and Tb.Th.
			17	Maxilla (posterior)	No	46.93 ± 26.2	24 ± 7	31 ± 11	340 ± 260	778 ± 422	1.56 ± 3.01	NR	NR	
Moon et al., 2004[42] (Micro-CT)	Cadavers (NR)	To compare microarchitecture of basal bone with alveolar bone in premolar region of mandible	10 (55.1)	Mandible (posterior)	No	43.74 ± 16.04	31 ± 8	0.51 ± 0.14	1.27 ± 0.24	NR	1.04 ± 0.55	NR	NR	Alveolar trabecular bone has low bone surface density, SMI, trabecular separation compared to basal portion, and higher bone volume fraction, Tb.Th, and Th.N.
Parsa et al., 2015[43] (Micro-CT)	Cadavers (NR)	To study correlation between micro-CT, multi-slide CT, and CBCT in human jaws	20 (NR)	Mandible (posterior)	No	36.79 ± 23.17	NR	NR	NR	NR	NR	NR	NR	CBCT represents a high reliability in bone quality assessment. However, unlike bone volume fraction measurement, accuracy for density measurement is unfavorable.
Silthampitag et al., 2012[44] (Micro-CT)	Living (NR)	To evaluate microstructure of mandibular and maxillary bone in ectodermal dysplasia and anodontia conditions compared to patients without such conditions	3 (NR)	Mandible (posterior)	No	37.75 ± 8.75	21 ± 3	0.28 ± 0.3	1.72 ± 0.18	–9.04 ± 14.9	–1.68 ± 1.46	NR	NR	Additional bone samples might provide more data on whether broader areas of bone harvesting, age, or sex might affect quality and quantity of bone and influence implant treatment outcomes in patients with or without ectodermal dysplasia.
			2	Maxilla (posterior)		29.8 ± 16.5	15 ± 1	0.36 ± 0.08	1.9 ± 0.04	13.47 ± 7.25	2.98 ± 1.05	NR	NR	

Table 1. (continued)

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Reference (methodology)	Specimen	Objective	N (age [years])	Location	Atrophic	TBV	Direct Metric Parameters				Non-Direct Parameters		BMD	Conclusion
							Tb.Th	Tb.Sp	Tb.N	Tb.Pf	SMI	DA		
Trisi and Rao, 1999[13] (Histomorphometry)	Living (whites)	To test and compare hand clinical assessment of bone quality to histologic structure quantified by histomorphometric evaluation of bone density	56 (NR)	NR	No	D1, 76.54 ± 16.19	NR	NR	NR	NR	NR	NR	NR	Hand-felt perception allows to identify very dense and very soft bone. However, intermediate bone densities (D2 and D3) cannot be reliably distinguished.
						D2, 66.78 ± 15.82	NR	NR	NR	NR	NR	NR	NR	
						D3, 59.61 ± 19.55	NR	NR	NR	NR	NR	NR	NR	
						D4, 28.28 ± 12.02	NR	NR	NR	NR	NR	NR	NR	
Stoppie et al., 2006[45] (Micro-CT)	Cadavers (whites)	To study correlation between structural and radiologic parameters using CT	24 (NR)	Maxilla and mandible	NR	34.12 ± 15.25	NR	NR	NR	NR	NR	NR	230 ± 80.9	For edentulous jaws with a thin cortical layer, CT can identify very precisely properties of trabecular bone. Conversely, CT does not seem to be as reliable in ridges with a thicker cortical layer.
Ulm et al., 1993[46] (Dual-photon absorptiometry)	Cadavers (whites)	To study relationship between age and sex with bone mineral content	28 (79.8)	Mandible (posterior, female)	No	NR	NR	NR	NR	NR	NR	NR	1.351 ± 0.254	There are significant differences between males and females in terms of bone density and advanced age that seems to influence this.
				Mandible (posterior, male)	No		NR	NR	NR	NR	NR	NR	1.585 ± 0.309	
Ulm et al., 1997[48] (Back-scattered electron microscopy)	Cadavers (whites)	To describe trabecula, volume and connectivity of edentulous mandibles	10 (78.6)	Mandible (posterior, female)	No	21.83 ± 9.87	NR	NR	NR	−0.219 ± 1.64	NR	NR	NR	Differences between sexes was important for bone volumetric factor and Tb.Pf factor but not statistically significant. In edentulous mandible, there was extreme range of variation in trabecular connectedness and trabecular bone volume.
			10	Mandible (posterior, male)	No	36.57 ± 20.78	NR	NR	NR	−2.292 ± 2.46	NR	NR	NR	

Table 1. (continued)

