BioMed Research International

Effect of Systemic Disease on Periodontal and Peri-Implant Tissues

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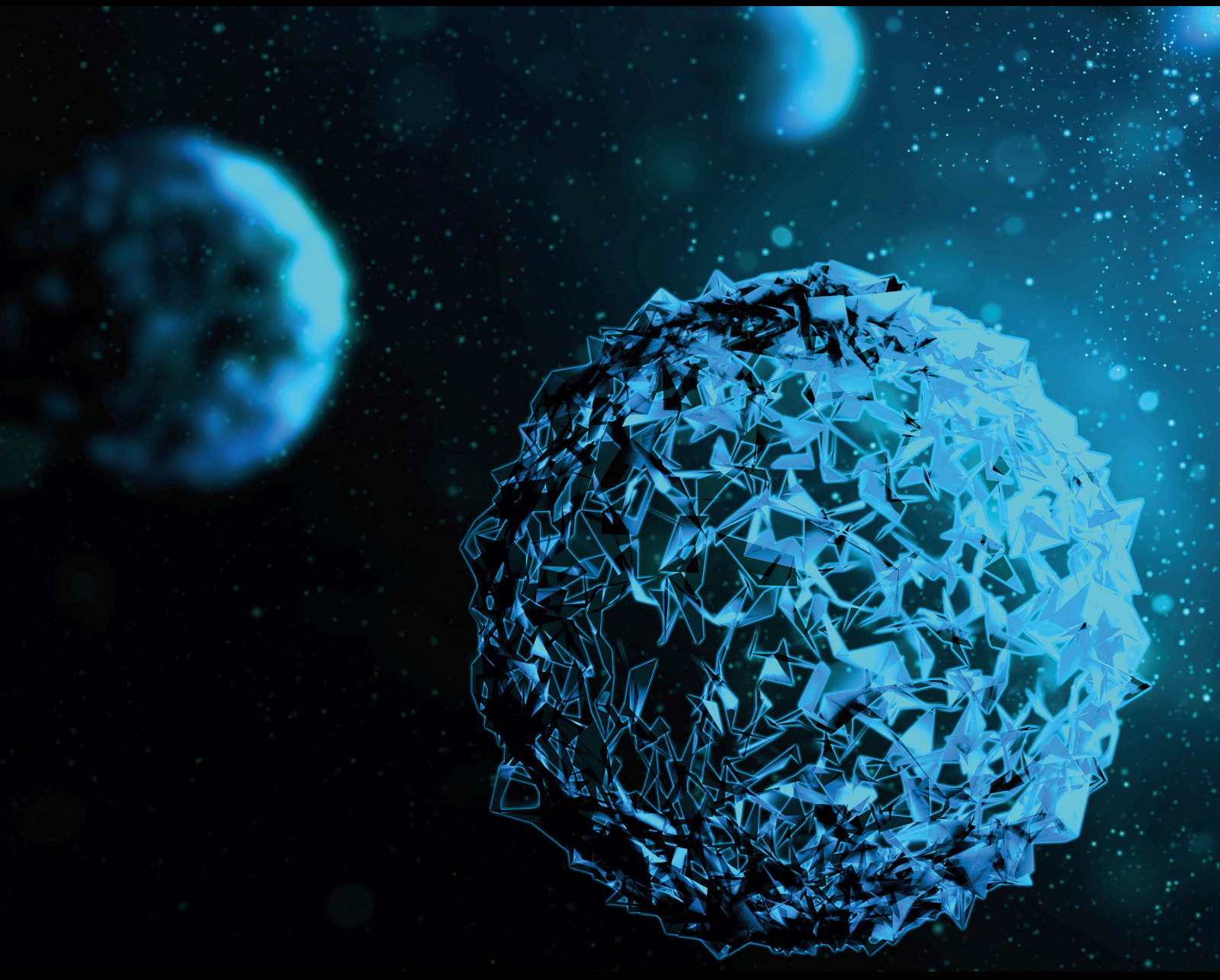
Guest Editors: Subraya Giliyar Bhat and Verica Pavlic



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https://doi.org/10.1155/2024/9838732

Retraction

Retracted: Use of Platelet-Rich Fibrin in the Treatment of Periodontal Intrabony Defects: A Systematic Review and Meta-Analysis

BioMed Research International

Received 12 March 2024; Accepted 12 March 2024; Published 20 March 2024

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Manipulated or compromised peer review

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

References

[1] L. Chen, Y. Ding, G. Cheng, and S. Meng, "Use of Platelet-Rich Fibrin in the Treatment of Periodontal Intrabony Defects: A Systematic Review and Meta-Analysis," *BioMed Research International*, vol. 2021, Article ID 6669168, 13 pages, 2021.

Hindawi
BioMed Research International
Volume 2024, Article ID 9817204, 1 page
https://doi.org/10.1155/2024/9817204

Retraction

Retracted: Effect of Platelet-Rich Plasma on Bone Healing in Immediate Implants Analyzed by Cone Beam Computerized Tomography: A Randomized Controlled Trial

BioMed Research International

Received 12 March 2024; Accepted 12 March 2024; Published 20 March 2024

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[1] A. S. Khan, N. Zaheer, A. M. Zaigham, M. Shahbaz, U. Zaheer, and M. K. Alam, "Effect of Platelet-Rich Plasma on Bone Healing in Immediate Implants Analyzed by Cone Beam Computerized Tomography: A Randomized Controlled Trial," *BioMed Research International*, vol. 2021, Article ID 6685991, 7 pages, 2021.

Hindawi
BioMed Research International
Volume 2024, Article ID 9786058, 1 page
https://doi.org/10.1155/2024/9786058

Retraction

Retracted: Periodontal Clinical Parameters as a Predictor of Bite Force: A Cross-Sectional Study

BioMed Research International

Received 12 March 2024; Accepted 12 March 2024; Published 20 March 2024

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[1] H. N. H. Alsharif, K. K. Ganji, M. K. Alam et al., "Periodontal Clinical Parameters as a Predictor of Bite Force: A Cross-Sectional Study," *BioMed Research International*, vol. 2021, Article ID 5582946, 8 pages, 2021.

Hindawi
BioMed Research International
Volume 2021, Article ID 9986375, 7 pages
https://doi.org/10.1155/2021/9986375

Research Article

Identification of Periopathogens in Atheromatous Plaques Obtained from Carotid and Coronary Arteries

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Received 21 March 2021; Revised 23 May 2021; Accepted 8 June 2021; Published 17 June 2021

Academic Editor: Iole Vozza

Increasing attention has been paid to the possible link between periodontal disease and atherosclerosis over the past decade. The aim of this study is to investigate the presence of five periopathogens: *Porphyromonas gingivalis* (*P.g.*), *Aggregatibacter actinomycetemcomitans* (*A.a.*), *Tannerella forsythia* (*T.f.*), *Treponema denticola* (*T.d.*), and *Prevotella intermedia* (*P.i.*) in atheromatous plaques obtained from the carotid and coronary arteries in patients who underwent coronary artery bypass graft surgery and carotid endarterectomy. Group I (carotid arteries) consisted of 30 patients (mean age: 54.5 ± 14.8), and group II (coronary arteries) consisted of 28 patients (mean age: 63 ± 12.1). Clinical periodontal examinations consisted of plaque index, gingival index, sulcus bleeding index, and periodontal probing depth and were performed on the day of vascular surgery. The presence of periopathogens in periodontal pockets and atherosclerotic vessels was detected using polymerase chain reaction. In both subgingival plaque and atherosclerotic plaque of carotid arteries, *P.g.*, *A.a.*, *T.f.*, *T.d.*, and *P.i.* were detected in 26.7%, 6.7%, 66.7%, 10.0%, and 20.0%, respectively, while for coronary arteries, *P.g.* was detected in 39.3%, *A.a.* in 25%, *T.f.* in 46.4%, *T.d.* in 7.1%, and *P.i.* in 35.7%. The presence of five periopathogens in carotid and coronary atherosclerotic vessels showed correlation in regard to the degree of periodontal inflammation. The present study suggests the relationship between periodontal pathogenic bacteria and atherogenesis. Further studies are necessary in relation to the prevention or treatment of periodontal disease that would result in reduced mortality and morbidity associated with atherosclerosis.

1. Background

Periodontal disease/PD is a chronic inflammatory disease that occurs in the teeth surrounding tissues in response to the presence of bacterial biofilm accumulation and characterized by complex host biofilm interactions [1, 2]. It affects up to 90% of the worldwide population (approximately 75% of the general population is affected by mild forms of periodontal disease including gingivitis, while the remaining 15% of the population has a moderate or severe form of periodontal disease). Therefore, it is ranked as a sixth most prevalent disease affecting humans [1, 2]. The presence of specific, predominantly Gram-negative anaerobic pathogenic periodontal microorganisms/periopathogens, such as *Porphyromonas gingivalis* (*P.g.*), *Aggregatibacter actinomycetemcomitans* (*A.a.*), *Tannerella forsythia* (*T.f.*), *Treponema denticola* (*T.d.*), and *Prevotella intermedia* (*P.i.*), and abnormal host response to periodontal disease are the key determinants of the onset and progression of periodontal disease [3]. In recent years, special attention has been paid to the possibility that the presence of periopathogens may influence systemic health [4–6].

Atherosclerosis is a chronic progressive narrowing of arteries that may lead to occlusion as a consequence of lipid

deposition [2]. It underlies coronary heart disease (80%), as well as myocardial and cerebral infarctions, therefore having a big socioeconomic importance [4]. The significant evidence proving the role of chronic inflammation in the pathogenesis of atherosclerosis and the destabilization of existing atheromatous plaques in the arteries has led many researchers to focus their attention to a search for the cause of the inflammation [7]. The link between periodontal disease and atherosclerosis was firstly given in 1963, when 25% higher risk of atherosclerotic plaque formation in a group of patients with periodontal disease was demonstrated [8, 9]. Since then, there is a growing amount of evidence regarding the contribution of chronic inflammation and presence of periopathogens seen in periodontal disease and the enhanced risk of atherosclerosis [7–10]. Increasing evidence over the past decade suggests that periopathogens from periodontal pockets can enter the systemic circulation directly and may be present in peripheral organs, such as atheromatous plaques of different blood vessels. The second mechanism proposed includes increasing levels of inflammatory mediators, such as lipopolysaccharides and other products from periopathogens' cell breakdown that may stimulate inflammatory cytokines, upregulate endothelial adhesion molecules, and induce a prothrombotic environment, enhancing the risk of an atherosclerosis [11]. The causal relationship between periodontal disease and atherosclerosis can be identified through the presence of periopathogens within atheromatous plaques [12].

The aim of the present study was to determine the association between the presences of periopathogens, namely, *P.g.*, *A.a.*, *T.f.*, *T.d.*, and *P.i.*, in subgingival and atheromatous plaques of coronary and carotid arteries in patients with chronic periodontitis, who were hospitalized and underwent surgery, by sampling DNA extract and amplification by polymerase chain reaction (PCR).

2. Materials and Methods

2.1. Patients. A total of 58 patients (male: 42, female: 16) with chronic periodontal disease and atherosclerosis participated in this study. Patients were divided into two groups depending on the atherosclerotic blood vessel, either carotid or coronary arteries. Group I consisted of 30 patients (male: 22, female: 8) from 32 to 83 years of age (mean age: 54.5 ± 14.8 years) scheduled for carotid endarterectomy. Group II consisted of 28 patients (male: 20, female: 8) from 28 to 94 years of age (mean age: 63 ± 12.1 years) with coronary artery disease scheduled for coronary artery bypass graft surgery (CABG).

Regarding periodontal disease, patients were recruited only if they were with at least 4 periodontal pockets. Periodontal disease (PD) was diagnosed if the subject exhibited clinical attachment level (CAL) > 1 mm and periodontal pocket depth (PPD) > 3 mm, at least at three sites in two different quadrants. According to CAL, patients with diagnosed PD were classified into two subgroups: patients with moderate chronic periodontitis (CP) (CAL = 3-4 mm) and severe CP (CAL ≥ 5 mm). PD was defined as localized or generalized depending on the number of affected sites [13]. Periodontal examination was performed by one trained and calibrated periodontist (D.S.). Periodontal and surgical interventions were performed in the Clinic of Dental Medicine, Faculty of Medicine, Military Medical Academy, Belgrade; Clinic of Dental Medicine, Faculty of Medicine, Kosovska Mitrovica; and Clinic for Vascular and Endovascular Surgery, Clinical Center Serbia.

The exclusion criteria were smoking, pregnancy, presence of systemic diseases, use of medication (antibiotic or corticosteroids), and periodontal treatment within the past 3 months. The medical and dental history of each subject was obtained by interwiev. Patients fulfilling the inclusion criteria were fully informed about the study and signed an informed consent form that was approved by the Ethics Committee of the Medical Faculty Kosovska Mitrovica, Priština.

2.2. Subgingival and Atheromatous Plaque Sample. On the same day of the surgical intervention for carotid endarterectomy and CABG, a complete periodontal examination was performed. Clinical examinations included plaque index (PI) (according to Silness Löe), gingival index (GI) (according to Löe Silness), sulcus bleeding index (SBI) (according to Mühlemann Son), and periodontal pocket probing depth (PPD) [13–16]. The subgingival plaque samples were collected using the paper point technique (Periopaper, Amityville, Pro Flow, NY, USA) from the bottom of two out of four present periodontal pockets. Each sample site was isolated with cotton rolls, gently scaled supragingivaly and air dried. A sterile paper point was inserted into the apical extent of each selected pocket, kept for 60 seconds, and transferred immediately to a sterile Eppendorf tube and kept on -70°C until the analysis.

The atheromatous plaque samples were obtained during the surgery, wherein the surgeon excised one or two small bits of atherosclerotic plaque from the edge of the blood vessel. In order to eliminate the blood contamination, the plaque samples were placed in a sterile Eppendorf tube with Tris-EDTA as a transport medium, mixed gently, and kept on -20°C until DNA preparation.

2.3. PCR Analysis. 16S rRNA PCR amplification was carried out to detect the presence of *P.g.*, *A.a.*, *T.f.*, *T.d.*, and *P.i.* in periodontal pockets and atherosclerotic vessels. The positive controls (American Type Culture Collection (ATCC)) consisted of DNA from pure cultures: *P.g.*—ATCC 33277, *A.a.*—ATCC 33384, *T.f.*—ATCC 43037, *T.d.*—ATCC 35405, and *P.i.*—ATCC 33563. PCR primers of microorganisms in the study are as listed in Table 1. Colonies obtained from cultures were suspended in sterile water and centrifuged and subjected to DNA extraction (positive control). Sterilized distilled water served as the negative control. 25 μl of aqueous mixture containing 2.5 μl of PCR buffer, 2.5 mM $MgCl_2$, 0.2 mM dNTPs, 0.2 μM of species specific primers, 1 U of DreamTaq DNA polymerase (all products from Thermo Fisher Scientific™; Waltham, MA, USA), and 5 μl of bacterial DNA isolate was used for the reaction. The temperature profile of the bacteria was 95°C (3 min), 35 cycles of 94°C (1 min), 60°C (1 min), and 72°C (1 min) and final

Table 1: Bacteria primer sequences used in the polymerase chain reaction (PCR) detection.

Periopathogens	Product size
Porphyromonas gingivalis (*P.g.*) CAA TAC TCG TAT CGC CCG TTA TTC	400 bp
Aggregatibacter actinomycetemcomitans (*A.a.*) CAC TTA AAG GTC CGC CTA CGT GC	600 bp
Tannerella forsythia (*T.f.*) GTA GAG CTT ACA CTA TAT CGC AAA CTC CTA	840 bp
Treponema denticola (*T.d.*) TAA TAC CGA ATG TGC TCA TTT ACA T TCA AAG AAG CAT TCC	316 bp
Prevotella intermedia (*P.i.*) GTT GCG TGC ACT CAA GTC CGC C	660 bp

extension at 72°C (7 min). The PCR reaction was carried out using a PCR thermocycler (PeqSTAR, PeqLAB Biotechnologie GmbH, Germany). After amplification, 10 μl aliquot of the amplified PCR product was subjected to electrophoresis in 8% polyacrylamide gel (0.5 x TAE buffer), stained with ethidium bromide, and finally visualized and photographed after exposure to UV light.

2.4. Statistical Analysis. The association between the periopathogens in the subgingival and atherosclerotic plaque samples was analyzed by calculating agreement statistics (absolute percentage agreement and Cohen's kappa statistic). The difference in average levels of various periodontal parameters between the patients with periopathogens present in both periodontal and arterial samples and those patients with negative results was tested using the Wilcoxon-Mann-Whitney test. P values less than 0.05 were considered statistically significant. All analyses were performed within the statistical software environment R (v4.0.2; R Core Team 2018), by using package irr [17].

3. Results

A total of 58 patients (male: 42, female: 16) with periodontal disease and atherosclerosis participated in this study. Totally, 58 atherosclerotic plaque samples (30 from carotid and 28 from coronary arteries) and 58 subgingival plaque samples were examined and compared for the presence of five periopathogens (*P.g.*, *A.a.*, *T.f.*, *T.d.*, and *P.i.*).

The presence of DNA of five periopathogens in subgingival and atheromatous plaques of carotid and coronary arteries is presented in Tables 2 and 3.

In all cases, the bacterial species found in atherosclerotic plaques were also found in the subgingival plaques, although the presence of the periopathogens in subgingival plaque was not always associated with its presence in the atheromatous plaques of the same patients.

The frequencies of bacteria in subgingival versus atherosclerotic samples of carotid arteries were as follows: *P.g.* (53.3%: 26.7%), *A.a.* (36.7%: 6.7%), *T.f.* (80%: 66.7%), *T.d.* (33.3%: 10.0%), and *P.i.* (76.7%: 20.0%) (Table 2). We found a significant agreement of *T.f.* in subgingival plaque and carotid plaque samples (Table 2). The frequencies of bacteria in subgingival versus atherosclerotic samples of coronary arteries were as follows: *P.g.* (57.1%: 39.3%), *A.a.* (42.9%: 25%), *T.f.* (82.1%: 46.4%), *T.d.* (10.7%: 7.1%), and *P.i.* (67.9%: 35.7%) (Table 3). We found a significant agreement of *P.g.*, *A.a.*, and *T.d.* in subgingival plaque and coronary plaque samples (Table 3).

The present study further analyzed the mean value of the selected periodontal parameters, namely, plaque index, gingival index, sulcus bleeding index, and periodontal pocket depth in patients positive to the presence of periopathogens in carotid and coronary atheromatous plaques (Tables 4 and 5). As for relationship between the presences of periopathogens in the carotid atheromatous plaques, all clinical periodontal parameters analyzed were nonsignificant (Table 4). However, the results showed a statistically significant relationship between the presences of *T.f.* in the carotid atherosclerotic plaque with periodontal pocket depth values, while all other periodontal parameters analyzed were nonsignificant (Table 5).

4. Discussion

PD represents chronic inflammation in tooth-supportive tissues (periodontal ligament, connective tissue, and alveolar bone); that, if left untreated, leads to periodontal pocket formation and consequent bone loss [18]. It has been suggested that periodontitis-associated bacteraemias and systemic dissemination of inflammatory mediators produced in the periodontal tissues may cause a systemic inflammation. To date, many authors have demonstrated such a relationship [19, 20]. Atherosclerosis, as a progressive disease of the medium and large elastic and muscular arteries, can lead to ischemic lesions of the brain, heart, or extremities and can result in thrombosis and infarction of affected vessels [7–10]. Mechanisms that have been proposed to explain the link between PD and atherosclerotic cardiovascular disease include the inflammatory pathways common to both diseases (increased levels of white blood cells, C-reactive protein/CRP, fibrinogen, intercellular adhesion molecule-1, and proinflammatory cytokines). Additionally, both diseases share similar risk factors such as smoking, poor oral hygiene, diabetes mellitus, obesity, stress, and reduced physical activities [21].

Among 58 patients included in this study, 42 of them (72.4%) were males, which make the prevalence of periodontal disease and atherosclerosis higher in man. Patients' mean age was 58.8 years. That is in correlation with common

Table 2: Presence of periopathogens in subgingival and atheromatous plaque of carotid arteries.

Periopathogens	Subgingival plaque	Atheromatous plaque		% agreement	Kappa	*P* value
		No	Yes			
Porphyromonas gingivalis (*P.g.*)	No	14	0	73.3	0.48	0.002
	Yes	8	8			
Aggregatibacter actinomycetemcomitans (*A.a.*)	No	19	0	70.0	0.22	0.054
	Yes	9	2			
Tannerella forsythia (*T.f.*)	No	6	0	86.7	0.67	<0.001
	Yes	4	20			
Treponema denticola (*T.d.*)	No	20	0	76.7	0.36	0.010
	Yes	7	3			
Prevotella intermedia (*P.i.*)	No	7	0	43.3	0.14	0.131
	Yes	17	6			

Table 3: Presence of periopathogens in subgingival and atheromatous plaque of coronary arteries.

Periopathogens	Subgingival plaque	Atheromatous plaque		% agreement	Kappa	*P* value
		No	Yes			
Porphyromonas gingivalis (*P.g.*)	No	12	0	82.1	0.65	<0.001
	Yes	5	11			
Aggregatibacter actinomycetemcomitans (*A.a.*)	No	16	0	82.1	0.62	<0.001
	Yes	5	7			
Tannerella forsythia (*T.f.*)	No	5	0	64.3	0.32	0.022
	Yes	10	13			
Treponema denticola (*T.d.*)	No	25	0	96.4	0.78	<0.001
	Yes	1	2			
Prevotella intermedia (*P.i.*)	No	9	0	67.9	0.42	0.007
	Yes	9	10			

understanding of periodontal disease's progress. The age itself is not a predetermining risk factor for periodontal disease, but due to the lower number of elastic and collagen fibers as well as mitotic activity of fibroblasts, it is usually seen in adults over 40 years.

This study has proved the presence of peripathogen DNA in atheromatous plaques of coronary and carotid atheromatous and subgingival plaque samples of the same patients. The results are suggesting that periopathogens from subgingival plaque are most likely invading the systemic circulation and therefore were detected in atherosclerotic plaques of nearby heart blood vessels, suggesting its impact on the progression of atherosclerosis.