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							Tb.Th	Tb.Sp	Tb.N	Tb.Pf	SMI	DA		
Ulm et al., 1999[47] (Histomorphometry)	Living (whites)	To analyze characteristics of trabecular bone in edentulous maxilla and structure of alveolar ridge	23 (72.5)	Maxilla (incisor, male)	UC	27.9 ± 8.64	133 ± 28.9	363 ± 93	2.07 ± 0.32	–1.1 ± 1.75	NR	NR	NR	Trabecular bone volume, thickness, and number differ for different locations in maxilla. Female maxilla display smaller amounts and lower connectivity of cancellous bone structure than in male maxilla.
			29	Maxilla (incisor, female)		20.2 ± 7.76	112 ± 33	480 ± 163	1.81 ± 0.47	0.17 ± 1.79	NR	NR	NR	
			18	Maxilla (premolar, male)		26.7 ± 11.36	138 ± 44.4	412 ± 151	1.91 ± 0.41	–0.56 ± 1.82	NR	NR	NR	
			29	Maxilla (premolar, female)		20.5 ± 8.50	121 ± 39.5	507 ± 159	1.68 ± 0.38	0.45 ± 0.60	NR	NR	NR	
			13	Maxilla (molar, male)		23.4 ± 9.49	118 ± 27.3	424 ± 140	1.95 ± 0.46	–0.70 ± 1.72	NR	NR	NR	
			22	Maxilla (molar, female)		17.1 ± 7.30	95 ± 19	535 ± 205	1.76 ± 0.61	0.12 ± 1.68	NR	NR	NR	
Ulm et al., 2009[5] (Histomorphometry)	Cadavers (whites)	To describe trabecular bone structure of edentulous mandibles in different locations	42 (77.58)	Mandible (incisor, male)	No	36.9 ± 12.4	208.5 ± 58	383.5 ± 140.3	1.77 ± 0.39	–3.0 ± 2.43	NR	NR	NR	Males generally display denser bone architecture. The difference between sexes might be attributable to postmenopausal events. The posterior molar region is lower in density, which might be because of early loss of molars.
			48	Mandible (incisor, female)	No	30.7 ± 9.91	193.3 ± 51.7	460.6 ± 140.9	1.50 ± 0.34	–1.44 ± 1.55	NR	NR	NR	
			60	Mandible (premolar, male)	No	35.9 ± 13.62	224.7 ± 62.3	436.7 ± 171.2	1.58 ± 0.32	–2.97 ± 2.79	NR	NR	NR	
			68	Mandible (premolar, female)	No	24.5 ± 8.45	167.5 ± 38	566.6 ± 201	1.47 ± 0.43	–1.11 ± 2.52	NR	NR	NR	
			23	Mandible (molar-male)	No	24.5 ± 7.93	174.9 ± 35.1	582.7 ± 182.5	1.38 ± 0.3	–1.34 ± 2.07	NR	NR	NR	
			37	Mandible (molar, female)	No	20.9 ± 9.65	165.9 ± 37.7	720.0 ± 275.3	1.22 ± 0.37	–0.05 ± 2.14	NR	NR	NR	

Table 1. (continued)
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Reference (methodology)	Specimen	Objective	N (age [years])	Location	Atrophic	TBV	Direct Metric Parameters				Non-Direct Parameters		BMD	Conclusion
							Tb.Th	Tb.Sp	Tb.N	Tb.Pf	SMI	DA		
Van Dessel, 2014[49] (Micro-CT)	Cadavers (NR)	To test accuracy of CBCT compared to micro-CT analysis to determine microstructure of edentulous mandible	8 (NR)	Mandible (posterior)	No	34.39 ± 5.41	180.5 ± 19.5	52.5 ± 14.8	1.92 ± 0.41	−65.71 ± 41.99	NR	NR	NR	High resolution CBCT represents a reliable tool for trabecular quantification and to determine bone quality in dentulous mandibles.

NR = not reported; UC = unclear.

age; 5) sex; 6) location; 7) vertical dimension (in millimeters); 8) horizontal dimension (in millimeters); 9) atrophy condition (according to each author's definition of atrophy); 10) TBV; 11) direct and non-direct parameters; 12) DA; 13) SMI; 14) thickness of the cortical layer (in millimeters); and 15) woven and lamellar bone (percentage). Moreover, to have better qualitative assessment of the included articles, the sections "objective" and "conclusion" were summed up for each study (Table 1). Conversely, the following were excluded for qualitative and quantitative assessments: 1) case reports or case series with less than five samples studied; 2) systematic reviews; 3) preclinical animal studies; and 4) human trials studying bone quality by means of indirect methods (i.e., Hounsfield unit [CT], "grayscale" [cone-beam CT (CBCT)], implant stability quotient [resonance frequency analysis], implant stability value [electronic mobility testing device], implant torque, or surgical feeling). Human trials with missing information were also excluded (see supplementary Table 1 in online *Journal of Periodontology*).

Risk of Bias and Qualitative Assessment

Two reviewers (AM and BE) designed and assessed the proposal for the present project to ensure the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed to avoid risk of bias and provide high-quality evidence. PRISMA consists of a 27-item checklist and a four-phase flow diagram.[31]

Two independent reviewers (AM and BE) evaluated all the included articles. The Newcastle-Ottawa scale (NOS) was proposed to assess the quality of such studies for a proper understanding of non-randomized studies.[32] Nonetheless, for these types of studies (morphometric examination of pristine bone in which no real intervention is evaluated), the nature of the research does not act as a determinant for the results. Therefore, a modified NOS scale was applied. Although it needs validation by additional studies, this novel qualitative assessment checklist, namely the Michigan scale, is proposed to be applied for future investigations on the study of pristine/grafted alveolar bone (see supplementary Fig. 1 in online *Journal of Periodontology*). It consists of a total of 10 items for critical appraisal of studies involving grafted bone and eight items for investigations on pristine bone divided into three sections: selection, comparison, and outcome (as proposed by the original NOS). Each item can be reached with a maximum of one star. Therefore, like NOS, quality is based on the number of stars reached.

Statistical Analyses

The primary outcome was the TBV of the alveolar bone. The value of TBV ranges from 0 to 1. The

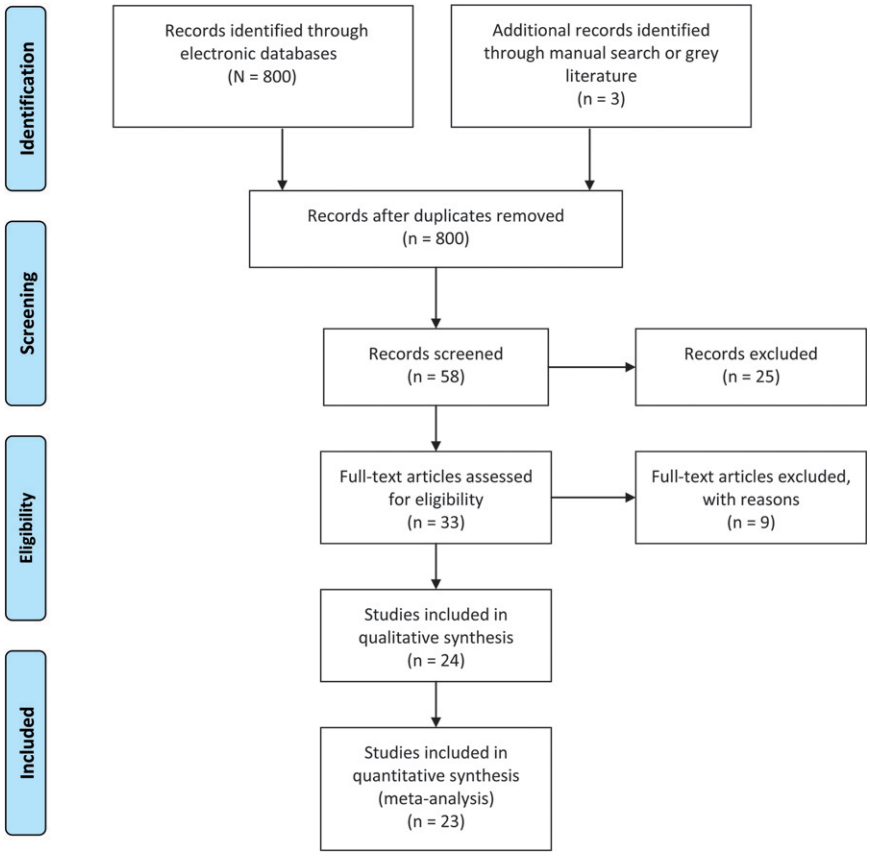

Figure 1.
PRISMA flowchart of the screening process in the different databases.[31]

pooled weighted mean (WM) and the 95% confidence interval (CI) of TBV were estimated using a computer program.‖ To further evaluate potential differences in TBV among various anatomic sites, WM of TBV and the 95% CI at four regions (maxillary anterior, maxillary posterior, mandibular anterior, and mandibular posterior) were calculated separately. Incisors and canines are considered anterior sites, and premolars and molars are considered posterior sites. The random-effect model was applied when performing meta-analyses to account for methodologic differences among studies. Forest plots were produced to graphically represent WM and 95% CI for the outcome using "site" as the analysis unit. To evaluate the possibility of atrophic status of alveolar bone on TBV, WM of TBV in atrophic and non-atrophic sites was calculated separately. The correlations of TBV with other bone parameters were plotted with commercially available software¶ and presented as R^2.

Heterogeneity and Publication Bias

Heterogeneities were examined by calculating Q with significance level at 0.1, I^2, and τ^2 using the same software. As a general guideline defined by the Cochrane Handbook for Systematic Reviews of Interventions, I^2 of 0% to 40% might suggest unimportance of heterogeneity, whereas 30% to 60% suggests moderate, 50% to 90% substantial, and 75% to 100% considerable heterogeneity. Publication biases were presented with a funnel plot for each meta-analysis.