These results are in accordance with many published studies on this topic [20–31]. The data of this study were consistent with those reported by Haraszthy et al. [20] (26% for *P.g.*, 18% for *A.a.*, 30% positive for *T.f.*, and 14% for *P.i.*), Nakano et al. [21] by specific PCR (20% for *P.g.*, 35% for *A.a.*, and 20% *T.d.*), Figuero et al. [25] by nested PCR (78.6% for *P.g.*, 66.7% for *A.a.*, and 61.9% *T.f.*), and Ohki et al. [26] (3.4% for *P.g.*, 19.7% for *A.a.*, and 2.3% *T.d.*). In contrast to the present study and the results of other authors cited above, Cairo et al. [12], when examining 40 samples of atherosclerotic plaques (obtained after carotid endarterectomy) by PCR, did not detect the presence of any periodontal pathogenic bacteria. Aimetti et al. [32] did not isolate any periopathogens in samples taken from atherosclerotic carotid arteries of patients with periodontal disease. These discrepancies in the results from different studies may be associated with the study population, host immune response, and varying methods of sampling and laboratory analysis [27].

In our study, the presence of five periopathogens in carotid and coronary atherosclerotic vessels showed correlation in regard to degree of periodontal inflammation (Tables 4 and 5). Even though most of these correlations were not found to be significant, the prevalence of almost all periopathogens was higher in patients with moderate and severe periodontal disease when compared to patients with average PPD. The possible explanation for this correlation could be that moderate to severe periodontitis increases the level of systemic inflammation. Consequently, periodontal treatment could efficiently reduce clinical signs of the disease and

Table 4: Clinical periodontal parameters for carotid arteries.

Variable	*P.g.* (+)	*P.g.* (-)	*P* value	*A.a.* (+)	*A.a.* (-)	*P* value	*T.f.* (+)	*T.f.* (-)	*P* value	*T.d.* (+)	*T.d.* (-)	*P* value	*P.i.* (+)	*P.i.* (-)	*P* value
Plaque index (PI)															
Mean	2.6	2.33	0.251	1.8	2.47	0.182	2.58	2.25	0.173	2.6	2.4	0.711	2.62	2.64	1
SD	0.47	0.58		0.42	0.53		0.52	0.46		0.52	0.54		0.44	0.49	
Gingival index (GI)															
Mean	2.79	2.39	0.038	2	2.57	0.433	2.59	2.45	0.296	2.9	2.47	0.06	2.73	2.73	0.717
SD	0.18	0.53		1.13	0.39		0.46	0.39		0.1	0.47		0.23	0.39	
Sulcus bleeding index (SBI)															
Mean	4.06	3.81	0.607	2.95	4.04	0.15	4.05	3.5	0.076	3.97	3.82	0.891	4.08	4.29	0.667
SD	0.75	0.91		1.34	0.69		0.81	0.56		1.05	0.77		0.71	0.69	
Periodontal pocket depth (PPD)															
Mean	5.63	4.86	0.254	3.5	5.26	0.082	5.25	4.83	0.518	6	5	0.23	5.83	5.86	0.431
SD	0.52	1.46		0.71	1.19		1.21	1.33		1	1.26		0.41	1.35	

Table 5: Clinical periodontal parameters for coronary arteries.

Variable	*P.g.* (+)	*P.g.* (-)	*P* value	*A.a.* (+)	*A.a.* (-)	*P* value	*T.f.* (+)	*T.f.* (-)	*P* value	*T.d.* (+)	*T.d.* (-)	*P* value	*P.i.* (+)	*P.i.* (-)	*P* value
Plaque index (PI)															
Mean	2.53	2.11	0.057	2.73	2.15	0.058	2.58	2.22	0.194	2.5	2.26	0.53	2.47	2.44	1.000
SD	0.65	0.59		0.23	0.68		0.44	0.6		0.71	0.6		0.43	0.53	
Gingival index (GI)															
Mean	2.58	2.36	0.172	2.32	2.28	0.085	2.37	2.38	0.103	2.85	2.45	0.394	1.65	2.49	0.675
SD	0.59	0.85		0.62	0.76		0.27	0.79		0.21	0.72		0.31	0.79	
Sulcus bleeding index (SBI)															
Mean	3.93	3.29	0.117	3.65	3.38	0.252	4.09	3.07	0.086	4.45	3.48	0.128	3.85	3.77	0.82
SD	0.88	0.97		1.23	1.02		0.6	1.2		0.64	0.86		0.67	0.8	
Periodontal pocket depth (PPD)															
Mean	5.73	4.38	0.015	5.25	4.59	0.021	6.08	4.33	0.004	6.5	4.77	0.21	6	4.8	0.057
SD	1.35	1.39		2.06	1.28		1.12	0.82		2.12	1.24		1.25	1.23	

decrease the level of systemic inflammatory mediators. Therefore, further studies with a larger number of patients related to prevention or treatment of periodontal disease that would result in reduced mortality and morbidity associated with atherosclerosis are necessary. Further *in vitro*, *in vivo*, and clinical studies with precise bacterial quantification with longer follow-up are essential in order to confirm the causal relationship between PD and atherosclerosis.

5. Conclusion

The present study suggests the relationship between periodontal pathogenic bacteria and atherogenesis. Even though the presence of periopathogens may not be the only factor that causes inflammatory disease associated with atherosclerosis, it should be considered a potential risk factor.

Data Availability

Data are available from the corresponding author upon request.

Conflicts of Interest

No conflict of interest exists.

Acknowledgments

The authors wish to thank to Prof. Sinisa Lakic, University of Banja Luka, Bosnia and Herzegovina, for his kind support in manuscript preparation.

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Hindawi
BioMed Research International
Volume 2021, Article ID 9931505, 9 pages
https://doi.org/10.1155/2021/9931505

Research Article

The Effect of Controlled Diabetes and Hyperglycemia on Implant Placement with Simultaneous Horizontal Guided Bone Regeneration: A Clinical Retrospective Analysis

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Received 10 March 2021; Revised 6 May 2021; Accepted 4 June 2021; Published 15 June 2021

Academic Editor: Marwa Madi

Diabetes represents a challenge in implant therapy because hyperglycemia may negatively affect bone regeneration, directly compromising clinical outcomes and increasing clinical failures. The aim of this retrospective study is to analyse the prognostic significance of HbA1c levels in patients undergoing implant placement associated with horizontal guided bone regeneration. Thirty-four patients were divided into 3 groups according to their HbA1c levels: nondiabetic normoglycemic patients (HbA1c < 5.7%), nondiabetic hyperglycemic patients (HbA1c < 6.5%), and controlled diabetic patients (HbA1c < 7%). Primary outcomes were dimensional changes in height (VDH) and width (DW) of the peri-implant defect. Secondary outcomes were evaluations of periodontal parameters of adjacent tooth sites, wound healing, marginal bone loss (MBL), and survival and success rates. At T_1 (6 months), mean VDH values in groups 1, 2, and 3 were, respectively, 0.07, 0.5, and 0.25 mm. Mean DW values in those same groups were, respectively, 0.07, 0.38, and 0.33 mm. HbA1c levels were not statistically related to VDH and DW values at T_1. No statistically significant differences were observed in MBL between groups ($p = 0.230$). Implant survival and success rates were, respectively, 98% and 96%. Simultaneous guided bone regeneration is a feasible procedure for the treatment of horizontal bone deficiencies in controlled diabetic patients.

1. Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. It is one of the most critical public health problems and the main cause of morbidity and mortality in modern societies. Recent data reveal that diabetes mellitus is increasing at an alarming rate in many countries, and it is estimated that 450 million people have the disease. Moreover, with the current striking plateauing of diabetes mellitus in adults, it is estimated that the rates may increase up to 71.1 million by 2040 in Europe [2]. The vast majority of diabetes cases fall into two main etiopathogenetic categories: type 1and type 2 [1].

The risk of developing type 2 diabetes increases with age, obesity, and lack of physical activity. It is often associated with a strong genetic predisposition or family history in first-degree relatives, more than type 1 diabetes. However, the genetics of type 2 diabetes are poorly understood [3].

In both type 1 and type 2 diabetes, various genetic and environmental factors can result in the progressive loss of β cell mass and/or function that manifests clinically as

hyperglycemia. Once hyperglycemia occurs, patients with all forms of diabetes are at risk for developing the same chronic complications, although the rates of progression may differ [3]. Enhanced blood glucose levels in chronic hyperglycemia increase the formation and accumulation of advanced glycation end products (AGEs), and the interaction between AGEs and their receptor, RAGE, plays a key role in the development of complications [4].

Diabetes mellitus has also been associated with the occurrence of a series of complications involving the skeletal system, collectively referred to as *diabetic bone disease* or *diabetic osteopathy* [5]. The diabetic skeletal phenotype presents the following features:

(i) Decreased linear bone growth during the pubertal growth spurt in adolescents with diabetes [6, 7]

(ii) Reduced bone mineral density and increased risk for osteopenia and osteoporosis [8]

(iii) Increased fracture risk [9]

(iv) Poor osseous healing characteristics and impaired bone regeneration potential [10–12]

Clinical and in vivo studies have established that impaired intramembranous and endochondral ossifications constitute dominant pathophysiological traits characterizing diabetic bone disease [13].

The currently available evidence seems to support the premise that hyperglycemia and/or hyperinsulinemia are the main mechanisms underlying diabetic bone pathophysiology [14].

Guided bone regeneration (GBR) was introduced as a therapeutic modality aiming to achieve bone regeneration by the use of barrier membranes [15–18]. From the evidence obtained through a literature search, no clinical study has assessed guided bone regeneration outcomes in people with a wide range of glycemic control, and studies are required in all major ethnic groups to establish more precisely the glycated haemoglobin (HbA1c) levels predictive of complications.

It should be considered that 30% of patients aged ≥30 years seen in general dental practices have dysglycemia. The rising number of diabetic patients and patients with dysglycemia represents a challenge for the high number of procedures involving bone replacement or augmentation, as hyperglycemia may delay and/or impair bone regeneration, directly compromising clinical outcomes and increasing clinical failures [13, 19].

The present study is aimed at assessing the prognostic significance of the glycated haemoglobin (HbA1c) levels in patients undergoing implant placement associated with horizontal GBR, as well as the correlation between glycemic control levels and clinical findings.

2. Materials and Methods

The study population consisted of all patients requiring implant placement associated with horizontal guided bone regeneration, who had been treated in the Oral Surgery and Implantology Department of the Catholic University in Rome. All reported investigations were carried out in accordance with the 1975 Helsinki Declaration, as revised in 2013 for ethical approval. All participants provided a written informed consent after being thoroughly informed about the study's objectives and procedures. Because of the retrospective nature of this study, it was granted an exemption in writing by the local ethics committee. All surgeries were performed by the same trained and experienced surgeon, and all clinical measures were recorded by the same examiner.

Inclusion criteria were as follows:

(i) Patients in need of one (or more) implants in the upper or lower jaw

(ii) Patients in need of horizontal bone augmentation

(iii) Bone defects which allowed us to obtain an adequate primary stability with a bone dehiscence that could be treated using a resorbable membrane

(iv) FMPS and FMBS below 15%

(v) Age > 20 years

(vi) HbA1C levels recorded in the clinical chart

Patients were excluded in the presence of any of the following conditions:

(i) General contraindications for implant placement and/or surgical treatment

(ii) Uncontrolled periodontal disease

(iii) Any drug or medication known to affect oral status and bone turnover or contraindicate surgical treatment (e.g., immunosuppressant, corticosteroid, or bisphosphonate therapy)

(iv) History of malignancy, radiotherapy, or chemotherapy for malignancy

(v) Smoker

(vi) Blood-related diseases

(vii) Excessive alcohol consumption

(viii) Conditions associated with an altered relationship between HbA1C and glycemia such as sickle cell disease, pregnancy, glucose-6-phosphate dehydrogenase deficiency, HIV, haemodialysis, recent blood loss or transfusion, or erythropoietin therapy

(ix) Unwillingness to return for follow-up examinations

2.1. Detected Parameters. The following data were collected from the clinical chart:

(i) Age

(ii) Sex

(iii) Race

(iv) Height and weight

(v) Oral hygiene maintenance therapy (yes: at least one prophylaxis per year; no: less than one per year or none)

(vi) Osteopenia/osteoporosis (yes/no)

Based on the case history of diabetes and the levels of HbA1c on admission, patients were divided into three groups:

(i) Nondiabetic normoglycemic patients (HbA1c < 5.7%)

(ii) Nondiabetic hyperglycemic patients (HbA1c < 6.5%)

(iii) Controlled diabetic patients (HbA1c < 7%)

The body mass index (BMI) of individuals in all groups was calculated by estimating the weight in kilograms (kg) and height in square metres (m^2), which were recorded in the patients' charts. The pharmacological therapy of each patient was recorded as well.

The peri-implant osseous defect was measured after implant placement using a periodontal probe and the following parameters were recorded in the clinical chart as previously described by Jung et al. [20]:

(i) Vertical defect height (mm) measured from the implant shoulder to the first bone-to-implant contact (BIC)

(ii) Infrabony defect height (mm) measured from the bone crest to the first BIC

(iii) Defect width (mm) measured from the mesial to the distal bone crests at the level of the implant shoulder

(iv) Horizontal defect depth (mm) measured from the bone crest to the implant surface in a direction perpendicular to the long axis of the implant

Clinical evaluations have been performed at baseline (T_0), 1 and 3 weeks, and 3, 6 (T_1), and 12 months (T_2) after surgery. Every patient underwent preoperative cone-beam CT scan with a resolution of 100 μm in order to complete the preoperative planning and evaluate the bone height and thickness of the cortical plates.

A cone-beam CT scan was taken at six months of healing. Primary outcomes were the measurement of dimensional changes in ridge width (mm) and height (mm) at six months after the procedure, assessed using a periodontal probe during the second-stage surgery. Secondary outcomes were the evaluations of periodontal parameters of the tooth sites adjacent to the treatment areas. The widths of keratinized tissue (KT), plaque index (PI), gingival index (GI), probing depth (PD), and bleeding on probing (BOP) were also measured at the tooth sites adjacent to the treatment areas at T_0 and T_1 and recorded.

The occurrence of adverse events (e.g., wound infection, exposure of the graft and soft tissue dehiscence, and necrosis) was recorded during the whole duration of the follow-up. Wound healing was assessed using the early wound healing score (EHS), which is composed of 3 parameters: clinical signs of reepithelialization, clinical signs of haemostasis, and clinical signs of inflammation. The summation of the points of these 3 parameters generates the EHS. The EHS for ideal wound healing is 10 points, while the worst possible score is 0 points. Recordings of EHS were performed every seven days for the first three weeks [21].

Marginal bone loss (MBL) was assessed immediately after prosthesis delivery and at 12 months from prosthesis delivery with intraoral radiography, utilizing the long cone parallel technique. A bite made of silicone (3M™ Express, 3M ESPE Dental Products, St. Paul, MN, USA) was placed in the holding system, allowing for it to be repositioned precisely during each follow-up visit. Linear measurements (mm) on the digital images were performed to record the distances of the most coronal points in the mesial and distal ridge aspects from the implant shoulder.

2.2. Surgical Procedures. Before surgery, patients received antibiotic therapy (2 × 1 g amoxicillin clavulanate). The perioral skin was disinfected by means of a sterile gauze mounted on Klemmer forceps and soaked in povidone-iodine solution. Patients were then covered with TNT drapes, leaving only the oral cavity uncovered; mucous membranes were cleaned with a gauze soaked in 0.2% chlorhexidine.

Surgery was performed under local anaesthesia (articaine 4% with epinephrine 1 : 100,000). The horizontal incision was placed crestal in the lower jaw and slightly buccal on the upper jaw, extending from the distal aspect of the mesial tooth to the mesial aspect of the distal tooth. The incision was continued intrasulcularly in both the buccal and lingual areas. Releasing incisions were performed at the buccal, mesial, and distal line angles. A mucoperiosteal flap was raised, and the bone was exposed and carefully curetted. The adjacent teeth were carefully cleaned using ultrasonic and manual instruments. The insertion of the bone level implants, with lengths between 8 and 12 mm and diameters between 4.1 and 4.8 mm, was carried out according to the manufacturer's protocol. During implant placement, primary stability was assessed via insertion torque and hand testing. Measurements of the defect were performed using a periodontal probe (UNC-15). The cortical plate was perforated by means of a round bur to favour bleeding and access to the marrow cavity. Periosteal releasing incisions were used to allow tension-free adaptation of the mucoperiosteal flaps. A resorbable collagen membrane was shaped according to the recipient site and fixed on the lingual/palatal side with two or three fixation pins. The autogenous bone chips were collected from the areas surrounding the peri-implant defect using a bone scraper; they were then placed adjacent to the implant surface and mixed with deproteinised bovine bone mineral using a 50 : 50 ratio to fill the defect area completely. The membrane was closed over the graft and fixed on the buccal side using two or three titanium pins. The crestal incision was sutured with PTFE internal horizontal mattress sutures; finally, PTFE single sutures were placed on the vertical incisions and between the mattress sutures. Patients were instructed to rinse twice a day with 0.2% chlorhexidine

mouth rinse and to continue the antibiotic regimen for 6 days. In addition, analgesics (500 mg ketoprofen) were prescribed for the next 3 days, according to individual needs. Patients were also instructed to refrain from mechanical plaque removal in the area for 2 weeks and to rinse twice daily with a 0.2% chlorhexidine mouth rinse. Sutures were removed 21 days following surgery. All patients were enrolled in a maintenance care program. The second surgery was carried out after six months.

2.3. Statistical Analysis. Descriptive statistics used for continuous factors included means and SDs, and medians and interquartile ranges (IQRs); in the case of categorical factors, absolute and relative frequencies (%) were employed. In order to assess whether glycemic status in patients with horizontal bone defects represents a factor capable of influencing clinical outcomes, patients were classified as "successes" and "non-successes," where success meant the achievement at T_1 of a vertical defect height and width equal to 0 mm. Correlations between categorical variables were made by using the chi square or Fisher exact test, while those between continuous variables were calculated by means of the Mann–Whitney U test.

Binary logistic regression was adopted to test the effects of the considered variables, treating the indication success/non-success as a dependent variable. In order to evaluate the possible influence of glycemic level on clinical results, we proceeded with a two-way mixed ANOVA model. A two-tailed value of $p < 0.05$ was considered significant. All analyses were conducted using the Stata version 14.2 software program (StataCorp, College Station, TX, USA).

3. Results

The study sample consisted of 34 patients (15 women and 19 men; mean age: 69.56 years; SD: 8.2 years). Fourteen patients (mean age: 71 ± 7 years; 7 females and 7 males) were included in group 1, 8 patients (mean age: 72 ± 5 years; 3 females and 5 males) were included in group 2, and 12 patients (mean age: 66 ± 9 years; 5 females and 7 males) were included in group 3. All participants received implant placement and simultaneous horizontal GBR between 1 January 2017 and 1 January 2019. Patients in group 3 were all affected by type 2 diabetes. In total, 50 implants were placed. Twenty-one participants (62%) received a single implant, while 13 (38%) received multiple implants (Table 1). All of the surgeries were successfully carried out, no intraoperative complications were recorded, and all implants obtained an adequate primary stability (insertion torque ≥ 25 Ncm).

3.1. Complications. Only one patient belonging to group 2 experienced a case of early implant loss, which was successfully replaced after three months, and two patients presented biological complications during the first 3 weeks after surgery.

All of the complications were cases of wound dehiscence, which were treated by local disinfection (rinsing with 0.2% chlorhexidine mouth rinse and applying 1% chlorhexidine gel), and all affected patients recovered completely after 2–3 weeks. Overall implant survival and success rates were, respectively, 98% and 96%. The implant survival rates were 100% in group 1, 93% in group 2, and 100% in group 3.

3.2. Clinical and Radiographical Parameters. 28 patients (82.4%) were classified as "success" and 6 patients (17.6%) as "no-success," where success meant the achievement at T_1 of a vertical defect height and width equal to 0 mm. The number of implants was placed, and the infrabony defect height and the EHS were the only variables statistically significant ($p < 0.05$).

Binary logistic regression outlined that the variable horizontal defect depth (HDD) was the only one statistically significant to obtain a successful result, which was considered to be the complete defect closure ($p = 0.009$, OR = 37.6 [95%CI = 2.5 – 563.2]), indicating that an increase of the HDD is associated with a higher success rate.

After six months, statistically significant reductions in vertical defect height (VDH) and defect width (DW) were recorded in all groups in comparison to the time of baseline evaluation ($p < 0.05$) (Figures 1 and 2). In detail, at T_0, the mean defects' heights in groups 1, 2, and 3 were, respectively, 2.50, 2.88, and 2.92 mm. In group 1, only one patient had a residual vertical defect height, while in group 2, there were two cases, and in group 3, there were three cases. The mean residual defect heights in groups 1, 2, and 3 were, respectively, 0.07, 0.5, and 0.25 mm, with no statistically significant difference between the groups ($p = 0.187$) (Table 2).

Mean defect widths were 3.50 mm in group 1, 3.38 mm in group 2, and 3.17 mm in group 3 at the baseline, while they were 0.07, 0.38, and 0.33 mm at T_1. Mean residual defect widths of the groups also showed no statistically significant difference between the groups ($p = 0.902$) (Table 3).

KT values at T_0 were significantly different from KT values at T_1. No statistically significant differences in postoperative width of keratinized mucosa were observed between the groups ($p = 0.499$).

HbA1c levels were not statistically related to ΔVDH and ΔDW ($p = 0.519$; $p = 132$). These variables showed a weak correlation with glycemic levels. In particular, for the variables ΔVDH and ΔDW, the best clinical outcomes occurred at low HbA1c levels (Figures 3 and 4).

No statistically significant differences were observed in peri-implant marginal bone loss (MBL) between the groups ($p = 0.230$), and none of the patients displayed marginal bone resorption of more than 1.5 mm at 12 months from prosthesis delivery.