RESULTS

Study Selection

An initial screening yielded a total of 800 articles (313 [PubMed Library], 313 [EMBASE], and 174 [Cochrane Library]), of which 33 potentially relevant articles were selected after an evaluation of their titles and abstracts. Full text of these articles was obtained and evaluated thoroughly. Of these, only 24 articles[5,11,13-17,33-49] fulfilled the inclusion criteria and subsequently were included in the qualitative synthesis (Fig. 1). Reasons for exclusion are displayed in supplementary Table 1 in online *Journal of Periodontology*. Of the 24 articles included in the systematic review, 23[5,11,13-17,33-45,47-49] were also included in the quantitative synthesis and meta-analyzed to extract the influence of the variables on bone density parameters. Details of all included studies are summarized in Table 1.

Qualitative Analyses

All the articles included in the present systematic review are prospective or retrospective non-randomized trials aimed at studying alveolar bone density. The Michigan scale was applied for studies involving pristine bone characteristics (see supplementary Fig. 1 in online *Journal of Periodontology*). According to this, a score of 6.95 ± 1.04 was obtained, showing the high quality of the studies included for the qualitative synthesis. A high inter-rater agreement was obtained (k = 0.89). Complete consensus was reached by discussion.

Influence of Location on Primary Outcome

A total of 23 publications with 1,095 study sites were available for data extraction. The TBV ranges from 0.15[36] to 0.59,[13] with the WM of TBV being 0.365 (95% CI = 0.278 to 0.452) (Fig. 2A). Taking anatomic location into consideration, the WM of TBV in the maxillary anterior, maxillary posterior,

‖ Comprehensive Meta-Analysis v.2, Biostat, Englewood, NJ.
¶ Excel, Microsoft, Seattle, WA.

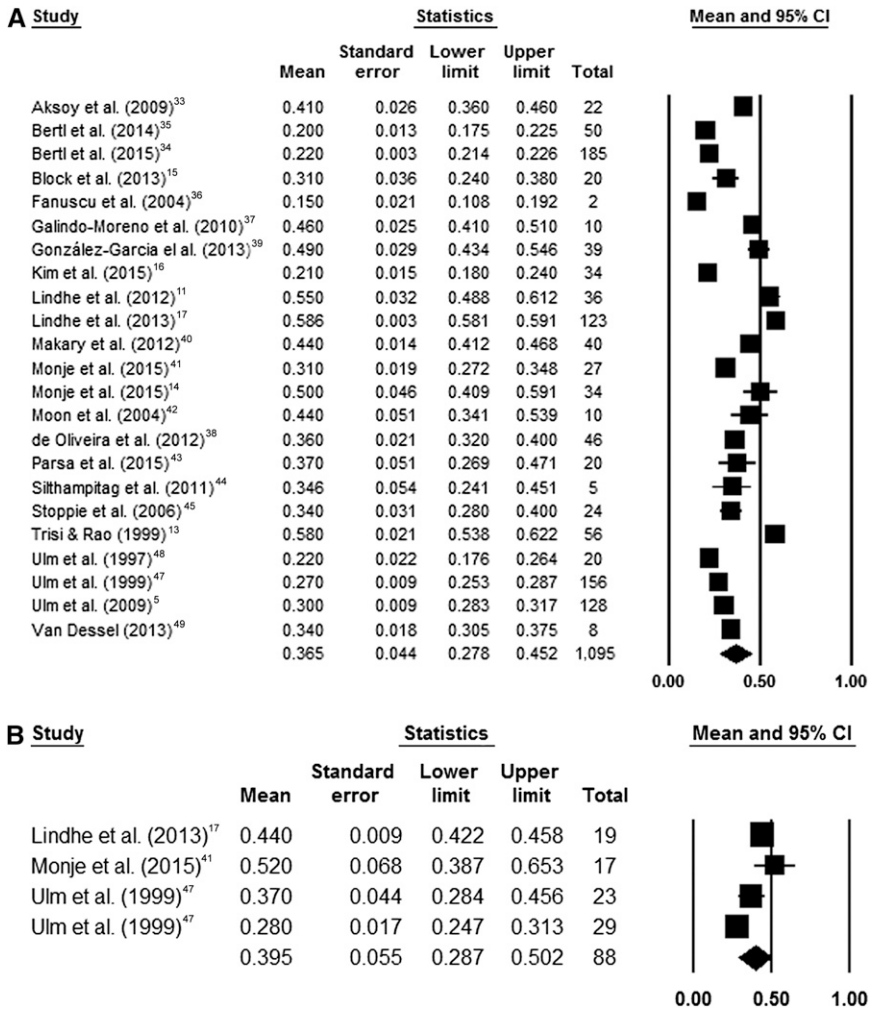

Figure 2.
A) *WM of TBV obtained from all the studies included in the quantitative analysis.* ***B)*** *WM of TBV in the maxillary anterior region.* ***C)*** *WM of TBV in the maxillary posterior region.* ***D)*** *WM of TBV in the mandibular anterior region.* ***E)*** *WM of TBV in the mandibular posterior region.*

mandibular anterior, and mandibular posterior regions are 0.395 (n = 88 sites, 95% CI = 0.287 to 0.502) (Fig. 2B), 0.357 (n = 219 sites, 95% CI = 0.233 to 0.481) (Fig. 2C), 0.375 (n = 301 sites, 95% CI = 0.102 to 0.648) (Fig. 2D), and 0.306 (n = 694 sites, 95% CI = 0.194 to 0.419) (Fig. 2E), respectively. Although there is a trend to show a higher TBV in the maxillary and mandibular anterior sites than in maxillary and mandibular posterior sites, there exist great variations within each anatomic location (Fig. 3).

Influence of Patient-Related Factors on Primary Outcome

The WM of TBV in atrophic sites is 0.268 (n = 258, 95% CI = 0.199 to 0.337) compared to 0.406 (n = 802 sites, 95% CI = 0.327 to 0.486) in non-atrophic sites (Fig. 4). No comparison of TBV between edentulous and dentate sites is available because no included study directly made such comparison; however, the results mentioned above suggested that the bone volume is statistically significantly higher in non-atrophic sites. The WM of TBV in the living individuals and cadaver specimens is 0.446 (n = 589 sites, 95% CI = 0.359 to 0.534) and 0.285 (n = 501 sites, 95% CI = 0.248 to 0.323), respectively. This result suggested that TBV might be higher in living individuals than in cadaver specimens.

Correlation of Secondary Outcomes With Primary Outcome

The R^2 of the correlation between TBV and Tb.Sp was 0.11 (Fig. 5), suggesting a weak correlation between the bone-related parameters mentioned above. Correlations between the other bone-related parameters were either below 0.1 or not available as a result of too few sample sizes available.