Probing depth, bleeding on probing, and width of keratinized mucosa showed no significant differences at T_1 between the three groups ($p = 0.418$).

No statistically significant differences in postoperative wound healing were observed for the first 3 weeks between the groups analyzing the EHS ($p > 0.05$).

4. Discussion

The worldwide incidence of diabetes is increasing at a rapid rate [22]. This trend should be considered of clinical relevance by clinicians, especially in an ageing population, in

Table 1: Patients' demographics and clinical features.

	Total ($n = 34$)		No success ($n = 6$)	Success ($n = 28$)	p value
Gender					
M (n, %)	19	55.9	4 (66.7)	15 (53.6)	0.672
F (n, %)	15	44.1	2 (33.3)	13 (43.4)	
Age (mean ± SD)	69.56 ± 8.2		72.5 ± 7.74	68.93 ± 8.3	0.413
BMI (mean ± SD)	26.9 ± 2.5		28.2 ± 1.8	26.6 ± 2.5	0.145
Osteopenia					
No (n, %)	26	76.5	5 (83.3)	21 (75.0)	0.662
Yes (n, %)	8	23.5	1 (16.7)	7 (25.0)	
Periodontal prophylaxis					
No (n, %)	14	41.2	4 (66.7)	10 (35.7)	0.162
Yes (n, %)	20	58.8	2 (33.3)	18 (64.3)	
BOP (bleeding on probing)					
No (n, %)	27	79.4	5 (83.3)	22 (78.6)	0.793
Yes (n, %)	7	20.6	1 (16.7)	6 (21.4)	
Glycemic level					
1	14	41.2	1 (16.7)	13 (46.4)	0.405
2	8	23.5	2 (33.3)	6 (21.4)	
3	12	35.3	3 (50.0)	9 (32.1)	
N. implants					
1	21	61.8	1 (16.7)	20 (71.4)	0.042
2	10	29.4	4 (66.7)	6 (21.4)	
3	3	8.8	1 (16.7)	2 (7.1)	
Infrabony defect height					
0	6	17.6	5 (83.3)	1 (3.6)	<0.0005
1	7	20.6	1 (16.7)	6 (21.4)	
2	16	47.1	0 (0.0)	16 (57.1)	
3	5	14.7	0 (0.0)	5 (17.9)	
VDH T_0 (vertical defect height) (mean ± SD)	2.74 ± 0.828		3 ± 1.09	2.68 ± 0.77	0.644
DW T_0 (defect width) (mean ± SD)	3.35 ± 0.950		3.50 ± 1.049	3.32 ± 0.945	0.708
HDD T_0 (horizontal defect depth) (mean ± SD)	1.59 ± 0.957		0.17 ± 0.408	1.89 ± 0.737	
KT T_0 (keratinized tissue) (mean ± SD)	3.94 ± 0.7		4.00 ± 0.894	3.93 ± 0.716	0.878
VDH T_1 (mean ± SD)	0.24 ± 0.554		1.33 ± 0.516	0 ± 0	<0.0005
DW T_1 (mean ± SD)	0.24 ± 0.554		1.33 ± 0.516	0 ± 0	<0.0005
KT T_1 (mean ± SD)	3.38 ± 0.739		3.0 ± 0.894	3.46 ± 0.693	0.297
EHS week 1 (early wound healing score)					
2	2	5.9	2 (33.3)	0 (0.0)	0.017
6	7	20.6	1 (16.7)	6 (21.4)	
7	20	58.8	2 (33.3)	18 (64.3)	
8	5	14.7	1 (16.7)	4 (14.3)	
EHS week 3 (early wound healing score)					
8	2	5.9	2 (33.3)	0 (0.0)	0.004
9	3	8.8	1 (16.7)	2 (7.1)	
10	29	85.3	3 (50.0)	26 (92.9)	
Complications					
No (n, %)	32	94.1	4 (66.7)	28 (100.0)	0.002
Yes (n, %)	2	5.9	2 (33.3)	0 (0.0)	

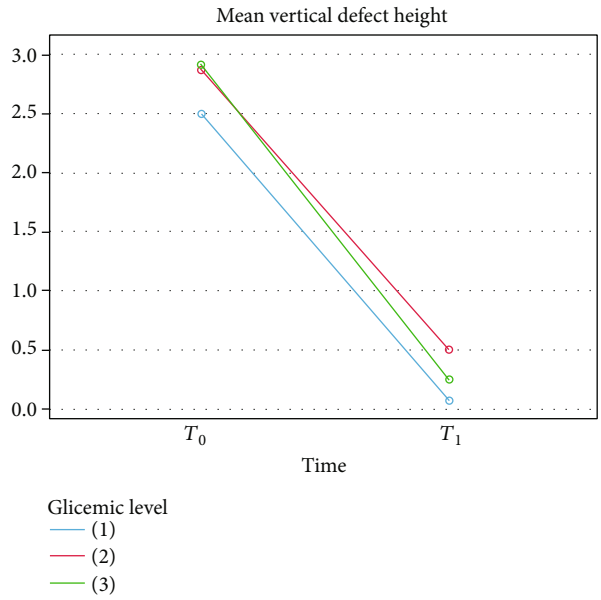

Figure 1: Vertical defect height changes from T_0 to T_1 for each group.

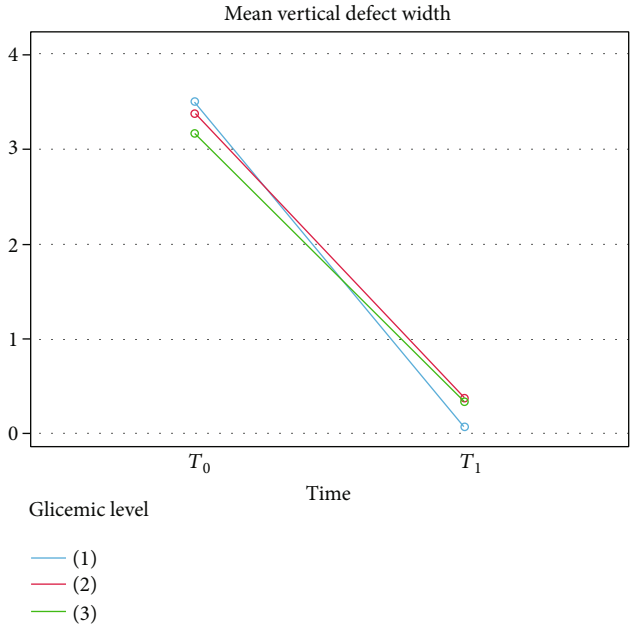

Figure 2: Defect width changes from T_0 to T_1 for each group.

relation to the placement and maintenance of oral implants. The results of various studies suggest that dental implants may be placed in diabetic patients with favourable outcomes, if glycemic status is within control ranges [23, 24] and patients are enrolled, after an accurate selection, in strict pre-, intra-, and postoperative programs [25, 26].

However, this disease represents a challenge because hyperglycemia may negatively affect bone regeneration, directly compromising clinical outcomes and increasing clinical failures [27]. This topic is relevant also because during an ordinary preparation of the osteotomic site or implant insertion, unplanned bone dehiscences or fenestrations may frequently occur in the diabetic and require an augmentation procedure in order to not leave the implant surface exposed [28].

Table 2: Vertical defect height changes from T_0 to T_1, measured in mm.

Descriptive statistics	Glycemic level	Mean	Std. deviation	N
VDH T_0 (vertical defect height)	1	2.50	0.760	14
	2	2.88	0.991	8
	3	2.92	0.793	12
	Total	2.74	0.828	34
VDH T_1	1	0.07	0.267	14
	2	0.50	0.926	8
	3	0.25	0.452	12
	Total	0.24	0.554	34

Diabetic patients may undergo complications related to the surgical procedure and the early postoperative phase, as well as to the long-term maintenance of the implants [29]. The first complications are related to surgery and mainly consist in impaired wound healing and decreased osteointegration. There are many mechanisms through which AGEs determine tissue damage: they suppress the production of collagen by the gingival and the periodontal ligament fibroblast [30, 31]; they contribute to delayed wound healing [32] and they inhibit the phenotypic expression of osteoblasts [33], while stimulating osteoclastogenesis with consequent bone resorption [34, 35]. In this regard, the diabetic bone is characterized by a reduced turnover that sees the reabsorption process prevail over the newly affixed one, with reduced mineral bone density [8], increased tendency to fracture [9], and poor bone healing and impaired bone regeneration potential [10–12]. Impaired wound healing is a well-known consequence of diabetes, which may be related to the local growth factors that influence cell migration, proliferation, and phenotypic expression [36]. For this reason, it can be suggested, although no direct data are available, that diabetics who are not optimally controlled may undergo an altered healing response after surgical procedures performed to correct osseous defects. Improved metabolic control is currently the only practical approach to managing this risk factor. Given current knowledge, it can be supposed that the clinical significance of the disease relative to its impact on the healing response will be a function of the control of glucose metabolism [37].

In our study, the EHS (early wound healing score) in each group showed a significant improvement from week 1 to week 3, with almost all of the patients reaching a final score of ten points, representing the best healing. In addition, the glycemic level seems not to have influenced the healing process outcome. Healing takes place following a well-organized chronology of biological events that are crucial for the quality of the final repair of wounded tissues [38]. In particular, the first postoperative week appears to be critical for the maintenance of wound stability. Wound healing should be monitored to identify early signs that may be related to healing

Table 3: Defect width changes from T_0 to T_1, measured in mm.

Descriptive statistics	Glycemic level	Mean	Std. deviation	N
DW T_0 (defect width)	1	3.50	0.941	14
	2	3.38	1.061	8
	3	3.17	0.937	12
	Total	3.35	0.950	34
DW T_1	1	0.07	0.267	14
	2	0.38	0.744	8
	3	0.33	0.651	12
	Total	0.24	0.554	34

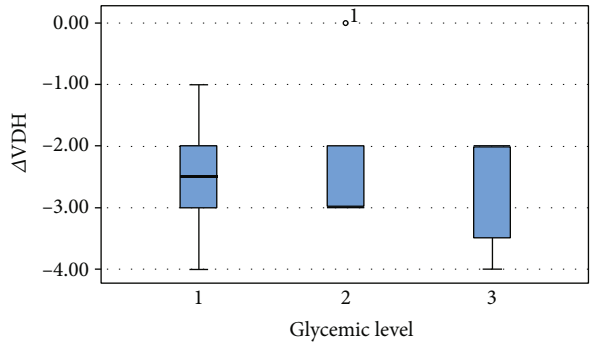

Figure 3: Difference of vertical defect height from T_0 to T_1 for each group.

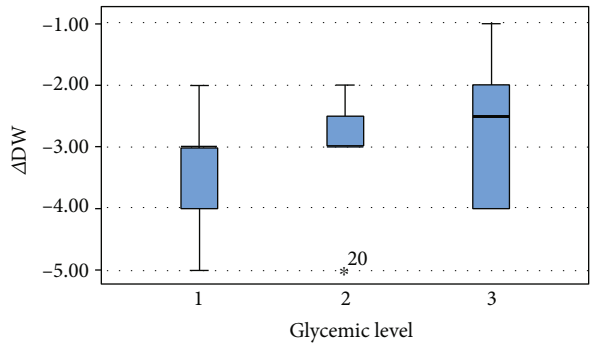

Figure 4: Difference of defect width from T_0 to T_1 for each group.

complications. Such findings might be associated with problems in different surgical procedures, and surgeons should be aware of these problems to consider prompt interventions [39–42]. In our study, 2 patients presented biological complications during the first 3 weeks after surgery. All of the complications were cases of wound dehiscence, which were treated by local disinfection, and all affected patients recovered completely after 2–3 weeks. The complication rate of the present study is in agreement with that of the study by von Arx and Buser (2006) [43], in which the main complications were small membrane exposures that went to reepithelialization within 2–4 weeks. On the other hand, a systematic review of Lim et al. (2018) [44] concludes that soft tissue complications after GBR are common, appearing in 18.6% of cases.

Impaired osseointegration could be one of the results of hyperglycemia's effect on the bone mineralization and remodelling process [45, 46], with reduced bone-to-implant contact (BIC) being reported in the literature [46]. However, it seems that good glycemic control based also on the administration of insulin improves osseointegration and implant survival [26], even if decreased BIC may be observed in comparison to nondiabetic subjects [19]. In the present study, the survival rate, meaning whether the implant was still physically in the mouth or had been removed [47], was 98%.

Furthermore, a statistically significant variation regarding the height and width of the peri-implant bone defects was observed after the procedure, with a decrease for both parameters after 6 months. No statistically significant differences were observed between the HbA1c levels and the variations of VDH and DW after surgery. However, it should be considered that the best clinical outcomes, regarding the variables ΔVDH and ΔDW, occurred in patients with lower HbA1c levels. Even subjects with controlled diabetes (HbA1c < 7%) have shown a significant reduction in the height and width of the bone defects. In our study, 82.4% of the patients achieved a residual height and width of the bone defect equal to 0 mm at T_1.

These findings are in agreement with those from a series of previous studies: histometric data on GBR in diabetic conditions [48, 49] confirm the potential of the GBR application to promote bone regeneration, even in the presence of uncontrolled experimental diabetes. Retzepi et al. [14] and Donos et al. [50] come to the same conclusion, adding that the diabetic status is associated with impaired healing and increased complications, which are improved when metabolic control via systemic insulin is performed. Retzepi et al. also underline that, following GBR execution in combination with implant placement, the type of the contact between the augmented diabetic bone and the implant surface is similar to that of the healthy bone.

Naujokat et al. (2016) [26], in a systematic review of the literature, say that no evidence was found that bone augmentation procedures such as guided bone regeneration and sinus lift provide higher complication and failure rates in patients with well- to fairly well-controlled diabetes.

In the present study, optimal results were recorded also for the periodontal parameters during the follow-up period, outlining that patient selection and the use of specific postsurgical cleansing protocols may play a key role in the healing process after an augmentation procedure in order to facilitate wound healing and closure [50, 51].

Long-term peri-implant success depends primarily on oral hygiene care. This success is inculcated within the patients by general practitioners and specialists that reinforce optimal oral hygiene maintenance, which actually prolongs treatment success.

Furthermore, in all the clinical conditions, the use of digital technologies in the preoperative phase (for planning the implant position and assessing the required bone volume to regenerate) as well as during the surgery (for customizing the membrane or the mesh) may help the clinician to improve the clinical results and avoid postoperative complications related to the operator [52].

The study presents some limitations: primarily its retrospective nature and the small sample of participants, in addition to a short-term follow-up and the absence of analysis of cellular or molecular factors, in order to elucidate the mechanism of bone healing. Surely, further large-scale studies with a longer follow-up and histological examinations would reinforce the significance of these results.

5. Conclusions

Simultaneous guided bone regeneration seems to be a feasible surgical procedure for the treatment of peri-implant dehiscences in controlled type 2 diabetic patients with HbA1c levels below 7%. The sample size of the present retrospective study consisted of a limited number of subjects with a short-term follow-up. Thus, prospective long-term study should be conducted to verify these findings.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

Paolo Francesco Manicone contributed equally as the co-first author.

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Hindawi
BioMed Research International
Volume 2024, Article ID 9786058, 1 page
https://doi.org/10.1155/2024/9786058

Retraction

Retracted: Periodontal Clinical Parameters as a Predictor of Bite Force: A Cross-Sectional Study

BioMed Research International

Received 12 March 2024; Accepted 12 March 2024; Published 20 March 2024

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Manipulated or compromised peer review

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] H. N. H. Alsharif, K. K. Ganji, M. K. Alam et al., "Periodontal Clinical Parameters as a Predictor of Bite Force: A Cross-Sectional Study," *BioMed Research International*, vol. 2021, Article ID 5582946, 8 pages, 2021.

Hindawi
BioMed Research International
Volume 2021, Article ID 5582946, 8 pages
https://doi.org/10.1155/2021/5582946

Research Article

Periodontal Clinical Parameters as a Predictor of Bite Force: A Cross-Sectional Study

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Received 13 January 2021; Revised 22 April 2021; Accepted 27 April 2021; Published 10 May 2021

Academic Editor: Marwa Madi

Objective. To investigate the correlation of periodontal parameters and bite force in different stages of periodontitis after phase I periodontal therapy. *Methods*. Periodontal clinical parameters such as mobility, attachment loss, gingival recession, and percentage of bone remaining were recorded at the mandibular first molar region after phase I therapy in subjects categorized according to the stage of periodontitis. Corresponding bite force was recorded at the first mandibular molar region using a bite force device after phase I therapy. ANOVA test was used to assess the significant difference among different groups. Pearson correlation coefficient was used to assess the correlation between measured variables. *Results*. The ANOVA test represents that there is no statistical significant difference between the bite force in stage I, stage II, and stage III type of periodontitis. A strong positive correlation was found ($r = 0.537$) between bite force and percentage of remaining alveolar bone support whereas negative correlation was observed in measured parameters such as mobility ($r = -0.0181$), attachment loss ($r = -0.608$), and gingival recession ($r = -0.435$). *Conclusion*. Among all periodontal clinical parameters, the percentage of remaining alveolar bone is the strong predictor of bite force and mobility; attachment loss and gingival recession cannot predict the bite force in the first molar region. Bite force is variable in different stages of periodontitis.

1. Introduction

Subjects with periodontal disease sometimes suffer from masticatory disturbance [1]. Ageing, female gender, and reduction in the number of present teeth were negatively associated with biting force [2, 3]. Biting force was also found to be positively correlated with salivary flow, regardless of age or gender [4]. The maximum biting force in healthy subjects was higher than that in subjects with temporomandibular joint disorders [5–7]. In addition, bite force tends to be increased by 20 years of age, retained continuously until 40-50 years of age, and then reduced. Periodontal disease is recognized as a causative factor for reduced bite strength, although temporomandibular disorder remains unclear as to how it affects power.

Piezoresistive sensor [8] and rigid sensors [9] were used to test bite force in humans, demonstrating that intraoral bite force recordings are possible and may offer new insights on the dynamics of human mastication with obvious effects for oral reconstruction [10]. Recently, it became possible to directly measure biting abilities (biting force, biting pressure, occlusal contact area) per person in the epidemiological study using the bite force device. Harada et al. [11] suggested a pressure-sensitive unit (Dental Prescale, Fuji Photo Film Co, Tokyo, Japan) as a simple indicator of postoperative healing and occlusal improvement in orthognathic surgery

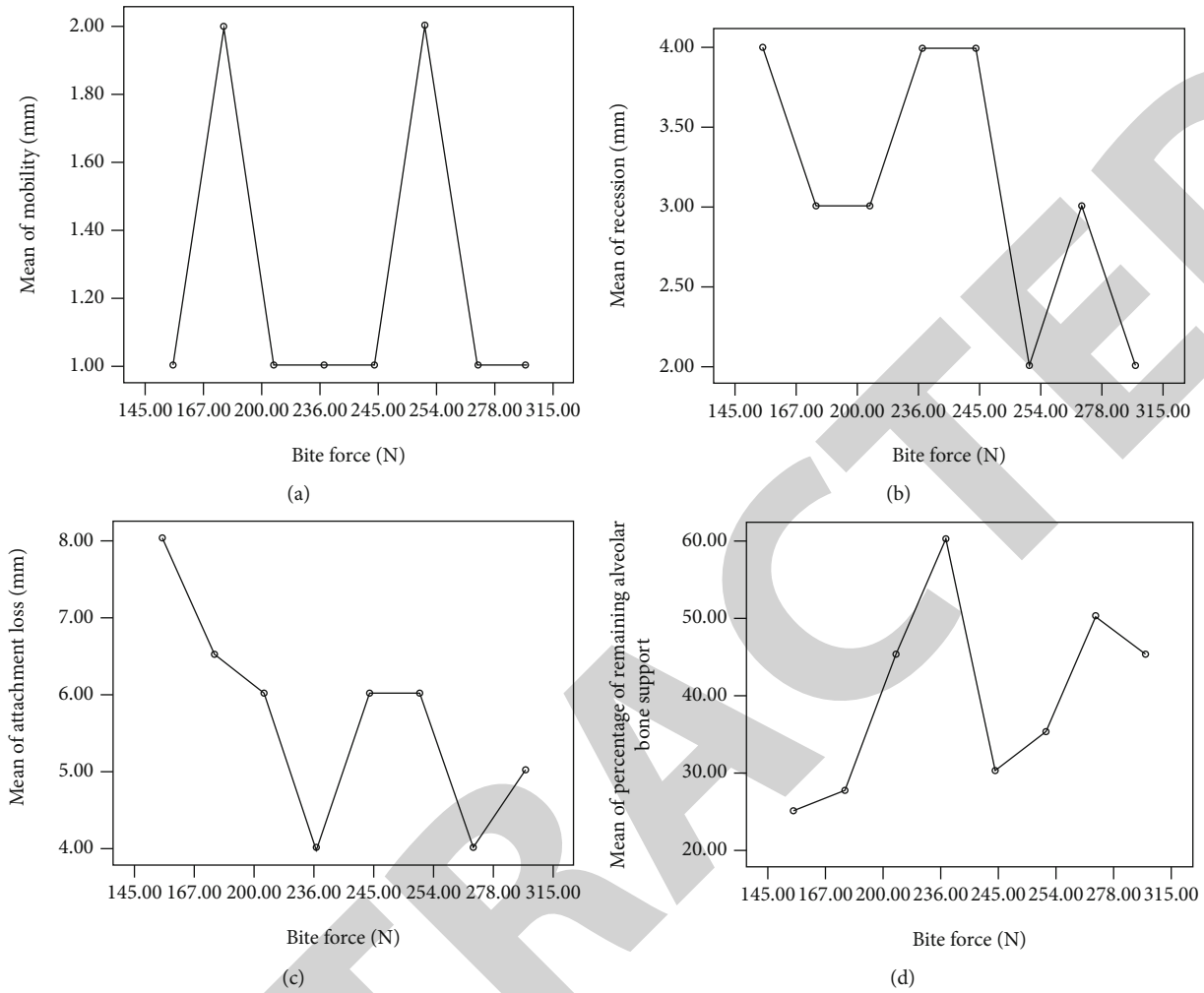
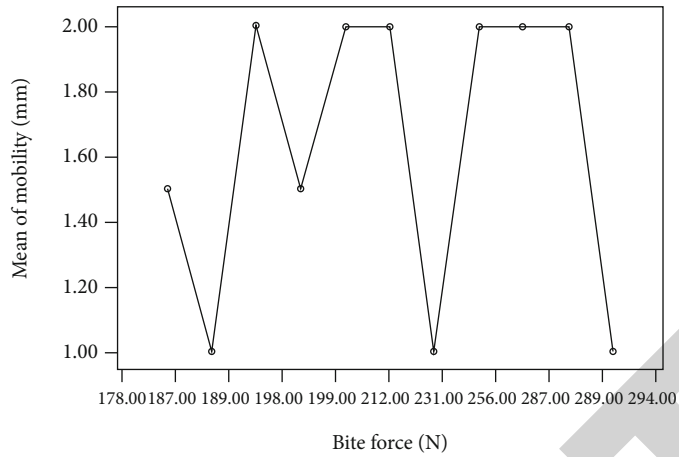


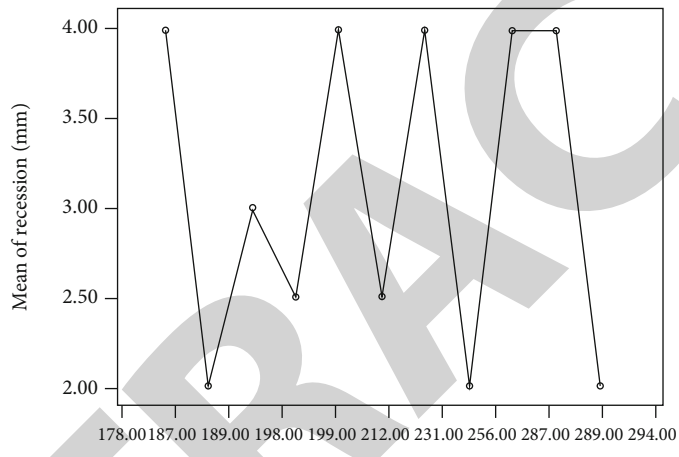
Figure 1: Relationship of mean bite force with mobility (a), gingival recession (b), attachment loss (c), and percentage or remaining alveolar bone support (d) in stage I periodontitis.

patients. The sensitivity and specificity of a new bite force sensor were checked in six subjects with maxillary removable partial dentures supported by conical crowns [12]. Nowadays, sensitive electronic sensors are used in most bite force applications. These devices can record a wide range of forces (50-800 N) with accuracy (10 N) and precision (80 percent) [12]. These systems utilize load cells (transducers) to transform stress into electrical energy and could be based on one of the following operating concepts, such as strain gauge transducer, piezoelectric transducer, and pressure transducers. Cheng et al. [13] suggested a hydrogel and a dielectric elastomer soft sensor. The sensor translates a mechanical force into a capacitance transition that is defined by the force under phase load at varying speeds and cyclic loads at differing frequencies. The biocompatible soft arrayed sensor can be readily tailored to each tooth surface and captures dynamic bite force in various regions of dentition.

Turkistani et al. have shown that Class III malocclusion subjects with decreased overjet and decreased overbite displayed higher bite force in the posterior teeth compared to other groups [14]. The spectrum of occlusal force differs widely among subjects linked to patient-specific factors such as age, gender, partial and full edentulism, existence of a maxillofacial defect, edentulous position, orthognathic profile, and vertical occlusal dimension magnitude [15]. Using a transducer occlusal force meter (GM10; Nagano Keiki, Tokyo, Japan), Al-Zarea [16] reported that the maximum occlusal bite force values on the dentate side are greater than those on the fixed partial denture side. Several studies have used the device (GM10; Nagano Keiki, Tokyo, Japan) successfully to record bite force in human dentition [17, 18]. Subjects felt no irritation or pain when biting on the device [18]. The periodontal status of the teeth is considered an important factor in determining the maximum bite force [19, 20]. In the absence of inflammation, Alkan et al. found that decreased periodontal support had a detrimental impact on biting abilities [20]. Periodontitis stage represents the nature of the condition and is manifested by attachment loss and bone loss, as well as tooth loss caused by periodontitis. It also represents the projected complexity of care needed to eradicate/reduce the existing degree of infection and inflammation, as well as to recover the patient's masticatory function [21]. The direct relationship of bite force in different periodontal conditions per person remains unclear. The



(a)



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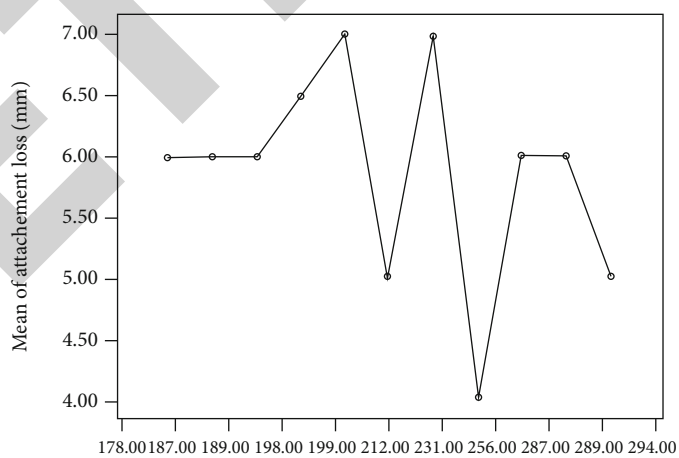
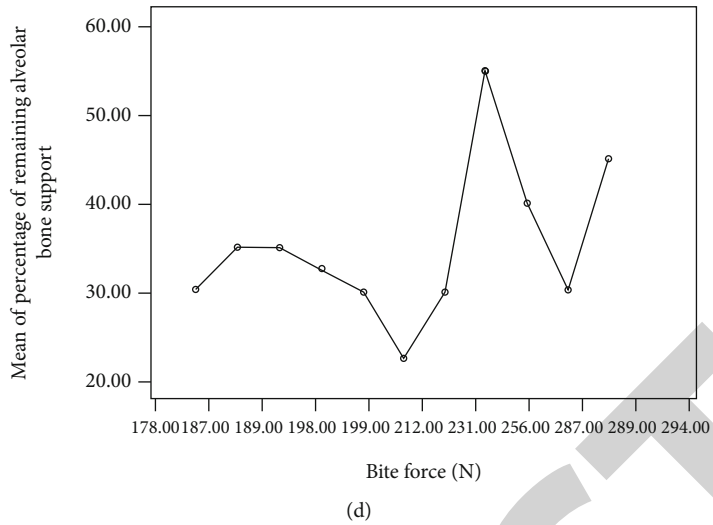


(c)

Figure 2: Continued.



(d)

Figure 2: Relationship of mean bite force with mobility (a), gingival recession (b), attachment loss (c), and percentage or remaining alveolar bone support (d) in stage II periodontitis.

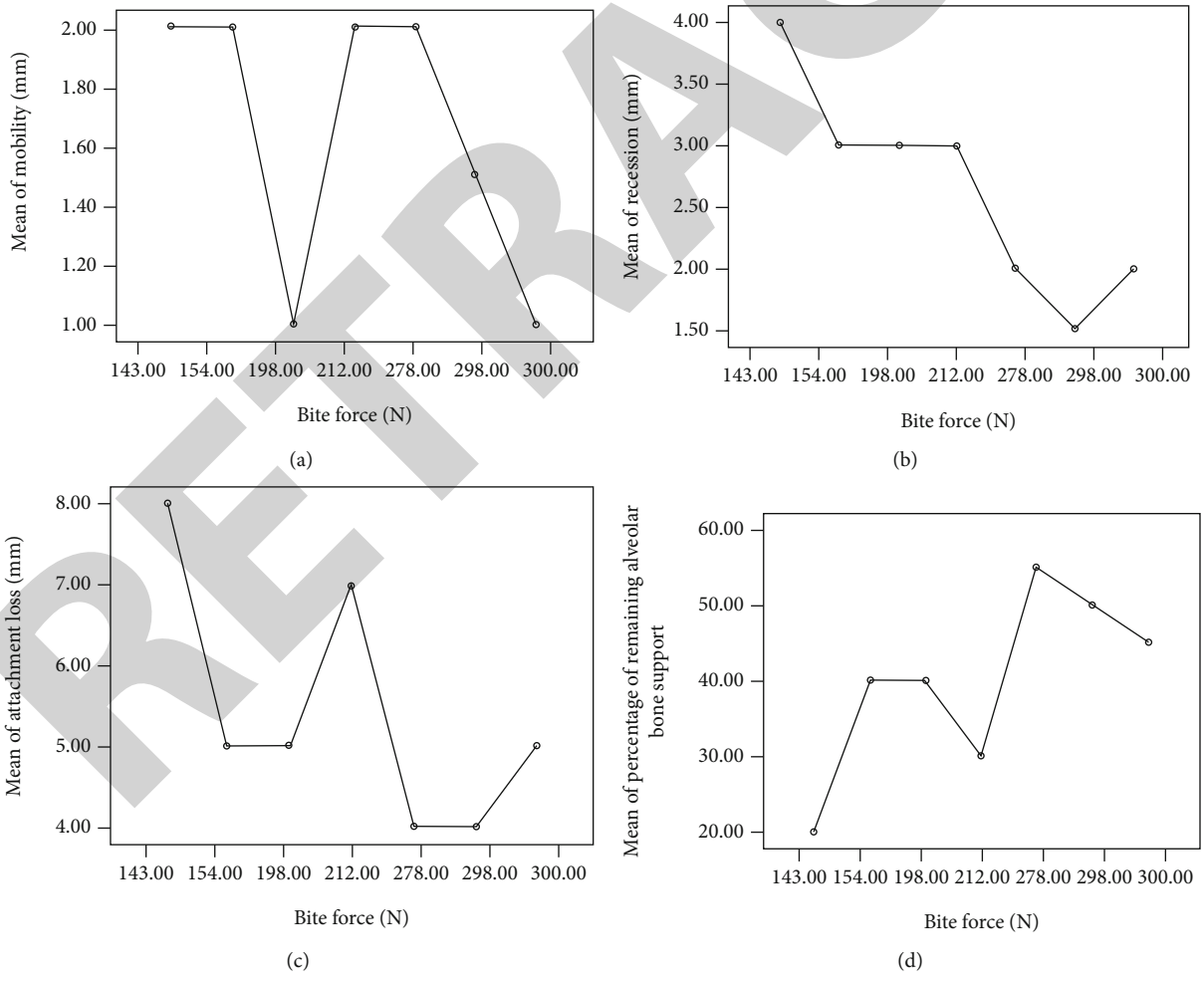


Figure 3: Relationship of mean bite force with mobility (a), gingival recession (b), attachment loss (c), and percentage or remaining alveolar bone support (d) in stage III periodontitis.

Table 1: ANOVA test result comparison of bite force variation in recession, attachment loss, and percentage of remaining alveolar bone support parameters for all the 3 groups (group I, group II, and group III).

Variables	Group comparison (group I, group II, group III)	Sum of squares	df	Mean square	F	Sig.
Recession	Between groups	2.054	2	1.027	1.318	0.284
	Within groups	21.817	28	0.779		
Attachment loss	Between groups	2.004	2	1.002	0.688	0.511
	Within groups	40.770	28	1.456		
Percentage of remaining alveolar bone support	Between groups	324.942	2	162.471	1.056	0.361
	Within groups	4308.929	28	153.890		

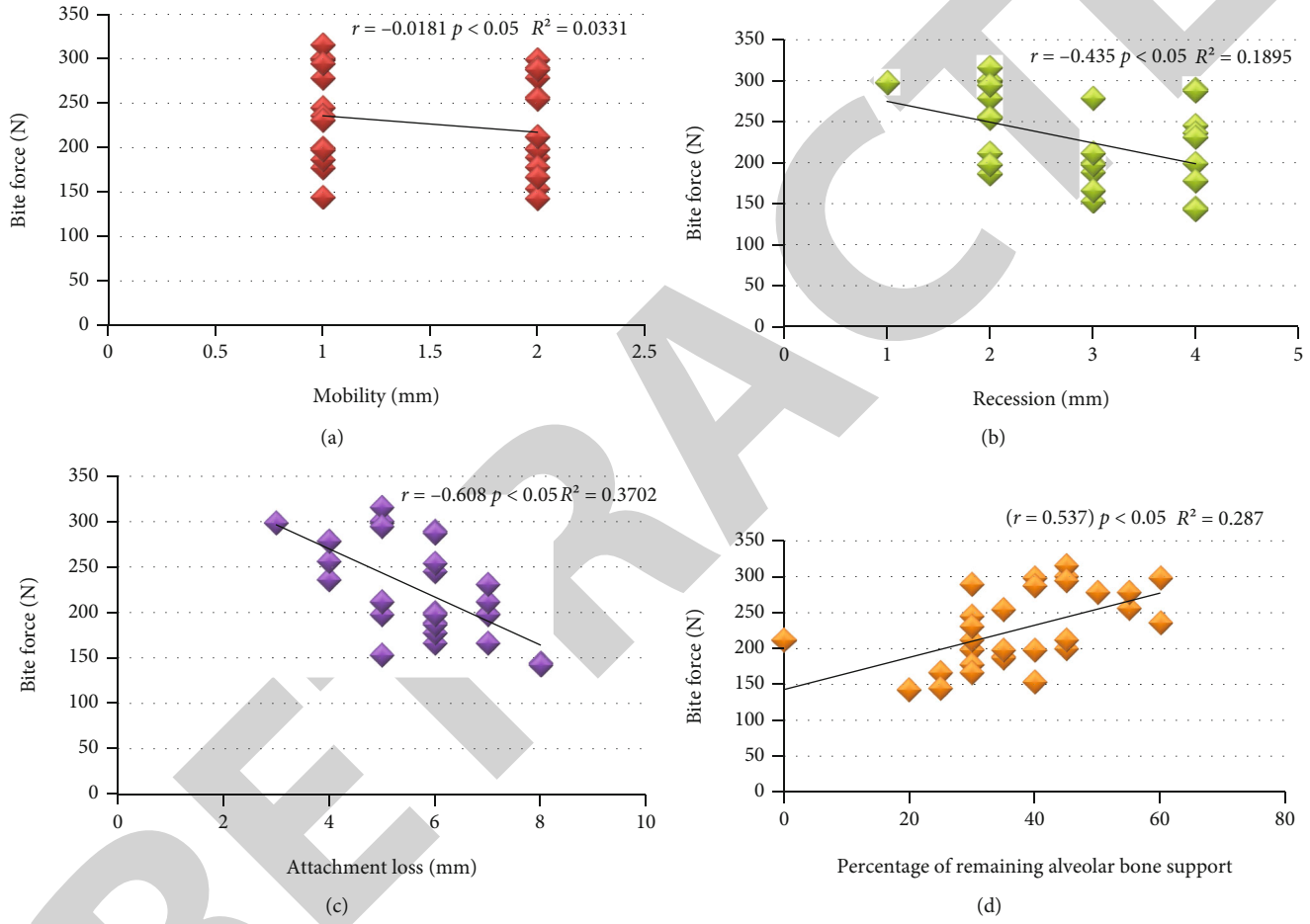


Figure 4: Correlation of bite force with mobility (a), gingival recession (b), attachment (c), and percentage of remaining alveolar bone support (d).

study was aimed at investigating the correlation of periodontal parameters and bite force in different stages of periodontitis after phase I periodontal therapy.

2. Subjects and Methods

This is a cross-sectional study, which included 65 subjects enrolled following screening with inclusion and exclusion criteria, who presented at the outpatient department section, College of Dentistry, Jouf University, from October 2019 to January 2020. The study received its ethical clearance from the local committee for bioethics, Jouf University, wide reference number LCBE#1-19-9/39. The subjects' age ranged from 35 to 45 years. Inclusion criteria included subjects who underwent phase I periodontal therapy and were also suffering from stage I to III periodontitis [21]. Individuals were excluded if they had missing opposing first permanent mandibular molar (right or left side), if the opposing first molar teeth were an implant and/or restored with crown, and if they had restorations serving as an abutment or pontic, as well as subjects with temporomandibular dysfunction who were undergoing drug therapy for muscles and joint disorders. Written informed consent was obtained from the subjects regarding willingness to participate in the current study. Phase I periodontal therapy was performed in the enrolled subjects, and then, the clinical parameters such as mobility, attachment loss, gingival

recession, and percentage of bone remaining were recorded at the mandibular first molar.

For group distribution, the subjects having met the inclusion criteria are categorized as follows:

Group I: subjects with stage I periodontitis [21]

Group II: subjects with stage II periodontitis [21]

Group III: subjects with stage III periodontitis [21]

Corresponding bite force as a dependent variable was recorded only once after one week of phase I therapy for the subjects in group I, group II, and group III at the first mandibular molar region using a force transducer occlusal force meter. The instrument used to determine the bite force was a force transducer occlusal force meter (GM10; Nagano Keiki, Tokyo, Japan) consisting of a digital hydraulic pressure gauge and a vinyl biting device protected by a plastic sheath. The optical hydraulic pressure gauge has an 8.6 mm thick bite part with a plastic cover for cross-infection control. Calibration of the device was done prior to each bite force assessment process as per manufacturer instructions. The subjects were instructed to bite on the device with maximum possible force, and the highest reading out of 2 attempts was recorded. Two investigators conducted the bite force evaluation and clinical assessment. A resting time of 30 minutes was maintained between the first and second investigators in evaluation of bite force values. Intraclass correlation coefficient statistics were used to verify intraexaminer reliability after the bite force values of group I, group II, and group III subjects were tested and assessed by two investigators (KKG and HNA) on the same day of the assessment. The value of the intraclass correlation coefficient was 0.98 ($p < 0.000$). The tests described above demonstrated high inter- and intraexaminer reliability. The Dahlberg and Houston [22] formulas and coefficients of reliability were used to measure method errors for numerical variables in this analysis. For all of the measurements, the variance varied between 0.2 and 0.11 percent, and the coefficient of reliability was above 96 percent, indicating sufficient agreement.

Other independent variables measured at the same site of bite force measurement were gingival recession (mm) (on the buccal aspect), attachment loss (mm), mobility (grade) using Glickman index [23], and percentage of remaining alveolar bone support. The percentage of remaining alveolar bone support was calculated using the technique proposed by Lira-Júnior et al. [24]; sample size estimation was done using G power computing tool utilizing the effect size ratio from the mean values and standard deviation of the similar previous studies where the same device was used. The data was documented onto Microsoft Excel sheet and was analyzed using the SPSS software version 18.0 (SPSS Chicago, IL, USA). One-way ANOVA was used to test the significant difference among the measured independent variables between the groups. Pearson's correlation test was used to identify the correlation between bite force and independent variables. Statistical significance was considered significant if $p < 0.05$.

3. Results

A total of 65 patients treated with phase I periodontal therapy were enrolled in 3 groups with a mean age of 40.5 (±2.35). The distribution of patients among the groups is based on stage of periodontitis: group I (19), group II (29), and group III (17). The study population consisted of 45 males and 20 females. All 65 patients completed all necessary clinical and radiographic examinations, as well as loading force measurements. Mean values of gingival recession (on buccal aspect), attachment loss, mobility, and percentage of remaining alveolar bone support in relation to bite force are presented in relation to different stages of periodontitis such as stage I (Figure 1), stage II (Figure 2), and stage III (Figure 3). Maximum bite force was presented in group I (315), and group II exhibited the least bite force (294). The ANOVA test represented that there is no statistical significant difference between the bite force of group I, group II, and group III evaluated in relation to the measured independent variables (Table 1). The Pearson correlation test revealed a positive correlation between the bite force and the percentage of remaining alveolar bone support ($r = 0.535$, $p < 0.05$) (Figure 4). The Pearson correlation coefficient with respect to attachment loss was $r = -0.608$ ($p < 0.05$), whereas that for mobility and recession was$r = -0.181$ ($p < 0.05$) and $r = -0.435$ ($p < 0.05$), respectively. The negative correlation with respect to mobility, attachment loss, and recession indicates that the severity of these parameters influences the bite force in a decreasing order.

4. Discussion

The results of this study found that patients with reduced periodontal tissue support, such as increased attachment loss and reduced residual bone support, were unable to generate maximum bite strength. Similar findings were found in a study conducted by Laurell and Lundgren [25] in patients with restored crossarch bilateral end abutment bridges. Our results are not consistent with the findings of the study done by Kleinfelder and Ludwig [26] who proposed that there was no correlation between periodontal ligament area and maximum bite force in nonsplinted teeth, indicating that even a reduced number of periodontal neural receptors may be sufficient for proper feedback for mechanisms that limit chewing and biting forces. Also, in their study, a loading force transducer was connected to a stainless steel clamp, amplifier, storage, monitor, and plotter in the force-measuring unit [26]. Variations in such differences are attributed to the type of device used and subjects enrolled in the present study with stage III severity of periodontitis involvement.

In the present study, a more comfortable bite force registration device was used where the device is in direct contact with the tooth surface area and therefore, the mechanoreceptors within the pulp and/or the temporomandibular joint are able to influence the production of the maximum biting force. The mean maximum bite force obtained in all categories of subjects evaluated in this study is 340 N. These findings are consistent with studies showing values for mean maximum bite force ranging from 176 N to 738 N [27, 28]. In the current study, the bite force was evaluated only on the mandibular 1st molar teeth because spreading the load from the molars to premolars using an acrylic splint would increase the bite force by twofold [26, 29]. First, the

mandibular molar region was chosen as an ideal site for evaluation of bite force. Bite force frequency varies from region to region of the oral cavity [30]. Turkistani et al. demonstrated that subjects with Class III decreased overjet and decreased overbite exhibited higher bite force in the posterior teeth relative to other classes [14]. Hence, bite-force feature should be seen as a significant parameter in the assessment of patients with dental or periodontal pathologies, especially those with oral parafunctions and bruxism, that may be impaired by excessive tooth stress. The more the posterior transducer is mounted in the dental arch, the greater the force of the bite [31]. This has been clarified by mechanical jaw-lever mechanism [28, 32]. In addition, more root surface area and the periodontal ligament around the multirooted roots provide a greater resistance to tolerate the bite force better [5].