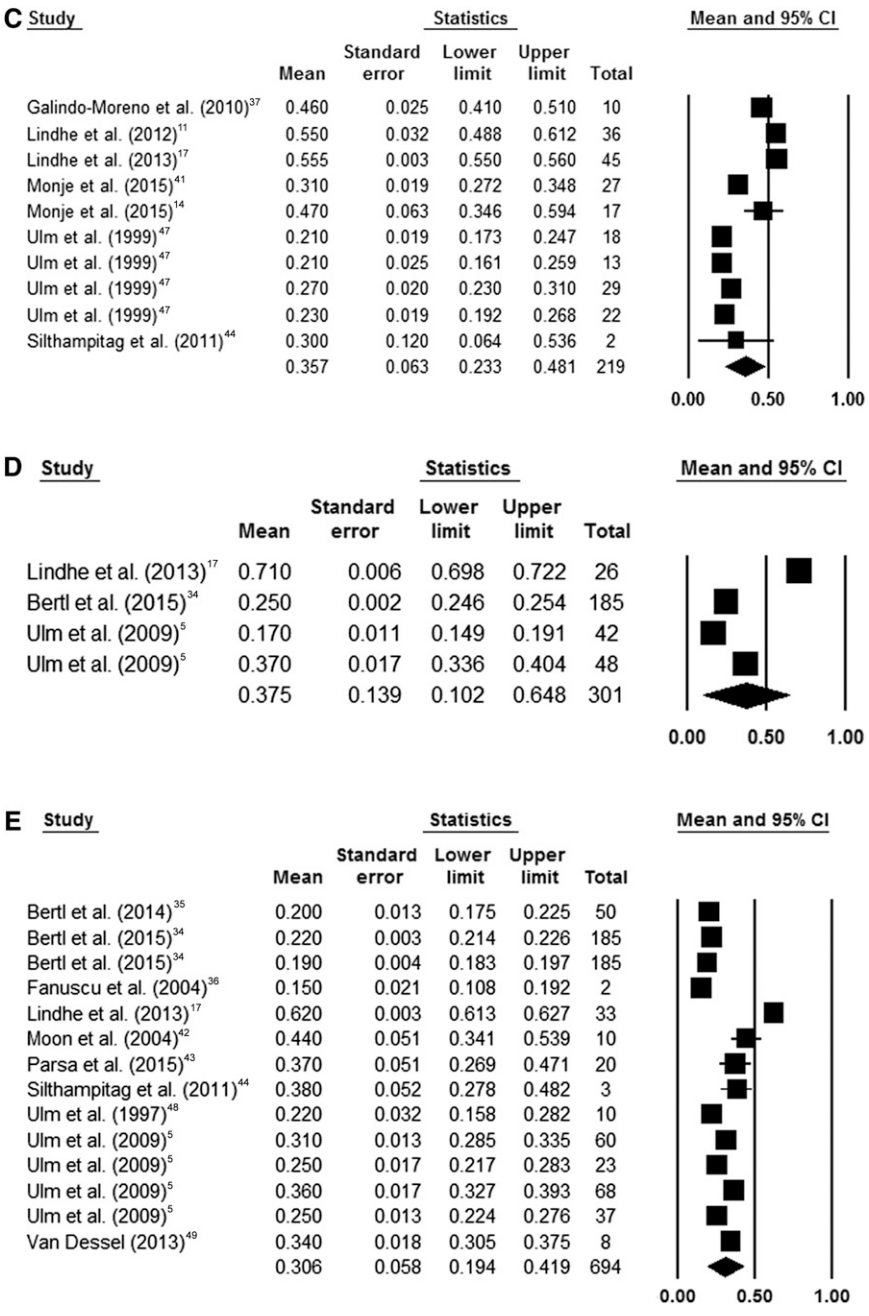

Figure 2.
(Continued)

Heterogeneity and Publication Bias

The *P* values of χ^2 tests for *Q* were generally higher than 0.1, suggesting non-significance of heterogeneity for most meta-analyses, except the studies evaluating atrophic sites ($P = 0.06$) and studies including cadavers ($P = 0.02$). The I^2 was 0 for most meta-analyses, suggesting a non-importance of heterogeneity, except the studies evaluating atrophic sites (56.28%) and cadaver sites (52.02%). The two meta-analyses were considered to have moderate to substantial heterogeneity. The τ^2 ranged from 0.004 for the meta-analysis evaluating only cadaver samples to 0.08 for the meta-analysis evaluating only samples from the mandibular anterior region. The τ^2 values ranged from 0.01 to 0.05 for the rest of the meta-analyses.

The mean TBV of each study was plotted in a funnel plot, with TBV at the horizontal axis and the standard error at the vertical axis for each meta-analysis (see supplementary Fig. 2 in online *Journal*

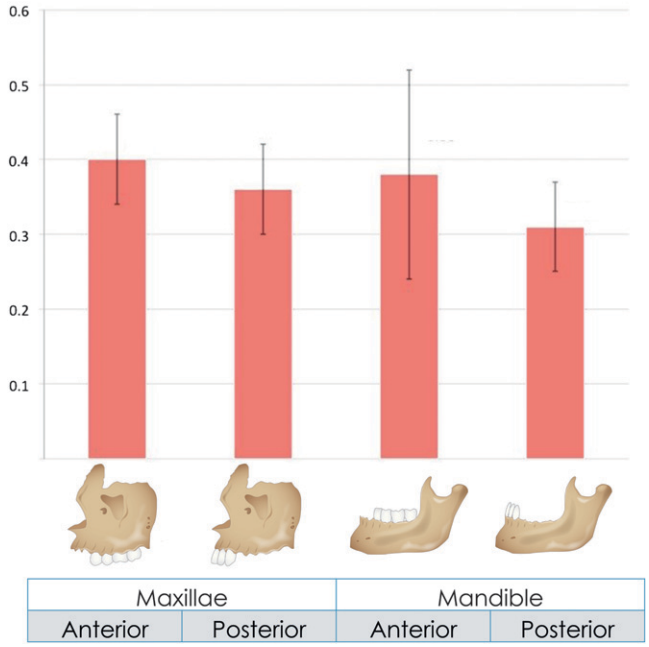

Figure 3.
Mean alveolar bone TBV with 95% CI in the different locations of the oral cavity. Note that each illustration represents each edentulous region analyzed.

of Periodontology). The plots showed overall symmetry of the distribution of studies in relation to the WM of TBV, suggesting a low publication bias. Because of the limited study sample size in atrophic, mandibular anterior, and maxillary anterior categories, symmetry could not be assessed.

DISCUSSION

Alveolar bone density has been regarded as one of the most crucial factors in influencing implant osseointegration in modern implantology.[50,51] It is a fact that primary or mechanical stability is required to have biologic integration,[52] particularly in scenarios in which immediate implant loading is to be applied. However, although recent literature[53] states that even over-drilled implants can achieve osseointegration, its degree still remains unclear. Early studies demonstrated higher implant success rate in the mandible because of its cortical (or compact) bone compared to the maxilla in which the cancellous bone presents with a more porous architecture.[18,54] Nonetheless, advances in the field along with the incorporation of mechanical engineering/designing (i.e., surface treatment or implant macro-design) have developed a more predictable mechanical stability and, ultimately, osseointegration, regardless of bone quality.[55,56] As a matter of fact, the term quality has been questioned from the biologic standpoint, claiming that a greater porosity can involve better tissue remodeling with optimum biomechanical integration.[22] According to this line of thinking, to confuse the higher mineral bone component with an improved bone quality is simplistic. Other parameters might be considered. During bone regeneration, osteocyte lacunar density and area undergo substantial changes.[57] The number of osteocytes plays a capital role. Osteocytes control resorption of the matrix in which they are embedded[58] and are sensors of biomechanical loading and signal the demand for bone remodeling.[59] During fracture healing, as in implant insertion, the osteocyte lacunar density is almost twice as high in woven bone compared to mature lamellar bone, exactly as in bone development, during which the density of osteocyte lacunae is higher in woven bone than in lamellar bone.[60]