The mechanoreceptors of the periodontal ligament regulate the loading forces during mastication caused by the masticatory muscles [26]. Thus, decreased periodontal support may decrease the threshold level of mechanoreceptor function [19]. This condition can cause changes in the biting function [20]. Williams et al. reported that people with lack of attachment showed diminished sensory function [1]. Alkan et al. confirmed that the biting abilities of healthy periodontium subjects were significantly greater than those of persons with chronic periodontitis [20]. These findings are consistent with those from another study in which there was a strong association between reduced periodontal support and decreased biting intensity. However, the findings of the present study did not agree with those of an epidemiological study using pressure-sensitive microcapsular sheets, which reported that stepwise multiple linear regression found no correlation between periodontal status and biting ability [3]. The reason for the discrepancy between the studies may be because of differences in the severity of periodontal disease.

The sensory feedback from the periodontal pressoreceptors has been suggested to play a crucial role in the regulation of bite force [33]. The periodontal ligament, according to Edel and Wills [34], is in charge of controlling the force aimed towards the teeth. Furthermore, it has been suggested that periodontal inflammation influences mechanoreceptor thresholds [35]. Williams et al. [1] have found that inflammatory disruption to the periodontal ligament would affect sensory performance, resulting in a loss of control over excessive bite power. In light of the above results, bite force in the current study was assessed after 1 week of phase I periodontal therapy to ensure that any inflammation-induced harmful effects on sensorial unit reactions are avoided.

Bite force is influenced by various morphologic and physiologic factors such as age [36], gender [30], periodontal status of the teeth [20], disorders of temporomandibular joint [37], and dentition status [38]. Keeping in mind these constraints except for the periodontal status of the teeth, the other factors were considered as constant; therefore, the bite force variation with different degrees and staging of periodontal diseases was chosen as an important variable for investigation in the current study. The novelty of the current study is that this is the first study of its kind relating bite force to the percentage of remaining alveolar bone support. Limitations of this study included the bite force which was measured at the first mandibular molar region; hence, the findings could be varied with different morphologies of the teeth as well as the occlusal contacts. More research with bite force measurement approach is required, wherein the variation of bite force values before and after periodontal therapy should be assessed with a greater sample population and a longer follow-up time.

5. Conclusion

Among all periodontal clinical parameters, the percentage of remaining alveolar bone is a strong predictor of bite force and mobility; attachment loss and gingival recession cannot predict the bite force in the first molar region. Bite force is variable in different stages of periodontitis.

Data Availability

Data set is available upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Hussain Nayef Hussain Alsharef, Kiran Kumar Ganji, and Mohammad Khursheed Alam contributed equally, and all 3 authors are first authors.

Acknowledgments

We thank our institutional statistician for his support in analysis, results, and interpretation.

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Hindawi
BioMed Research International
Volume 2021, Article ID 5518195, 9 pages
https://doi.org/10.1155/2021/5518195

Research Article

Association between Periodontal Disease and Comorbidities in Saudi's Eastern Province

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Received 4 February 2021; Revised 29 March 2021; Accepted 1 April 2021; Published 17 April 2021

Academic Editor: Iole Vozza

The incidence of periodontal diseases is associated with multiple comorbidities that influence a patient's treatment planning. This study evaluates the relation between periodontal disease and multiple comorbidities reported in the Saudi population from the Eastern province. This study was conducted on 190 patients, who visited the periodontology clinics at Imam Abdulrahman Bin Faisal University, Saudi Arabia. Demographic data, smoking habits, past medical and dental histories, blood pressure, random blood glucose, and recent haemoglobin A1c were recorded. A comprehensive periodontal examination included the number of missing teeth, pocket depth (PD), clinical attachment level (CAL), bleeding on probing (BOP), and mobility of all teeth except third molars. Radiographic bone loss was measured on standardized full-mouth periapical radiographs. Multivariable regression models were calculated aiming to see the association between different comorbidities and alveolar bone loss with confounders controlled. Out of 190 periodontitis patients, 56 (29.5%) were males and 134 (70.5%) were females. More than half of the patients (60%) were between 26 and 50 years, 30% of them had diabetes, and 18% were smokers. The risk of alveolar bone loss was higher in persons who had diabetes and those who had both diabetes and coronary heart disease than those who did not, although the association was not statistically significant ($B = 1.26$, 95%CI = −0.30, 2.82, and $B = 2.86$, 95%CI = −1.25, 6.96, respectively). The risk of alveolar bone loss was significantly higher among persons with diabetes and hypertension ($B = 2.82$ and 95%CI = 0.89, 4.75). Collectively, the risk of alveolar bone loss in periodontitis patients increases with diabetes in the presence of other comorbidities regardless of smoking or gender.

1. Introduction

Periodontal diseases comprise periodontitis and gingivitis, which are responsible for the destruction of the supporting tissues of the tooth apparatus and are the major cause for loosing teeth among adults [1]. Periodontal diseases are common, and their prevalence varies in different populations including adolescents, adults, and older individuals, which might represent a public health concern [2]. At the age of 40, the prevalence of severe periodontitis peaks and then remains stable in older ages [3]. It is important to highlight that the prevalence of periodontal disease will be increasing in the world in the coming years due to the aging of the population, especially in high-income countries, and increased retention of natural teeth [4]. Nazir et al. reported disparities in the severity of periodontal

disease among countries, where high-income countries had the highest prevalence of pocket depth [5]. Another study assessed the prevalence of plaque-induced gingivitis and found that 100% of 385 adult subjects aged between 18 and 40 years old had gingivitis [6]. Overall, about 20-50% of the population around the world has periodontal disease [2] with the most severe form affecting 11.2% of the world's population [3].

The systemic immune response might be influenced by periodontal pathogens as well as their metabolic by-products [7]. Advanced alveolar bone loss during periodontal infection is due to dysregulated inflammation and/or immunopathology, loosely reminiscent of the pathogenic mechanisms underlying certain systemic conditions [8]. Studies have reported a relationship between periodontal disease and a wide range of comorbidities including cardiovascular disorders (CVD), hypertension (HTN), diabetes mellitus (DM), rheumatoid arthritis, osteoporosis, Parkinson's disease, Alzheimer's disease, respiratory infections, and psoriasis [9]. In addition, the severity of periodontitis was linked with multiple comorbidities including gender, smoking, alcohol consumption, and pulmonary, endocrinal, metabolic, cardiovascular, neurological, hematological, and skeletal disorders [10]. Interestingly, it was found that individuals who had periodontal disease have a higher susceptibility for systemic comorbidities [11]. The majority of periodontitis cases exist in association with comorbidities including allergies, HTN, hyperlipidemia, and endocrine, pulmonary, musculoskeletal, and neurological disorders [12].

Over recent decades, there has been an increase in the global prevalence of DM [13]. Nearly, 451 million individuals have DM worldwide in 2017 [14]. In Saudi Arabia, DM is highly prevalent among the population, which represents a serious public health problem [15]. There is a bidirectional relationship between periodontitis and DM. DM augments periodontitis risks, and contrariwise, the inflammation in periodontal tissues negatively distresses glycemic control [7]. A recent observational study found that periodontitis is more prevalent in diabetic people than nondiabetic ones, with no difference in terms of gender and age [16]. Another study found that patients with DM type 2 and severe periodontal disease might counter higher mortality risk (3.2 times) as compared to no or mild periodontitis [2]. Moreover, the incidences of gingivitis and periodontitis were 21% and 6%, respectively, in type 1 diabetic children and adolescents [7]. On the other hand, there was a global increase in HTN prevalence of 5.2% over 10 years [17]. In Saudi Arabia, there are no current, accurate population-based estimates regarding the prevalence of HTN. Studies demonstrated that patients with periodontitis have higher systolic and diastolic pressures [18]. In 2010, the association between blood pressure values and periodontitis was examined in a large study, and the results showed a linear positive correlation [19]. The association between periodontitis and CVD was reported in several epidemiological investigations [7]. Studies have found that CVD risks could be 19% increased by periodontal diseases, whereas the risks might extend to 44% in elderly patients over 65 years [2]. The association between periodontitis and coronary heart disease (CHD) risks is independent of other risks such as smoking, DM, and socioeconomic status [2].

A variety of systemic and environmental risk factors may increase the prevalence and severity of chronic periodontitis. In addition, periodontal diseases may influence the pathogenesis of several systemic conditions such as CVD [20], DM [21], oral and colorectal cancers [22], and gastrointestinal [23] and respiratory diseases [24]. Recognizing the prevalence of multiple comorbidities in dental patients, especially with periodontitis, is a clinically important aspect that affects the patient's treatment protocol as well as its implications for public health strategy, guidelines, and health care worker training. Thus, the aim of our study was to assess the association between multiple comorbidity models and periodontal disease in a Saudi population from the Eastern province using regression analysis.

2. Materials and Methods

Participants eligible for this cross-sectional study were adult patients (>18 years old), who attended the periodontology clinic from September 2018 through September 2020 at the College of Dentistry at Imam Abdulrahman Bin Faisal University (IAU, Saudi Arabia). The current study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Exclusion criteria were individuals who underwent periodontal treatment over the last three months or were under continuous use of anti-inflammatory drugs, the presence of less than 12 teeth, malignancy, pregnancy, breastfeeding, and antibiotic use within 3 months prior to the study.

The study protocol was approved by the institutional review board, IAU (IRB-2021-02-034). Eligible participants were informed about the aims of the research and signed informed consent prior to entry into the study. Then, scheduled appointments were given for complete periodontal examination by two precalibrated examiners.

Patients' information regarding gender; age; nationality; medical history; use of medications; current systemic diseases, e.g., DM, HTN, hyperlipidemia, and CVD; and smoking habits (presence/absence) was collected. The fasting blood glucose level was measured, and serum levels of haemoglobin A1c (HbA1c) were recorded. DM was defined as $HbA1c \geq 6.5\%$ (≥ 47.5 mmol/mol) or $FPG \geq 7.0$ mmol/L. Systolic and diastolic blood pressures (SBP and DBP, respectively) were measured using an automatic blood pressure monitor. HTN was defined as $SBP \geq 140$ mmHg or $DBP \geq 90$ mmHg. Serum concentrations of triglyceride, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL), and cholesterol were collected from recent medical records. Abnormal serum lipid levels were defined as $triglyceride \geq 150$ mg/dL and/or HDL $cholesterol < 40$ mg/dL. Then, patients were further categorized depending on the presence of one or more comorbidity having DM and/or HTN as a main common disease.

Periodontal clinical examination was performed for all teeth except third molars, teeth with extensive carious lesions hindering the cementum-enamel junction (CEJ) determination, teeth with iatrogenic restorative procedures preventing

the completion of the exam, teeth with Class 3 mobility, and unrestorable teeth indicated for extraction [25]. The following periodontal parameters were evaluated in all teeth present at six sites (mesiobuccal, distobuccal, buccal, lingual, mesiolingual, and distolingual) using a manual periodontal probe (UNC-15, Hu-Friedy, Chicago, IL), clinical mirror, and gauze. Clinical parameters included (1) probing depth (PD); (2) clinical attachment level (CAL); (3) bleeding on probing (BOP) which was assessed and categorized into <10%, 11–30%, and >30%; (4) number of missing teeth due to periodontal disease which was assessed and grouped as 0-2, 3-5, and >5 teeth; and (5) radiographic bone loss (RBL) which was measured on standardized bitewings and periapical radiographs that were done recently at the time of examination. RBL was calculated as the distance between the CEJ and the alveolar bone crest subtracted by 2 mm.

Severity of periodontal disease was reported using the suggested 2017 World Workshop Periodontal diseases and conditions [26]. Periodontitis was defined as having more than 2 detectable interproximal CAL, mild stage I periodontitis: the greatest interproximal CAL = 1–2 mm and *RBL* < 15%; moderate: stage II periodontitis: CAL = 3–4 mm and RBL = 15-33%; and severe periodontitis: stages III and IV without/with potential of edentulism (CAL ≥ 5 mm and RBL ≥ 30% or RBL ≥ 50%). Periodontal examinations were conducted by two precalibrated examiners. Intra- and inter-examiner agreements were carried out on 20 individuals. Kappa values for PD and CAL proved to be higher than 0.90.

Statistical analysis was carried out using the statistical package for the social sciences (SPSS for Mac OS X, version 20.0, Inc., Chicago, IL, USA). Descriptive statistics were displayed as the mean ± standard deviation for quantitative variables, while frequencies and percentages were used for qualitative variables. We evaluated the normality of our data using the Kolmogorov-Smirnov test. The Mantel-Haenszel test of trend and Monte Carlo test were used to check association between comorbidities and severity of periodontal disease. Four main multivariate regression models were calculated, where CAL was the dependent variable in two of them and alveolar bone loss in the other two. Those models were aimed at classifying the individuals based on the presence of comorbidities, either DM alone or with the presence of other comorbidities (HTN, hyperlipidemia, or CHD), and its association with CAL and alveolar bone loss in 2 models. The other two models assessed the association between the presence of HTN alone and with other comorbidities (hyperlipidemia or CHD) and CAL and alveolar bone loss. All reported *P* values were considered statistically significant if less than 0.05.

3. Results

3.1. Characteristics of the Study Sample. Among 300 patients examined, the data of 190 patients (more than half of them aged 25-50 years; 134 females and 56 male) were included in the study. Exclusion criteria for the 110 subjects were subjects who underwent periodontal surgery within the last three months, patients under continuous use of anti-inflammatory drugs, patients under chemo- or radiotherapy, the presence of less than 12 teeth, pregnant and breastfeeding female patients, and subjects that did not show up in their scheduled appointment. Table 1 shows the demographic data and oral health characteristics of the participants. The most common comorbidities found were DM (16.3%), followed by HTN (15.3%). Almost half of the patients had more than 5 teeth missing (49.5%). The mean pocket depth was found to be 3.6 ± 1.4, mean alveolar bone loss was 3.2 ± 3.8, and mean clinical attachment loss was 3.09 ± 2.58. The severity of periodontal disease among participants is presented in Figure 1; almost 30% of the participants had moderate periodontitis.

Table 1: Sample demographics and oral health characteristics ($N = 190$).

Variables		Frequency, *n* (%)
Age	18-25 years	30 (15.8)
	26-50 years	112 (58.9)
	>50 years	48 (25.3)
Gender	Males	56 (29.5)
	Females	134 (70.5)
Nationality	Saudi	61 (67.9)
	Non-Saudi	60 (32.1)
Smoking	Yes	33 (17.4)
	No	157 (82.6)
Comorbidities	DM	31 (16.3)
	HTN	29 (15.3)
	DM & HTN	17 (8.9)
	DM & hyperlipidemia	8 (4.2)
	DM & CHD	3 (1.6)
	HTN & hyperlipidemia	7 (3.7)
	DM & CHD	3 (1.6)
No. of missing teeth	0 to 2	15 (7.9)
	3-5	81 (42.6)
	>5	94 (49.5)
BOP (%)	1%-10%	43 (22.6)
	11-30%	95 (50.0)
	>30%	52 (27.4)
Pocket depth (mean ± SD)		3.6 ± 1.4
Amount of bone loss (mean ± SD)		3.2 ± 3.8
Clinical attachment loss (mean ± SD)		3.09 ± 2.58

3.2. Results of Linear Regression Analysis between Each Variable. Results of association between frequency of multiple comorbidities and severity of periodontal disease are shown in Figure 2. There was a statistically significant linear association between the presence of DM alone and HTN alone with the severity of periodontal disease ($P < 0.001$, 0.008, respectively). Also, there were significant associations when DM was combined with HTN or with CHD

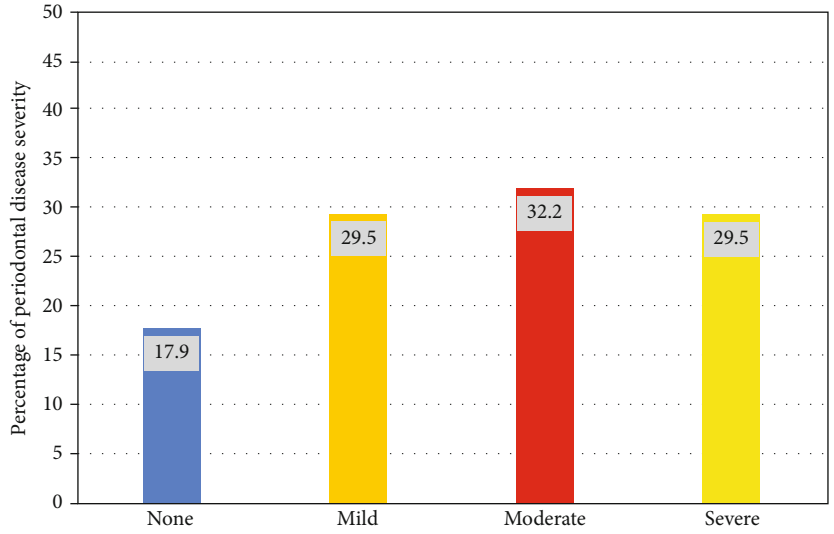

Figure 1: Severity of periodontal disease among participants.

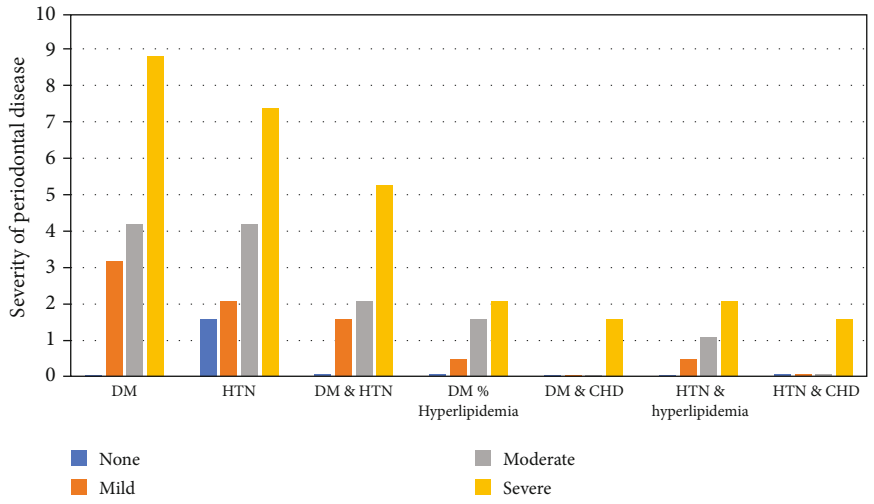

Figure 2: Frequency of multiple comorbidities according to the severity of periodontal disease. *Significant at $P \leq 0.05$. $^{\$}$Test of significance: Mantel-Haenszel test of trend with DM: $^{*}P < 0.001$; HTN: $^{*}P = 0.008$, and DM & HTN: $^{*}P = 0.002$. †Test of significance: Monte Carlo test used with DM & hyperlipidemia: $P = 0.052$, DM & CHD: $^{*}P = 0.03$, HTN & hyperlipidemia: $P = 0.051$, and HTN & CHD: $^{*}P = 0.03$.

($P = 0.002$, 0.03, respectively) and when HTN was combined with CHD ($P = 0.03$).

3.3. Linear Regression Analysis with Clinical Attachment Loss as the Dependent Variable. Tables 2 and 3 present the results of the linear regression analysis with CAL as the dependent variable. Table 2 shows that the risk of CAL was significantly higher in persons whose age ranged from 25 to 50 years in DM, DM and HTN, DM and hyperlipidemia, and DM and CHD models ($B = 1.43$, 95%$CI = 0.07$, 2.76; $B = 1.51$, 95%$CI = 0.13$, 2.84; $B = 1.53$, 95%$CI = 0.21$, 2.90; and $B = 1.52$, 95%$CI = 0.14$, 2.95, respectively). Also, the risk of CAL was found to be statistically higher in patients who had 3 to 5 missing teeth in the 4 models ($B = 1.18$, 95% CI =0.09, 2.60; $B = 1.15$, 95%$CI = 0.16$, 2.75; $B = 1.16$, 95%$CI = 0.14$, 2.76; and $B = 1.22$, 95%$CI = 0.22$, 3.22, respectively). As for the comorbidities, patients suffering either from DM alone or from DM and HTN had significantly higher risk for CAL ($B = 1.88$, 95%$CI = 0.43$, 3.40, and $B = 2.01$, 95%$CI = 0.49$, 3.75, respectively). It was also higher in individuals with DM and hyperlipidemia or DM and CHD ($B = 1.78$, 95% $CI = -2.24$, 3.01, and $B = 0.96$, 95%$CI = -3.04$, 4.82, respectively); however, these associations were not statistically significant. Table 3 also shows that HTN alone or with hyperlipidemia or CHD had higher risk for CAL; however, this was not statistically significant. On the other hand, patients whose ages were between 25 and 50 and those who had 3 to 5 missing teeth had significantly higher risk of CAL in the 3 models.

3.4. Linear Regression Analysis with Alveolar Bone Loss as the Dependent Variable. Tables 4 and 5 present the results of the linear regression analysis with average alveolar bone loss as

Table 2: Association between CAL and DM with other comorbidities.

Factor		Model 1 DM		Model 2 DM & HTN		Model 3 DM & hyperlipidemia		Model 4 DM & CHD	
		B (95% CI)	*P* value	*B* (95% CI)	*P* value	*B* (95% CI)	*P* value	*B* (95% CI)	*P* value
Age	>50	1.05 (-0.97, 2.49)	0.34	1.36 (-0.53, 3.11)	0.14	1.47 (-0.35, 3.17)	0.08	1.76 (-0.13, 3.42)	0.07
	25-50	1.43 (0.07, 2.76)	0.04*	1.51 (0.13, 2.84)	0.03*	1.53 (0.21, 2.90)	0.03*	1.52 (0.14, 2.95)	0.03*
	18-<25	Reference		Reference		Reference		Reference	
Gender	Males	0.73 (-2.09, 0.63)	0.29	0.57 (-1.94, 0.81)	0.42	0.57 (-1.92, 0.81)	0.41	0.47 (-1.86, 0.91)	0.50
	Females	Reference		Reference		Reference		Reference	
Nationality	Saudi	0.49 (-0.50, 1.57)	0.32	0.41 (-0.59, 1.42)	0.25	0.32 (-0.68, -1.32)	0.53	0.40 (-0.61, 1.41)	0.44
	Non-Saudi	Reference		Reference		Reference		Reference	
Smoking	Yes	0.30 (-1.10, 1.67)	0.67	0.39 (-1.07, 1.86)	0.59	0.31 (-1.12, 1.73)	0.67	0.14 (-1.28, 1.56)	0.85
	No	Reference		Reference		Reference		Reference	
Number of missing teeth	>5	0.89 (-2.66, 0.81)	0.33	0.66 (-2.45, 1.12)	0.47	0.51 (-2.29, 1.28)	0.58	0.61 (-2.34, 1.19)	0.52
	3-5	1.18 (0.09, 2.60)	0.02*	1.15 (0.16, 2.75)	0.02*	1.16 (0.14, 2.76)	0.02*	1.22 (0.22, 3.22)	0.01*
	0-2	Reference		Reference		Reference		Reference	
Comorbidity	Yes	1.88 (0.43, 3.40)	0.01*	2.01 (0.49, 3.75)	0.04*	1.78 (-2.24, 3.01)	0.11	0.96 (-3.04, 4.82)	0.81
	No	Reference		Reference		Reference		Reference	

Model 1: effect of DM on CALs with other confounders controlled, adjusted $R^2 = 0.08$, *P value = 0.004. Model 2: effect of DM and HTN on CALs with other confounders controlled, adjusted $R^2 = 0.10$, *P value = 0.01. Model 3: effect of DM and hyperlipidemia on CAL with other confounders controlled, adjusted $R^2 = 0.06$, *P value = 0.01. Model 4: effect of DM and CHD on CAL with other confounders controlled, adjusted $R^2 = 0.05$, *P value = 0.02.

Table 3: Association between CAL and HTN with other comorbidities.

Factor		Model 1 HTN		Model 2 HTN & hyperlipidemia		Model 3 HTN & CHD	
		B (95% CI)	*P* value	*B* (95% CI)	*P* value	*B* (95% CI)	*P* value
Age	>50	1.44 (-0.45, 0.32)	0.13	1.47 (-0.31, 3.16)	0.11	1.76 (-0.13, 3.42)	0.07
	25-50	1.48 (0.09, 2.83)	0.03*	1.53 (0.16, 2.91)	0.02*	1.52 (0.14, 2.95)	0.03*
	18-<25	Reference		Reference		Reference	
Gender	Males	0.51 (-1.87, 0.87)	0.47	0.54 (-1.90, 0.83)	0.44	0.47 (-1.86, 0.91)	0.42
	Females	Reference		Reference		Reference	
Nationality	Saudi	0.42 (-0.55, 1.43)	0.41	0.33 (-0.67, 1.33)	0.52	0.40 (-0.61, 1.41)	0.73
	Non-Saudi	Reference		Reference		Reference	
Smoking	Yes	0.19 (-1.23, 1.62)	0.79	0.28 (-1.13, 1.70)	0.69	0.14 (-1.26, 1.54)	0.08
	No	Reference		Reference		Reference	
Number of missing teeth	>5	0.67 (-2.45, 1.13)	0.46	0.49 (-2.27, 1.29)	0.59	0.61 (-2.34, 1.19)	0.52
	3-5	1.22 (0.23, 3.02)	0.01*	1.13 (0.12, 2.32)	0.02*	1.21 (0.24, 3.22)	0.01*
	0-2	Reference		Reference		Reference	
Comorbidity	Yes	0.83 (-0.84, 2.09)	0.40	2.12 (-0.44, 4.03)	0.10	0.58 (-3.35, 4.31)	0.80
	No	Reference		Reference		Reference	

Model 1: effect of HTN on CAL with other confounders controlled, adjusted $R^2 = 0.06$, *P value = 0.02. Model 2: effect of HTN and hyperlipidemia on bone loss with other confounders controlled, adjusted $R^2 = 0.06$, *P value = 0.01. Model 3: effect of HTN and CHD on CAL with other confounders controlled, adjusted $R^2 = 0.05$, *P value = 0.03.

the dependent variable. In Table 4, DM was the main comorbidity assessed whether alone or combined with other comorbidities. The risk of alveolar bone loss was higher in persons who had DM ($B = 1.86$, 95%$CI = 0.30$, 3.82) and those that had both DM and HTN ($B = 2.82$, 95%$CI = 0.89$, 4.75), with significant differences. The risk of alveolar bone loss was also higher among persons with DM and hyperlipidemia ($B = 0.39$, 95%$CI = -2.24$, 3.01) or CHD ($B = 2.86$ and 95%$CI = -1.25$, 6.96), but these differences were not statistically significant. For other independent variables, age and

Table 4: Association between alveolar bone loss and DM with multiple comorbidities.

Factor		Model 1 DM		Model 2 DM & HTN		Model 3 DM & hyperlipidemia		Model 4 DM & CHD	
		B (95% CI)	*P* value	*B* (95% CI)	*P* value	*B* (95% CI)	*P* value	*B* (95% CI)	*P* value
Age	>50	2.39 (0.43, 4.35)	0.017*	2.20 (0.41, 4.21)	0.02*	-2.74 (0.81, 4.07)	0.005*	2.65 (0.75, 4.43)	0.005*
	25-50	1.54 (0.11, 2.97)	0.03*	1.56 (0.14, 2.97)	0.03*	1.59 (0.16, 3.02)	0.03*	1.62 (0.16, 3.02)	0.03*
	18-<25	Reference		Reference		Reference		Reference	
Gender	Males	0.81 (-0.30, 1.91)	0.15	0.51 (-0.91, 1.92)	0.48	0.79 (-0.32, 1.90)	0.16	0.65 (0.46, 1.76)	0.25
	Females	Reference		Reference		Reference		Reference	
Nationality	Saudi	0.15 (-1.72, 0.15)	0.78	0.14 (-0.99, 1.07)	0.79	0.09 (-1.63, -0.05)	0.87	0.18 (-0.1.67, -0.07)	0.73
	Non-Saudi	Reference		Reference		Reference		Reference	
Smoking	Yes	1.40 (-0.39, 1.78)	0.21	1.78 (0.62, 3.61)	0.02*	1.29 (-0.43, 1.75)	0.23	1.32 (-0.29, 1.89)	0.06
	No	Reference		Reference		Reference		Reference	
Number of missing teeth	>5	0.69 (-1.64, 2.12)	0.80	0.78 (-1.56, 2.13)	0.76	0.60 (-1.48, 2.28)	0.67	0.57 (-1.44, 2.29)	0.65
	3-5	1.63 (-2.66, -0.58)	0.01*	1.52 (0.06, 3.49)	0.02*	1.64 (0.70, 3.59)	0.02*	1.65 (0.69, 4.61)	0.02*
	0-2	Reference		Reference		Reference		Reference	
Comorbidity	Yes	1.86 (0.30, 3.82)	0.01*	2.82 (0.89, 4.75)	0.004*	0.39 (-2.24, 3.01)	0.60	2.86 (-1.25, 6.96)	0.17
	No	Reference		Reference		Reference		Reference	

Model 1: effect of DM on amount of bone loss with other confounders controlled, adjusted $R^2 = 0.20$, $^*P$ value < 0.001. Model 2: effect of DM and hypertension on bone loss with other confounders controlled, adjusted $R^2 = 0.22$, $^*P$ value < 0.001. Model 3: effect of DM and hyperlipidemia on bone loss with other confounders controlled, adjusted $R^2 = 0.19$, $^*P$ value < 0.001. Model 4: effect of DM and CHD on bone loss with other confounders controlled, adjusted $R^2 = 0.19$, $^*P$ value < 0.001.

Table 5: Association between alveolar bone loss and HTN with other comorbidities.

Factor		Model 1 HTN		Model 2 HTN & hyperlipidemia		Model 3 HTN & CHD	
		B (95% CI)	*P* value	*B* (95% CI)	*P* value	*B* (95% CI)	*P* value
Age	>50	2.17 (0.29, 4.12)	0.03*	2.72 (0.85, 4.60)	0.005*	2.65 (0.79, 4.50)	0.005*
	25-50	1.48 (0.05, 2.90)	0.04*	1.59 (0.15, 3.02)	0.03*	1.63 (0.18, 3.03)	0.02*
	18-<25	Reference		Reference		Reference	
Gender	Males	0.59 (-0.83, 2.01)	0.41	0.71 (-0.73, 2.15)	0.34	0.59 (-0.85, 2.02)	0.42
	Females	Reference		Reference		Reference	
Nationality	Saudi	0.19 (-0.85, 1.23)	0.72	0.08 (-0.97, 1.13)	0.88	0.18 (-0.86, 1.23)	0.73
	Non-Saudi	Reference		Reference		Reference	
Smoking	Yes	1.44 (-0.39, 2.91)	0.05	1.30 (-0.20, 2.80)	0.09	1.32 (-0.16, 2.79)	0.08
	No	Reference		Reference		Reference	
Number of missing teeth	>5	0.75 (-1.61, 2.11)	0.79	0.68 (-1.47, 2.29)	0.67	0.42 (-1.44, 2.29)	0.65
	3-5	1.65 (0.28, 2.62)	0.02*	1.63 (0.09, 3.58)	0.03*	1.81 (0.69, 3.61)	0.02*
	0-2	Reference		Reference		Reference	
Comorbidity	Yes	1.67 (0.15, 3.18)	0.03*	0.31 (-2.40, 3.03)	0.82	2.96 (-1.05, 6.96)	0.15
	No	Reference		Reference		Reference	

Model 1: effect of HTN on amount of bone loss with other confounders controlled, adjusted $R^2 = 0.21$, $^*P$ value < 0.001. Model 2: effect of HTN and hyperlipidemia on bone loss with other confounders controlled, adjusted $R^2 = 0.19$, $^*P$ value < 0.001. Model 3: effect of HTN and CHD on bone loss with other confounders controlled, adjusted $R^2 = 0.20$, $^*P$ value < 0.001.

number of missing teeth were significantly associated with alveolar bone loss, where patients who were older than >25 years or had 3 to 5 missing teeth had higher risk of alveolar bone loss in all the 4 DM models. HTN was the main comorbidity assessed in Table 5, whether alone or with other comorbidities, where patients with HTN had significantly higher risk for alveolar bone loss ($B = 1.67$, $95\%CI = 0.15$, 3.18). In addition, age and number of missing teeth were significantly associated with alveolar bone loss.

4. Discussion

The association between periodontitis and immunomediated inflammatory disorders and comorbidities including HTN, type

2 DM, osteoporosis, hyperlipidemia, rheumatoid arthritis, and psoriasis has been extensively studied [9, 27, 28]. In our study, the severity of PD was shown to increase by the presence of one or more comorbidity. The Paksoy et al. study demonstrated that periodontitis severity was linked with multiple comorbidities including pulmonary, endocrinal, metabolic, cardiovascular, neurological, haematological, and skeletal disorders [10]. Similarly, our findings showed a linear pattern regarding the severity of periodontal disease in relation to the presence of one or more comorbidity presented in different models.

Our results showed that patients with DM (model 1), DM and HTN (model 2), and DM and hyperlipidemia (model 3) had 1.88, 2.01, and 1.78 times more probability to have deeper CAL than normal patients. Nevertheless, in HTN models, patients who had both HTN and hyperlipidemia presented 2.12 times more chance to develop deep CAL. Similarly, Mendes et al. [27] observed that psoriasis patients had 1.72 times more chance to present periodontitis as well as having deeper pockets than controls. Zhao et al. [11] observed that individuals with periodontal disease have higher susceptibility for systemic comorbidities after examining almost 500 records. Likewise, Lee et al. [29] collected data from 149,785 adults; they concluded that higher risk of periodontal disease could be predicted by a greater value of the Charlson comorbidity index especially in Korean patients above 60 years old.

Sperr et al. [12] conducted a study to evaluate 1199 Austrian individuals with periodontitis; they observed that majority of periodontitis cases are having comorbidities including allergies, HTN, and hyperlipidemia. Existing evidence showed that the local inflammatory response triggered in the periodontal tissue has systemic effects on inflammatory markers that negatively affect the cardiovascular system [30–32]. Thus, many cardiovascular risk factors and interrelated diseases, as well as HTN [33, 34] and atherosclerosis [35, 36], have been correlated with periodontitis. Moreover, previous studies showed that some periodontopathic bacteria are capable of inducing immune response activation and triggering neutrophil chemotaxis, thus inducing inflammation at remote sites. Similarly, the inflammatory response in periodontitis and other comorbidities is almost purely of neutrophilic nature [37, 38].

In the current study, 30% of the periodontitis patients reported one or multiple comorbidities. Peacock [39] observed that 52% of periodontal patients had systemic diseases. The difference could be due to the small sample size that was included in our study. Georgiou et al. [40] observed that almost 60% of periodontal patients are suffering from at least one comorbidity. They also observed that the prevalence of multiple medical conditions was higher in patients visiting periodontologists compared with patients in general practices. Georgiou et al. [40] reported also that periodontitis patients from all the three studied age groups (20-39, 40-59, and 60-79 years old) had a higher prevalence of DM. Similar to our findings, DM was also the most prevalent comorbidity reaching 16% among the examined patients.

Almost 60% of our study sample was in the middle age group (26-50 years), and 70% were female. The middle age (25-50 y) patients who had DM and/or HTN showed 1.4 times more CAL and 1.5 times more RBL, while patients older than 50 y showed almost 1.4 times more CAL and two times more RBL regardless of suffering from DM and/or HTN.

Many previous reports showed that the prevalence of systemic conditions increased with increasing age in both patients treated by a general practitioner vs. periodontist [39, 40]. A previous study on systemic disease prevalence of elder patients has shown that 64% of the candidates have at least one systemic disease [41]. Studies on periodontitis patients found that 47% of them reported having a systemic disease. However, as age increased, a steady increase was found in the percentage of systemic conditions reported. The frequency of systemic disorders in these patients increased from 21.1 percent in the youngest age group to 76.9 percent in the oldest age group [39, 42].

Tooth loss is considered the final sequel of untreated periodontal and dental diseases. It strongly affects the quality of oral health as well as influence the patient's quality of life [25]. In the present study, individuals with severe periodontitis coupled with DM and HTN presented a significantly higher number of missing teeth than the controls and remained as so in the final multivariate model. Similar results were reported in previous studies, in which patients suffering from psoriasis and periodontitis showed more tooth loss than control [25, 43, 44].

In our study, smoker patients showed more CAL and RBL in all comorbidity models than nonsmokers. Smoking, which is an environmental factor, could affect periodontal disease progression in adolescents [45–47]. Smoking promotes the destructive effect of inflammation in periodontitis [48]. Furthermore, smoking tobacco increases the risk for many other oral health problems, including oral cancer and CHD, and mortality [49].

A limitation of the current study was the relatively small number of patients; thus, this could affect the prevalence of some of the reported comorbidities. Thus, future studies containing a bigger sample are highly recommended. Also, prospective clinical studies are required to provide further clarification regarding the influence of periodontal treatment on the patient's systemic health.

5. Conclusions

There appears to be a positive association between multiple comorbidities and periodontal disease severity in terms of increased attachment loss, bone loss, and increased number of missing teeth.

Data Availability

Data will be provided upon request from the corresponding author.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgments

The authors extend their appreciation to the Deputyship of research & innovation, Ministry of Education – Kingdom of Saudi Arabi, for funding this research work through the project number IF-2020-006-Dent, at Imam Abdulrahman Bin Faisal University, College of Dentistry.

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Hindawi
BioMed Research International
Volume 2021, Article ID 6639523, 7 pages
https://doi.org/10.1155/2021/6639523

Review Article

The Possible Role of Vitamin D Deficiency in Early Implant Failure

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Received 28 December 2020; Revised 2 March 2021; Accepted 22 March 2021; Published 7 April 2021

Academic Editor: Verica Pavlic

Background. Dental implants are one of the most successful treatments for restoring tooth function and beauty. Identifying the causes of dental implant failure is useful and vital. This review was aimed at studying the possible role of vitamin D in early implant failure. *Method and Material*. This review was designed based on the PRISMA guideline. Data was collected using keywords including implant, vitamin D, deficiency, failure, dental, OR tooth in international databases including PubMed, Scopus, Web of Science, Cochrane, and Embase, until 2020. Based on the inclusion and exclusion criteria, data were extracted and gathered in a checklist. *Results*. Finally, twelve studies were selected from five different countries. In 6 studies (2 animal studies and four human studies), there was no significant relationship between vitamin D deficiency and dental implant failure. In the other six studies (1 animal study and five human studies), there was a significant relationship in this regard. *Conclusion*. It is difficult to conclude the association between vitamin D and implant failure based on the literature's researches. However, vitamin D appears to play an essential role in implant success through its effects on immune system modulation.

1. Introduction

Tooth decay is one of the main problems in aged people worldwide [1]. It can affect their chewing and tooth function and, as a result, the quality of their lives [2, 3]. Depending on the patient's clinical condition and needs, dentists use conventional tooth-supported, implant-supported, or combined tooth implant-supported prosthetic [4]. The implant-supported dental prosthesis is now widely used to replace one or more missing teeth [4]. Currently, dental implants are among the most successful treatments for restoring tooth function and beauty [5, 6].

Osseointegration helps create a direct interface between the implant and the bone, an essential element for successful dental implant procedures. During the initial recovery period, it is crucial to (1) insert the implant into the bone correctly and (2) maintain the implant in its position over time [7–9]. The amount of bone accumulation in dental implants depends on several factors, including surgical and prosthetic factors (surgical technique and experience of the surgeon, timing and type of prosthesis, and also its quality), implant-related factors (materials, design, and surface), and patient-related factors (bone volume, the quality of the bone, and the host's response) [10–12].

Dental implant failure usually refers to implant failure to osseointegrate accurately with the bone, or vice versa, also when it is lost and mobile or indicates peri-implant bone loss of more than 1 mm in the first year and more than 0.2 mm in the second year [13]. Based on time criteria, failures can be classified as Early Dental Implant Failures (EDIFs) and Late Dental Implant Failures (LDIFs). EDIFs are due to unsuccessful reabsorption representing impairment in the bone repair, while LDIFs are due to loss of osseointegration [14, 15]. Factors causing EDIFs include diabetes, tobacco use, history of periodontitis, length and diameter of the implant, foreign body reaction, and localized bone necrosis due to heat production during bone preparation or implant replacement [15, 16].

Given that DIFs occur in a specific group of patients, this may be related to the patient's systemic health [17, 18]. Therefore, identifying systemic risk factors may lead to a reduction in these failures. Some of these factors, especially vitamin D deficiency, can play an essential role in the development of EDIFs [14, 15, 18].

Vitamin D (vitamin D3 or cholecalciferol) is a steroid hormone that can be consumed orally or, to some extent, be made from cholesterol in the skin by exposure to sunlight (UV light) [19]. Cholesterol is converted to previtamin D3 and isomerized to vitamin D3, and then, after binding to its binding protein, it will be transported to the liver where hydroxylated CYP27A1 enzyme catalyzes its conversion to 25-hydroxy vitamin D3 [19]. Serum level of 25(OH)D or 25-hydroxyvitamin D less than 10 ng/ml is considered severe deficiency; 24-10 ng/ml, deficiency; and 25-80 ng/ml, normal [20].

Since dental protein rearrangement is determined by bone metabolism, low levels of vitamin D can negatively impact the process of repair and new bone formation on the implant surface [21]. Low vitamin D levels are associated with an increased risk of peripheral joint infections [22]. In rodents, vitamin D causes bone formation around the implant. Several studies reported the association between vitamin D deficiency and DIFs in animal models [23, 24]. Some researchers examined the relationship between bone metabolism, vitamin D, and early implant failure in humans, but the reported association is still controversial [25–27]; therefore, a comprehensive study in this field seems necessary. The present study was aimed at evaluating the association between vitamin D and EDIFs.

2. Method and Material

2.1. Study Design. The present review was designed based on the PRISMA guideline [28].

2.2. Search Strategy. Data was collected using keywords including vitamin D, vitamin D deficiency, dental implants, and implant failure in international databases including PubMed, Scopus, Web of Science, Cochrane, and Embase, until 1 February 2020. All the references were checked manually. For the PubMed database, this syntax was used: ("vitamin d deficiency"[MeSH] OR "vitamin D deficiency"[TIAB] OR "Vitamin D"[Mesh] OR "Vitamin D"[TIAB]) AND ("Dental Implants"[MeSH] OR "Dental Implants"[TIAB] OR "implant failure"[TIAB]).

2.3. Inclusion Criteria. First, the title and then the abstracts were independently reviewed by two authors (LHK and SB). Studies investigating the effect of vitamin D deficiency on dental implants and the failure of dental implants due to vitamin D deficiency in humans and animals were included in this study. The success of dental implants is commonly defined by implant survival. Serum level of 25(OH)D or 25-hydroxyvitamin D less than 10 ng/ml is considered severe deficiency; 24-10 ng/ml, deficiency; and 25-80 ng/ml, normal [20].

2.4. Exclusion Criteria. The exclusion criteria consisted of topic irrelevance, duplicate, or incomplete data. Review articles were excluded from the study.

2.5. Data Extraction. Data were extracted by year, location, the purpose of study, method of study, and results. Information was categorized by authors' name, year of publication, study location and type of study, and the number, age, and sex of patients.

3. Result

In the initial search, 1200 articles were found. After eliminating unrelated, duplicate, and incomplete information, twelve studies were finally entered in this study. The steps for selecting studies are given in Figure 1.