Conversely, angiogenesis plays a pivotal role in skeletal development and bone fracture repair, and inadequate neoangiogenesis is considered a crucial factor in failed bone formation and remodeling.[61] It is one of the first events during wound healing and is regulated by a complex growth factor–mediated biochemical signaling system.[62] In vitro and in vivo studies of osteogenesis and fracture repair have provided a better understanding of the recruitment of vasculature in skeletal development and repair.[63] The number and distribution of vessels in the non-mineralized bone properties act importantly on bone maturation.[64] As such, bone non-mineralized fraction and its components might be highlighted in future classification on bone quality.

Hence, it becomes of great importance to apply the adequate loading protocol to avoid its disruption. However, from the clinical point of view, simpler parameters, such as hardness or stiffness of bone, help the clinician in the decision-making processes. For that reason and to provide guidance to clinicians, several classifications based on location or bone quality were proposed.[65-67] The most popular classification used four scale categories: D4 indicates that poorer bone is found primarily in the posterior maxilla and the denser bone (D1) is often located in the anterior mandible.[65] It is important to note that these classifications of alveolar bone were based primarily on clinicians' clinical experience and the much higher failure rate obtained from smooth surface implants.[68,69] Many local (i.e., atrophy or edentulism) or intrinsic (i.e., age or sex) factors have been identified to influence the bone characteristics,[47,48,70] and results presented have not been able to distinguish the intermediate types of bone.[13] In fact, Lindhe et al.[11] showed that in the posterior maxilla, which was described classically as soft bone supplying limited mechanical resistance, such an impression might be only because of a random