Tables 1 and 2 provide information on the 12 main studies, including the author's name, year of publication, location, sample size, method, and study results. These studies were selected from five different countries (Italy, Brazil, Spain, United States, Korea, and Germany). The highest number of studies was in Brazil, with four studies. This review included nine human studies in Table 1 and 3 animal studies in Table 2. In 6 studies (2 animal studies and four human studies), there was no significant relationship between vitamin D deficiency and dental implant failure. In the other six studies (1 animal study and five human studies), there was a significant relationship in this regard. The study quality was also checked, and low possibility of bias was reported for them.

In a review study of Tabanella, the author concluded that the numbers of osteoclasts formed and their resorption activity is enhanced by the addition of 1.25-(OH)2D3 [29]. In Insua et al.'s study, osteocytes and immune cells' influence was key regulators during dental implant osseointegration and maintenance [9].

4. Discussion

This review was aimed at studying the possible role of vitamin D in DIFs. In the present review, twelve original articles were studied. Despite the high success rate of dental implants, implant failure has been reported in some cases. Baqain et al. in Oman studied 169 patients with a total of 399 implants. They found that fifteen implants in 14 patients (8%) were unsuccessful [30]. In a study by Jafarian et al. in Iran, out of 1533 dental implants in 250 patients, 61 (4%) failed [31]. They observed that the maxilla had the highest fracture rate (9 out of 132 implants (6.8%)) [31]. There are several reasons for failure in dental implants, including vitamin D deficiency. There are also several studies indicating the high prevalence of vitamin D deficiency worldwide [32–34]. Vitamin D deficiency is a global health problem for all age groups, especially in the Middle East [35]. Due to the increasing prevalence of vitamin D deficiency worldwide, dental implant failure rates may increase over time. In the investigated researches, a remarkable variation in the studied populations was apparent. Mangano et al. reported the largest sample sizes with 885 samples.

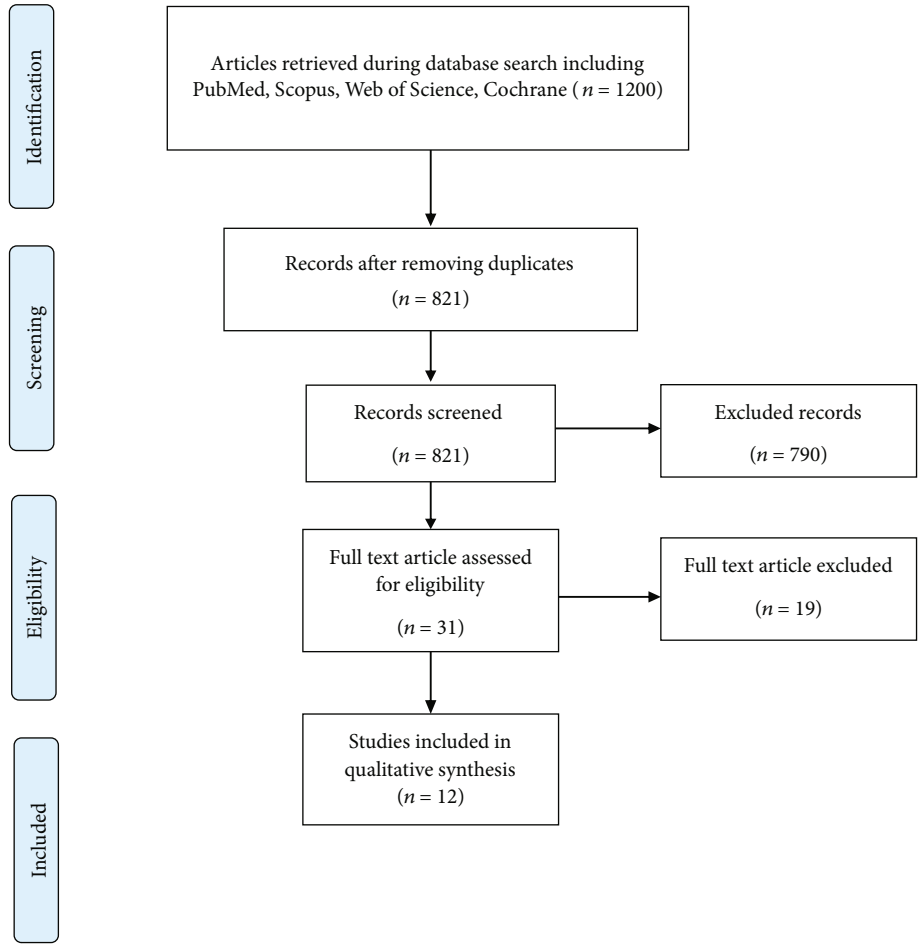

Figure 1: Flowchart describing the study design process.

On the other hand, Bryce and MacBeth's studies were conducted just by one sample involved [26, 36]. Twenty-five percent of these studies used animal models, including dogs and rabbits. Human studies were performed as a randomized controlled trial, case control, and case report. These variations will make it difficult to make a solid conclusion on the subject. The most reliable studies after systematic review and meta-analysis are the RSTs. These types of studies can guide scientists accurately to resolve scientific gaps. However, case report studies in case of lacking good sample size can help the researchers. Cross-sectional studies are performed to study deceptive aspects of a population in a specific time but cannot determine the relation or cause of something.

Six of the investigated studies found a significant association between vitamin D deficiency and DIFs, but there was no significant relationship between these two criteria in the other six studies. Our results showed few pieces of evidence of the association between vitamin D levels and the success rate in dental implantation. Because of the contradictory results obtained from those studies, it is recommended to conduct comprehensive studies with larger sample sizes.

The role of vitamin D in the calcium economy is extremely important. During osteointegration, calcitriol affects the processes of activation and differentiation of osteoblasts and osteoclasts. Vitamin D has also been found to be essential for the maturation and proper functioning of bone cells by the production of a factor stimulating osteoclast precursor fusion and stimulation of osteoblast differentiation. Vitamin D also increases osteoid mineralization [37]. Also, this mechanism can play an important role in the stabilization phase of the implant, after stabilization is achieved by loading it with a prosthetic crown.

In addition to its role in calcium and bone homeostasis, vitamin D plays a vital role in modulating the innate and adaptive immune responses [38]. Recent studies suggest that vitamin D, as an essential immune response regulator, mostly targets innate immune response because all immune cells express the vitamin D receptor (VDR) response [39, 40]. Changes in cytokine secretion due to vitamin D deficiency can impair osteoclast activation and differentiation through VDR activation [41]. It is hypothesized that metallic particles affect macrophages and lymphocytes to release inflammatory cytokines, leading to increased osteoclastogenesis and decreased osteoblastogenesis, which eventually results in peri-implant bone degeneration [42]. Vitamin D may also be essential for the antibacterial response because it affects the monocyte-macrophages [43]. Xu et al. showed that vitamin D could inhibit gingivalis-induced proinflammatory cytokine expression and, at the same time, improves the expression of anti-inflammatory cytokines in macrophages [44].

Table 1: Clinical studies about the relation between vitamin D and early implant failure.

Author name	Country	Sample size	Gender		Method	Result	Conclusion	Reference
			Male	Female				
Mangano et al., 2018	Italy	885 humans	455	430	Cross-sectional	No significant relationship was found between implant failure and vitamin D deficiency	A dramatic increase in EDIFs with the lowering of vitamin D levels in the blood has been reported	[36]
Mangano et al., 2016	Italy	822 humans	429	398	Cross-sectional	No significant relationship was found between implant failure and vitamin D deficiency	Vitamin D deficiency has no impact on implant failure	[45]
Fretwurst et al., 2016	Germany (Freburg)	2 humans	2	—	Case report	Implant placement was successful after vitamin D supplementation in patients with vitamin D deficiency and early failed implants	Standard screening of vitamin D in dental implantology may be helpful given the evidence	[46]
Boas et al., 2019	Brazil	10 humans	—	—	Case control	Despite altered serum levels of vitamin D, there is no clinical correlation with osseointegration deficiency and bone remodeling system	Vitamin D insufficiency is not a real contraindication for implant placement	[8]
Vedururu et al., 2016	United States (Buffalo)	362 humans	—	—	Cross-sectional	Sixty-three (30%) patients had intake supplemented with vitamin D and 5 (1.3%) failures were reported. The number of failures in patients who are not taking vitamin D supplementation is 10 (2.7%)	The data suggest that vitamin D intake may minimize dental implant loss	
Bryce and MacBeth, 2014	England	1 human	1	—	Case report	Five months postoperatively, no osseointegration of the implant was found. The patient was severely vitamin D deficient, and this may have contributed to the implant failure	Vitamin D deficiency may play a role in the failure of osseointegration in dental implants	[26]
Pereira et al., 2019	Brazil	244 humans	82	162	Case-control	The allele G of rs3782905 in the recessive model, together with the number of installed implants and gingival index, was significantly associated with implant failure	It is suggested that the allele G of rs3782905 in the recessive model may be a new genetic risk marker for dental implant loss	[47]
Alvim-Pereira et al., 2008	Brazil	207 humans	50	87	Case-control	No association between genotypes or alleles of VDR TaqI polymorphism and implant loss was found	More studies considering other polymorphic regions of the VDR gene might be performed to clarify its importance in implant loss physiopathology	[25]
Schulze-Späte et al., 2016	United States	20 humans	13	7	Randomized, double-blind, placebo-controlled trial	No significant difference in bone formation or graft resorption was detected between groups. However, in the vitamin D3 group, a significant association was found between increased vitamin D levels and a number of bone-resorbing osteoclasts around graft particles	Vitamin D3+ calcium supplementation improves serum vitamin D levels and potentially impacts local bone remodeling on a cellular level	[48]

Table 2: Animal studies about the relation between vitamin D and early implant failure.

Author name	Country	Sample size	Result	Conclusion	Reference
Salomo-Coll et al., 2015	Spain	24 dogs	No statistically differences could be found between the two groups	With the limitation of animal studies, topical application of vitamin D on dental implants could reduce crestal bone loss and increase 10% more bone-to-implant contact at a 12-week follow-up period	[49]
Naito et al., 2014	Brazil	28 rabbits	The 1.25-(OH)2D3-coated implants tended to osseointegrate better than the noncoated surfaces. The differences were not significant	Future studies are recommended to investigate a base substrate's development that can maintain 1.25-(OH) 2D3 for a long period	[24]
Cho et al., 2011	Korea	12 rabbits	A significant relationship was found between the case and control groups	This study demonstrated that the PLGA/1α,25-(OH)2D3 solution coating resulted in submicron-sized particles, which may stimulate bone formation adjacent to the surface of implants inserted into bone	[50]

Vitamin D affects different stages of peri-implant bone formation. It has become an active factor in dental and implant surgery because of its effects on bone metabolism and the immune system. Given the high percentage of patients with vitamin D deficiency, it seems necessary to examine vitamin D deficiency before implant and dental surgery. It is recommended to conduct comprehensive studies with larger sample sizes to determine the exact mechanism involved. The limitations of the study include the limited number of clinical studies and small sample sizes. Our search shows that there are few clinical studies in this field; also, some of them contain a small sample size; this point should be resolved in future studies.

5. Conclusion

It is difficult to conclude the association between vitamin D and implant failure based on the current research in the literature. The studies' findings were inconsistent, but some of this research noted the effect of vitamin D on implant failure. Vitamin D may play a role in improving implant success through its effects on the immune system modulation. This hypothesis needs more clinical studies to be approved.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Hindawi
BioMed Research International
Volume 2024, Article ID 9817204, 1 page
https://doi.org/10.1155/2024/9817204

Retraction

Retracted: Effect of Platelet-Rich Plasma on Bone Healing in Immediate Implants Analyzed by Cone Beam Computerized Tomography: A Randomized Controlled Trial

BioMed Research International

Received 12 March 2024; Accepted 12 March 2024; Published 20 March 2024

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

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The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] A. S. Khan, N. Zaheer, A. M. Zaigham, M. Shahbaz, U. Zaheer, and M. K. Alam, "Effect of Platelet-Rich Plasma on Bone Healing in Immediate Implants Analyzed by Cone Beam Computerized Tomography: A Randomized Controlled Trial," *BioMed Research International*, vol. 2021, Article ID 6685991, 7 pages, 2021.

Hindawi
BioMed Research International
Volume 2021, Article ID 6685991, 7 pages
https://doi.org/10.1155/2021/6685991

Research Article

Effect of Platelet-Rich Plasma on Bone Healing in Immediate Implants Analyzed by Cone Beam Computerized Tomography: A Randomized Controlled Trial

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Received 2 January 2021; Revised 26 February 2021; Accepted 1 March 2021; Published 15 March 2021

Academic Editor: Marwa Madi

The possibility of platelet-rich plasma (PRP) on the improvement of bone and adjacent tissue recovery has previously been validated. However, there is insufficient data supporting the use of platelet-rich plasma to improve the healing of bone and adjacent tissues around an implant in the oral cavity. The purpose of this randomized controlled trial was to observe the effect of platelet-rich plasma (PRP) concentrate on marginal bone loss and bone density around immediate implant placement using Cone Beam Computerized Tomography (CBCT). This clinical study was conducted over a period of six months on 12 subjects, who were equally categorized into two groups. Group I was the control, whereas the subjects in Group II received PRP therapy at the surgical site. All subjects were given a standard treatment with a single implant system (DIO UFII hybrid sandblasted acid-etched implants). Inserted implants were analyzed through CBCT, and records were registered at baseline, at the 12th week before functional loading and the 26th week after functional loading. The bone loss was calculated at the proximal (mesial and distal) side of the implant and bone density at baseline, 12th week, and 26th week after implant placement. SPSS version 23.0 was used for statistical analysis of data. The changes in bone levels were measured and compared between the two groups using the Mann–Whitney U test, with no significant difference. Bone density was analyzed by an independent sample t-test, p value $\leq$ 0.05 was considered statistically significant. Again, no significant difference in bone density was observed between both groups at all three instances. Therefore, it can be concluded that local injection of PRP after immediate implant placement did not show any decrease in marginal bone loss or improvement in bone density. This trial is registered with NCT04650763.

1. Introduction

Tooth loss is a distressing experience and affects the quality of life [1]. Implants provide a fixed replacement option improving the patient's confidence and have psychological benefits [1, 2]. Bone requires approximately 2 to 3 months for remodeling after extraction of the tooth, and it has been suggested healing time of common commercial titanium implants is 3-6 months before loading becomes clinically feasible [1, 3]. The elaborate treatment planning, followed up with the surgical procedure as well as the use of a removable prosthesis temporarily till definitive prosthetic replacement,

decreases the willingness of the patients who tend to prefer early restoration of function and esthetics [1].

The immediate implant placement in an extraction socket seems to have some benefit when compared to delayed implant placement, such as less time and reduced surgical procedures [2, 4]. Previously, many studies have concluded that immediate implant placement minimizes bone resorption by maintaining the periodontal architecture [2, 5, 6]. However, recent clinical studies have reported increased failure rates due to a decrease in primary stability and a reduction in bone volume around immediately placed implants, suggesting that it did not effectively prevent vertical and horizontal changes in ridge volume [2, 7, 8]. Nonetheless, there was no significant difference in bone loss between the two groups [8].

The prognosis of immediate implants may be compromised by the presence of residual dental infection or any bony defect. However, at sites with intact socket walls of the alveolar bone intact have been reported to have a similar survival rates to that of implants placed into healed ridges [2, 8].

Platelet-rich plasma (PRP) is an autologous concentrate of platelets in a minute amount of plasma [9]. It is considered a first-generation concentrate using calcium glutamate/-thrombin to activate coagulation and an anticoagulant solution of citrate phosphate dextrose adenine (CPDA) [10, 11]. After activation by thrombin or calcium chloride, the platelets in PRP release various essential growth factors documented to be produced by platelets [12]. These growth factors consist of 3 isomers of platelet-derived growth factors (PDGF$\alpha\alpha$, PDGF$\beta\beta$, and PDGF$\alpha\beta$), 2 transforming growth factors-β (TGFβ1 and TGFβ2), epithelial growth factor, and vascular endothelial growth factor [2, 9]. Once used locally, platelet concentrates increase the production of osteoprogenitor cells, initiate osteoblast activity, accelerate epithelialization of the gingiva, promote cell recruitment at the site of surgery, and stimulate angiogenesis [9]. Apart from these benefits, PRP may play anti-inflammatory and analgesic roles during the early period after surgery, as documented in some randomized clinical studies [13, 14]. The inclusion of leukocytes in PRP releases VEGF and TGF that, again, improves chemotaxis and angiogenesis [10], mainly due to the control of the inflammatory process by anti-inflammatory cytokines IL-4, IL-6, and IL-10 also having an antimicrobial potential [10]. Antimicrobial activities of platelet concentrates against some oral microbes reduce the incidence of postoperative infection, which is an advantage when treating cases with an infected postextraction sockets [14].

However, there is no consensus on whether or not platelets must be previously activated before their application and with which agonist [12]. Thrombin and calcium chloride, which are aggregation inducers, are used to activate platelets and stimulate degranulation, causing the release of the growth factors. Some authors activate platelets, whereas others apply platelets without previously activating them, arguing that better results are obtained [12]. While working on this trial, there was still no definitive outcome as to the adverse effects of using thrombin to release growth factors. Recent studies found that such aggregators are not necessary because at the time of administration the platelets are automatically released and ready to exert their function [12]. Thus, thrombin was replaced with normal saline for this study [2, 12]. Moreover, this technique/protocol of preparing and using PRP is generally followed in Pakistan's hospitals for clinical uses. So, PRP was the preferred choice for this study.

PRP containing platelet growth factors has been used widely in multiple procedures, and evidence showed improved tissue healing, but its positive effect on hard tissue healing still needs more research [15, 16]. Some clinical studies reported controversial results in the bone formation and marginal bone preservation around immediate implants when platelet-rich plasma was used [2, 9]. Thus, further research is needed to determine the influence of PRP on the bone.

The objective was to study the effect of platelet-rich plasma concentrate on marginal bone loss and bone density in immediate implant placement through CBCT in a human clinical trial.

2. Methodology

A randomized control trial was conducted at the Department of Prosthodontics, Institute of Dentistry, CMH, Lahore Medical College, over a period of six months from October 2018 till March 2019. Approval was taken from the ethical committee of the Institute of Dentistry, CMH, Lahore Medical College (Reference #466/ERC/CMH/LMC), and the study was registered in ClinicalTrials.gov (NCT04650763). Twelve systemically healthy subjects above the age of twenty were selected including both genders. The sample size was estimated by using 95% confidence level, 80% power with an expected mean change in bone loss for PRP and control group in 12-week time as 0.27 ± 0.07 and 0.65 ± 0.28, respectively [1]. Subjects included were patients maintaining good oral hygiene, having adequate bone quantity at the implant site, and patients requiring extraction and replacement of at least one tooth by a prosthesis supported on the implant with or without the application of PRP.

Patients with active infection around the implant site, immunocompromised state, with current major systemic disease (uncontrolled diabetes, rheumatoid arthritis, etc.) or oral pathologies, history of bleeding disorders or on anticoagulant therapy, or patients on bisphosphonates were excluded from the study. Subjects who were physically and mentally challenged (lack of manual dexterity) and those who were noncompliant for regular visits and follow-ups were also excluded from the study. Personal information of the patients was kept confidential. Informed consent was obtained for documentation and public presentation of their clinical data.