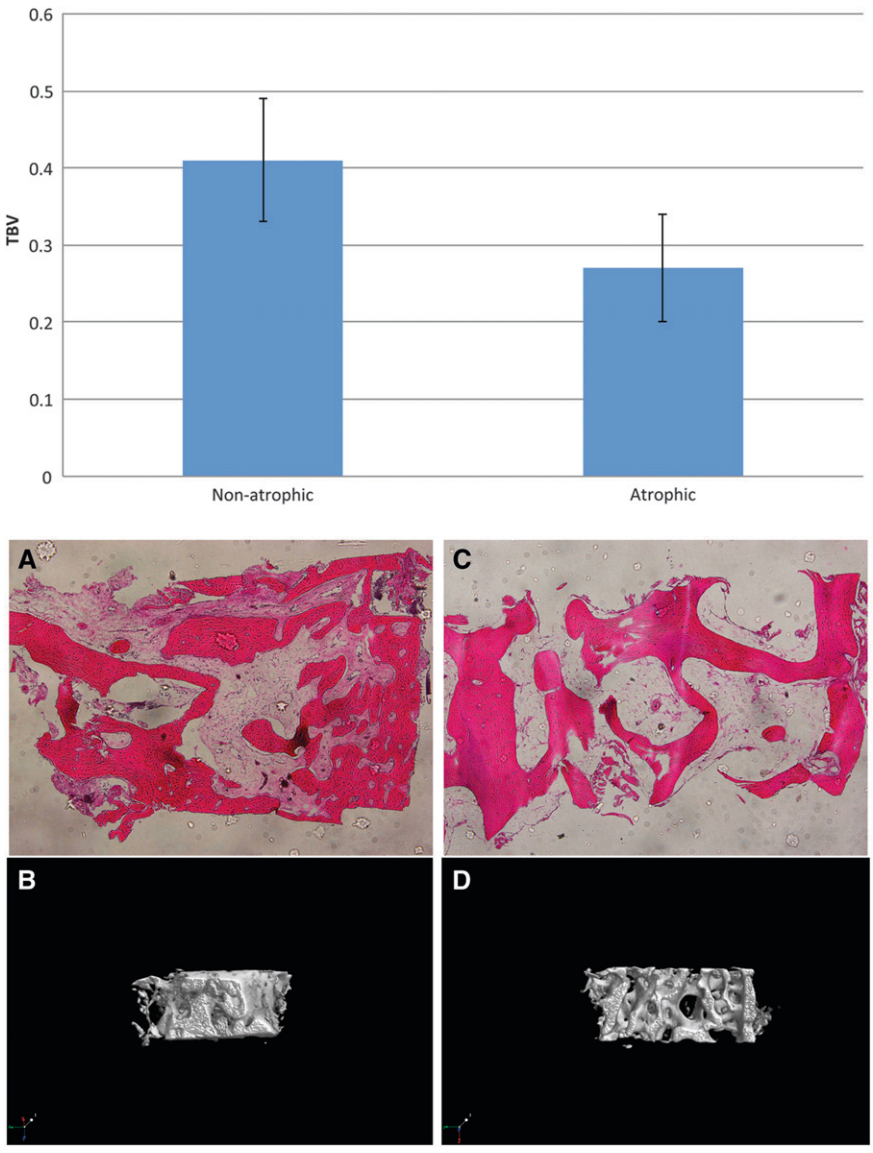

Figure 4.
Alveolar bone TVB (Mean ± 95% CI) of the atrophic and non-atrophic ridges. ***A)*** *Hematoxylin and eosin (H&E) histomorphometric analysis for alveolar bone retrieved from the non-atrophic posterior maxilla. Note that although not very compact bone, Tb.N and Tb.Th indicates denser bone.* ***B)*** *Micro-CT analysis shows the moderate trabecular density.* ***C)*** *H&E histomorphometric analysis for alveolar bone retrieved from the atrophic posterior maxilla. Note that the large Tb.Sp displayed indicates lower density.* ***D)*** *Micro-CT analysis shows the low trabecular density.*

trabecular direction other than the lower density. Hence, this study aims at investigating systematically alveolar bone architecture in the different locations and the factors that could inject bias. Results from this study showed that: 1) although location may lead to discriminating the TBV, it failed to reach statistical significance; and 2) as studied previously,[41,47,48] the atrophy degree influences negatively TBV. Hence, the data suggest that bone characteristics should not be classified based only on the location but also on examining each case independently, for example, using CBCT to assess alveolar bone architecture.[71-73] Because of the high heterogeneity among the articles in reporting their results, only a slightly negative correlation could be observed between TBV and Tb.Sp, which is in agreement with some of the previous findings.[14,39]

When the influence of specimen type (cadavers versus living humans) on TBV was analyzed, cadaver studies[16,35] have generally underestimated the overall TBV when compared to living individuals. Interestingly, to the best of the authors' knowledge, this is the first study to actually report this difference. The observation may be explained by the longer exposure to non-buffered/buffered formalin of the cadaver bone that may eventually alter bone tissue properties.[74,75] Another reason could be the age of the individuals analyzed. Albeit, the influence of TBV could not be studied because of the wide range, studies investigating alveolar bone in cadavers reported older ages compared to living individuals. Consequently, it could be assumed, although not stated, that bone metabolic diseases (e.g., osteoporosis or arthritis) might exist. Moreover, the likelihood for greater atrophy with age is explained by the "ontologic adaptation" against the mechanical loadings.[76] As reported previously, sex could be a determinant for bone characteristics (e.g., postmenopausal bone loss).[70] Again, as a result of the high heterogeneity, this factor could not be studied.

In summary, the results indicate that alveolar bone microarchitecture should not be standardized based only on the location because it has a wide variation in every location.

Several limitations were associated with current study. First, it is important to mention that the samples included did not necessarily follow similar methodology regarding their harvesting or processing. To minimize the risk of bias in this regard, only studies aimed at describing alveolar bone characteristics for implant site evaluation were selected. Hence, the commensurate features were assumed.

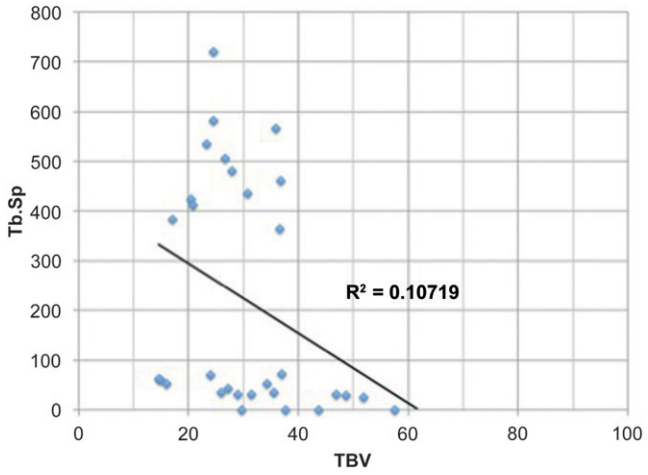

Figure 5.
The correlation between TBV and Tb.Sp. Mean Tb.Sp was plotted against mean TBV of available studies, with $R^2 = 0.11$, suggesting a low correlation.

Second, based on the Cochrane Database of Systematic Reviews, only randomized clinical trials should be included for evaluation.[77] Nonetheless, randomization within these types of intervention cannot be performed because of ethical issues. Hence, the attempt to rank the risk of bias of studies evaluating bone characteristics could not be performed for the NOS. Therefore, a novel scale to score non-randomized case series on bone characteristics for grafted/pristine sites was proposed. High inter-rater agreement was found for appraising all the studies, but it needs additional validation.

CONCLUSIONS

The present systematic review did not suggest a difference in TBV of alveolar bone among anatomic locations. Likewise, none of the other bone-related parameters studied showed significance. Factors such as status of atrophy and the nature of specimens influence TBV. Hence, implant treatment planning should be based on the actual bone properties and not the anatomic location.

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