All chosen individuals who agreed to be part of the research received standard treatment with a single implant system (DIO UFII implants, hybrid, sandblasted and acid-etched surface). Randomization of subjects was done (6 in each group) by nonprobability consecutive sampling. Another researcher allocated random numbers to the

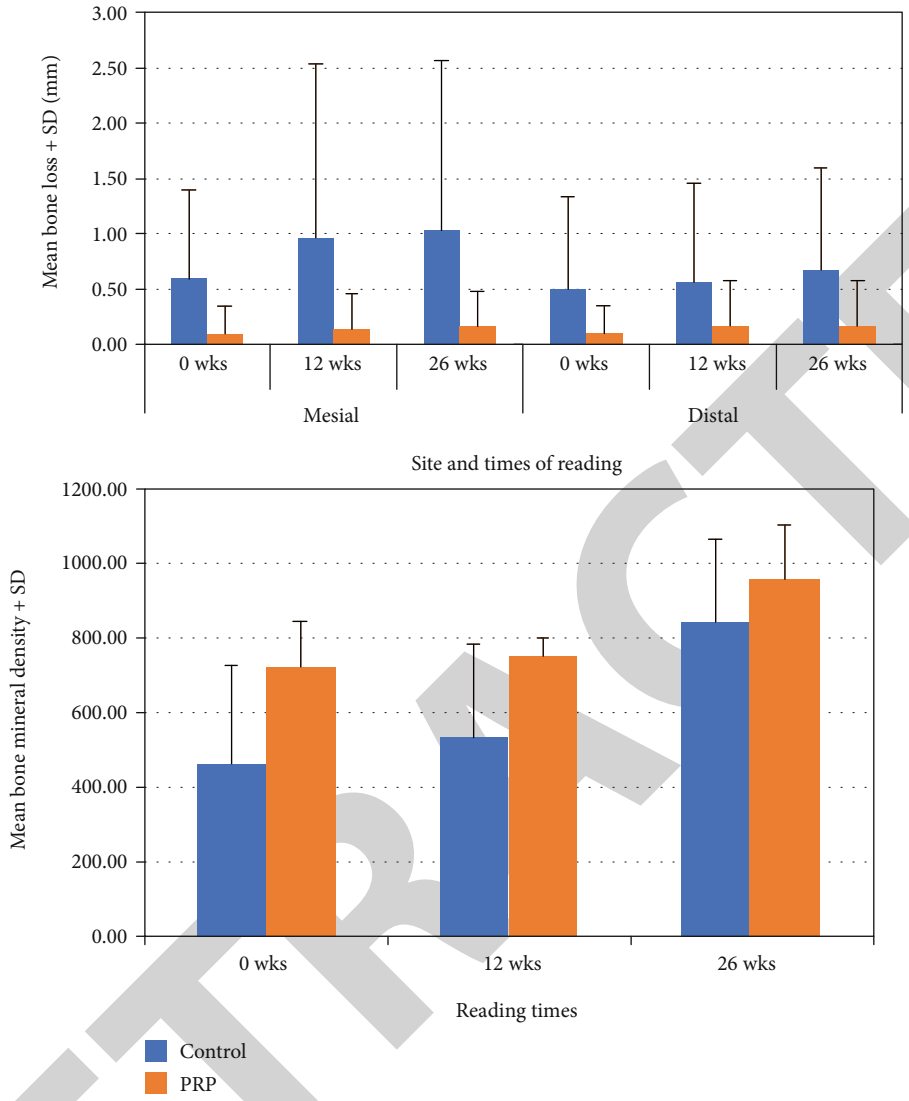


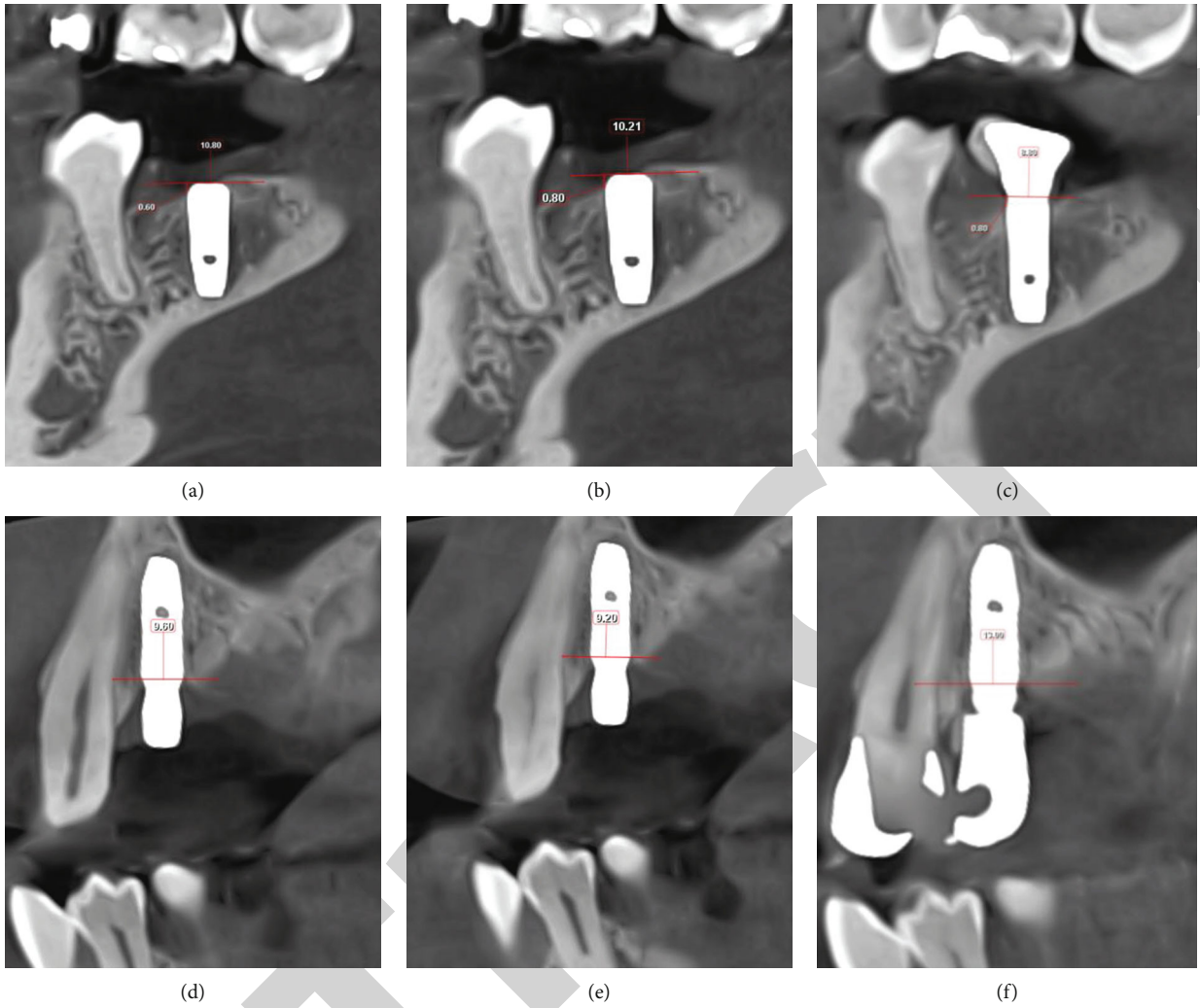
Figure 1: Bone loss and bone density at mesial and distal sites in two groups at baseline, 12 weeks, and 26 weeks.

participants for the purpose of concealment and to avoid bias. Half of the participants were assigned odd numbers, and half were assigned even numbers randomly. Odd numbers were added in Group I, the control group (non-PRP group), and even numbers were added in Group II (PRP group), which was a test group that received PRP therapy. There were 6 cases in each group. Analyses of inserted implants were done as per CBCT. Clinical records were noted at baseline and at each follow-up visit after 12 weeks before functional loading and 26th-week follow-up after functional loading.

The data was measured for bone loss at the mesial and distal sites and bone density at baseline, 12-week, and 26-week time. The changes between baseline and 12 weeks, baseline to 26 weeks, and 12–26 weeks were measured and compared between the two groups (Figure 1). The data was significantly deviating from normality for bone loss at both sites for at least one of the groups. Mann–Whitney U test was applied to compare two groups. The data for bone density was normal, so an independent sample t-test was applied. p value ≤ 0.05 was considered significant. SPSS version 23.0 was used for statistical analysis of data.

3. Procedure

3.1. Preparation of PRP. The PRP was made ready for use just before placement at the surgical site. 9 ml of blood was taken from the antecubital vein and put in the test tube containing 3.8% trisodium citrate acting as an anticoagulant [2]. An automated blood cell centrifuge was utilised to extract PRP. The product code ORG having premarket review showing Center for Biologics Evaluation and Research (CBER). The submission type is 510(k) with regulation number 864.9245. The device is class 2 with total product life cycle (TPLC) code report. The sample of blood was immediately centrifuged at 5800 rpm for 8 minutes at room temperature to separate poor platelet plasma from RBCs and PRP and then centrifuged at 2400 rpm for an additional 5 min to obtain further separation of PRP from RBCs [2]. After centrifugation, the top buffy coat was collected into a syringe and



(a) (b) (c)

(d) (e) (f)

Figure 2: Marginal bone loss: (a) day 0, baseline control group; (b) 12 weeks, control group; (c) 26 weeks, control group; (d) day 0, PRP group; (e) 12 weeks, PRP group, (f) 26 weeks, PRP group.

injected or mixed with saline to form a liquid solution, to inject at the surgical site [2, 12].

3.2. Surgical and Prosthetic Phase. During surgery, a full thickness mucoperiosteal flap was reflected [17], and the osteotomy was done through sequential drilling for both groups. To determine the size of the implants, presurgical radiographic evaluation and diameter apical to crestal bone along with length of socket was analyzed through CBCT [18, 19]. The implant was inserted in the osteotomy site until the crest module of the fixture was at the same level with the crest of the margin. The immediately prepared liquid solution of PRP was injected on the labial aspect between the implant surface and buccal alveolar wall [2]. Then, sutures were placed to close the flap. PRP has osteoconductive properties which imply that cell growth and differentiation factors from the surrounding bone must be recruited and directed toward the surgical site to accomplish their regenerative action. Osteoinductive mediators serve as crucial elements necessary to achieve a proper osseointegration, as they stimulate various stages of bone regeneration [2].

After 12 weeks, CBCT was taken before functional loading. Soft tissue thickness and interocclusal space were evaluated with WHO periodontal probe for placement of an appropriate size of the abutment on the fixture. A torque of 30 N cm was used for the placement of the abutment after a one-stage non-functional immediate prosthetic protocol. Instructions on the maintenance of hygiene and soft diet plan were emphasized. Three months after insertion of the implant, the definitive prosthesis was cemented with zinc phosphate cement, and the excess cement was wiped immediately after crown placement and further removed with an explorer after setting.

3.3. Radiographic Evaluation. The crestal bone changes were measured at the time of implant placement (baseline), before functional loading, at the 12^{th} week, and the 26^{th} week after functional loading. CBCT (Planmeca Romexis 5.1.0.4) with voxel size 200 μm was used for analysis and measurement.

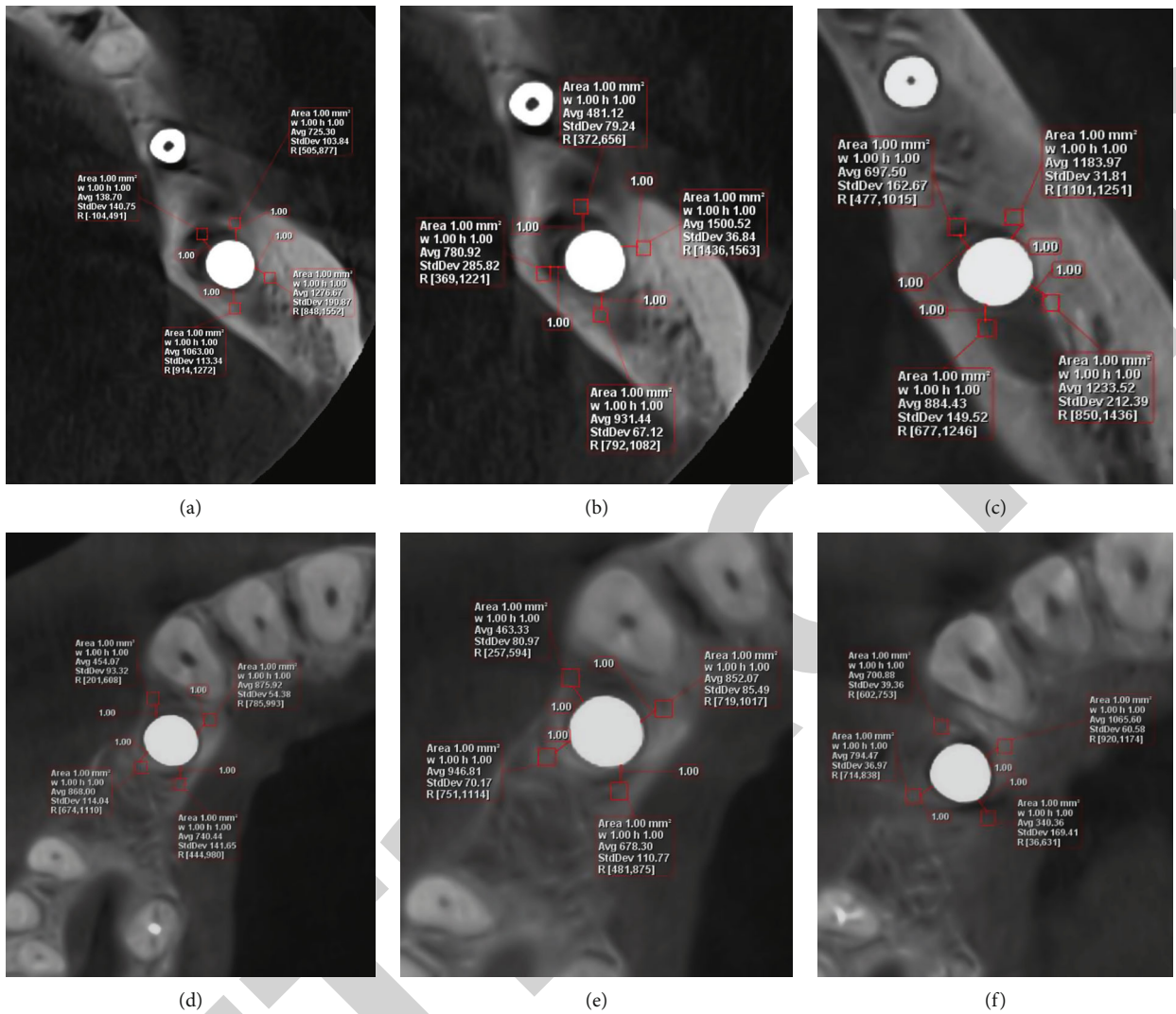


Figure 3: Bone density: (a) day 0, baseline control group; (b) 12 weeks, control group; (c) 26 weeks, control group; (d) day 0, PRP group; (e) 12 weeks, PRP group; (f) 26 weeks, PRP group.

Marginal bone loss was measured in millimetres from the reference line, the maximum height of the crest module to the first visible bone level to implant contact on the mesial and distal sides [20]. Two perpendicular lines were dropped from the reference line on the mesial and distal aspect of the implants to the first bone-to-implant contact. Bone loss was compared in the individual patients in a sagittal view as mesial and distal sides through CBCT at the 12^{th} and 26^{th} weeks (Figure 2).

The baseline reference direction for the short and long axes was set at the bottom of the inner basic lamellae of the cortical bone at the coronal portion of the implant and the implant surface. To assess the bone density at the coronal portion of the implants, three-dimensional bone morphometrical analyses were done on a region within 1 mm from the baseline of the long axis in the apical direction and within 0.6 mm from the baseline of the short axis. The short axis will further be divided into two regions: from the surface to 0.2 mm (near zone) and from 0.2 to 0.6 mm (far zone). Bone density was evaluated in an axial view of CBCT in grey value by Hounsfield unit [21] (Figure 3).

4. Results

The average bone loss at mesial site was 0.37 ± 0.80 in the control group between baseline and 12^{th} week, while in the PRP group it was 0.03 ± 0.08. The comparison between the two groups was insignificant, with a p value of 0.461. The largest change at the mesial site was observed in the control group in 26-week time from baseline, while the bone loss in the PRP group for the same duration was 0.07 ± 0.10 still, the difference was statistically insignificant with a p value of 0.212. At the distal site, the mean bone loss was 0.07 ± 0.016 between baseline and 26^{th} week while it was 0.0 between 12 and 26 weeks in the PRP group, which was insignificant compared to the control group with p values 0.290 and 0.140, respectively. There was no significant difference in changes in bone density between the two groups with p values > 0.05 for all three instances (Table 1).

Table 1: Comparison of bone loss at mesial and distal sites and bone mineral density between the two groups at different times.

Variable	Change between	Group				p value
		Control		PRP		
		Mean	SD	Mean	SD	
Measurement of bone loss at mesial site	Baseline–12 wk	0.37	0.80	0.03	0.08	0.461[a]
	Baseline–26 wk	0.43	0.77	0.07	0.10	0.212[a]
	12–26 wk	0.07	0.10	0.03	0.08	0.523[a]
Bone loss at distal site	Baseline–12 wk	0.07	0.10	0.07	0.16	0.673[a]
	Baseline–26 wk	0.17	0.20	0.07	0.16	0.290[a]
	12–26 wk	0.10	0.17	0.00	0.00	0.140[a]
Bone mineral density	Baseline–12 wk	69.25	65.46	28.37	83.74	0.368[b]
	Baseline–26 wk	378.27	270.86	233.10	212.08	0.326[b]
	12–26 wk	309.02	234.53	204.73	159.30	0.389[b]

[a]The p value is calculated by Mann–Whitney U test. [b]The p value is calculated by independent sample t-test. SD: standard deviation.

5. Discussion

The bone quality and quantity around implants affect the osseointegration phase and influence soft tissue architecture [1]. Assessment of marginal bone levels and bone density as well as soft tissue has become a basic element of the evaluation of the implant patient and is usually a significant tool for the assessment of implant success [1, 20, 21].

The amount and quantity of bone around the implant can be enhanced by providing a stimulus to improve the regenerative potential of the tissue [1, 2]. Multiple growth factors are expressed during tissue healing tissue. Therefore, the introduction of growth factors through platelet concentrate can act as healing agents to accelerate both peri-implant soft and hard tissue repair [2].

The present study did not show any significant difference in marginal bone loss and bone density, following PRP's use with immediate implant placement, compared to the control group. Other studies have also concluded that no difference was found in PRP and non-PRP groups on hard tissue assessment [2] and that the effect of PRP on the height of bone was not significant [22, 23]. Despite the nonsignificant outcomes, when we look closely at the graphical data, along with radiographic parameters though CBCT radiographs, PRP did show promising effects in reducing marginal bone loss and improving bone density which implies that PRP therapy does improve osseointegration [15] and bone density around the implant surface, thus leading to better stability [24]. Other studies also reported significant results when PRP was used and concluded that it enhances osseointegration and reduces marginal bone loss [25, 26].

Nevertheless, statistical analysis showed nonsignificant results which might be because of small sample size and because PRP was injected primarily on the labial aspect between the implant surface and buccal alveolar wall, rather than moistening the implant surface with PRP before placement of implant in the socket, as done by other researchers [15, 24]. Other reasons for the differences in results might be because the preparation systems are not the same [27]; the centrifuge machines vary in revolutions per minute [27], challenges in obtaining a homogenous composition of PRP as there is variation between different people [28] and it is not noticeably clear how will this affect the stem cell behavior in different individuals [29].

6. Conclusion

Based on the radiographic images of CBCT and the graphical data obtained from this study, PRP's effects on marginal bone loss and bone density around immediate dental implants were promising. Although the results were statistically insignificant, the increased sample size might improve the validity of the results and achieve statistically significant results in the future. In further studies, bone density can be analyzed through a Dual Energy X-ray Absorptiometry (DEXA) scan of the mandible after the use of PRP on the implant surface or in the extraction socket before implant placement to better understand the effects of PRP on the bone. More research can be done to gather long-term and robust evidence on PRP's success so that it can be incorporated in regular practice after implant placement to improve the prognosis of treatment.

Data Availability

The pictures of data used to support the findings of this study are included within the article. The entered Excel sheet data of this study are available from the corresponding author upon request.

Conflicts of Interest

All researchers have no conflict of interest related to this study.

Supplementary Materials

Supplementary 1. Supplementary file 1: CONSORT 2010 checklist.

Supplementary 2. Supplementary file 2: CONSORT 2010 flow diagram.

Hindawi
BioMed Research International
Volume 2024, Article ID 9838732, 1 page
https://doi.org/10.1155/2024/9838732

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[1] L. Chen, Y. Ding, G. Cheng, and S. Meng, "Use of Platelet-Rich Fibrin in the Treatment of Periodontal Intrabony Defects: A Systematic Review and Meta-Analysis," *BioMed Research International*, vol. 2021, Article ID 6669168, 13 pages, 2021.

Hindawi
BioMed Research International
Volume 2021, Article ID 6669168, 13 pages
https://doi.org/10.1155/2021/6669168

Review Article

Use of Platelet-Rich Fibrin in the Treatment of Periodontal Intrabony Defects: A Systematic Review and Meta-Analysis

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Received 22 December 2020; Revised 5 January 2021; Accepted 22 January 2021; Published 4 February 2021

Academic Editor: Marwa Madi

Background. Platelet-rich fibrin (PRF) is a kind of autologous platelet concentrate which is easy to obtain and cheap. In recent years, it has been studied to improve the effect of periodontal regeneration. However, few studies have systematically evaluated the complementary effect of PRF in the treatment of intrabony defects. The present review is aimed at systematically assessing the effects of PRF on clinical and radiological outcomes of the surgical treatment of periodontal intrabony defects. *Methods*. The protocol was registered at PROSPERO (International Prospective Register of Systematic Reviews) as CRD42020206056. An electronic search was conducted in MEDLINE, Cochrane, and EMBASE databases. Only randomized clinical trials were selected. Systematically healthy patients with two or three walls of intrabony defects were considered. Intrabony defect (IBD) depth reduction and bone fill (BF) % were set as primary outcomes while probing depth (PD) reduction, clinical attachment level (CAL) gain, and gingival margin level (GML) gain were considered as the secondary outcome. When possible, a meta-analysis was performed. *Results*. Eighteen articles fulfilled the inclusion criteria, and seventeen studies were quantitatively analyzed. Of 17 studies, four were rated as high risk of bias and thirteen as the moderate risk of bias. Two comparisons were set: (1) open flap debridement (OFD) combined with PRF and OFD alone and (2) bone grafting (BG) combined with PRF and BG alone. Compared to OFD alone, OFD+PRF showed significantly greater in all primary and secondary outcomes. Compared to BG alone, BG+PRF showed significantly greater in IBD depth reduction, PD reduction, CAL gain, and GML gain. *Conclusions*. The use of PRF was significantly effective in the treatment of periodontal intrabony defects. The benefit of OFD+PRF may be greater than BG+PRF. PRF can promote early wound healing in periodontal surgery. As all included studies were not at low risk of bias, well-designed RCTs having a high methodological quality are needed to clarify the additional effectiveness of PRF in the treatment of intrabony defects in the future.

1. Introduction

Periodontitis is defined as a chronic inflammatory disease caused by periodontopathic bacteria and is characterized by inflammation and the progressive destruction of tooth-supporting tissues [1], which is the major cause of tooth loss in adults. Regeneration of the periodontal tissues and a return to clinically healthy status are the ultimate goals of the treatment of periodontal diseases. Periodontal regeneration involves the reconstruction of alveolar bone, periodontal ligament, and cementum [2], which is a multifactorial and complex process. Alveolar bone resorption is a typically pathological manifestation of periodontal diseases and a signature event in the diagnosis, which can cause vertical and/or horizontal bone defects and contribute to tooth mobility and even the loss of tooth. Horizontal bone defects are usually difficult to regenerate, while vertical bone defects, especially intrabony defects, are considered to have good regeneration potential. A variety of different surgical techniques, usually including guided tissue regeneration, various types of bone grafts or bone substitutes techniques, growth and differentiation factors, root surface demineralization, enamel matrix

proteins or various combinations thereof, have been investigated to regenerate periodontal tissues [3, 4].

Platelet α-granules contain a great number of growth factors: vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF), platelet factor interleukin (IL), platelet-derived angiogenesis factor (PDAF), insulin-like growth factor (IGF), and fibronectin [5–7], which play an important role in wound healing and regeneration. In recent years, autologous platelet concentrate has been widely used in oral tissue regeneration [8] and wound healing [9]. Platelet-rich plasma (PRP) is the first generation of platelet concentrate, mainly produced by two-step centrifugation and the addition of bovine thrombin and calcium to activate platelets and release growth factors [10]. However, growth factors in PRP are released quickly. Platelet-rich fibrin (PRF) was developed in France by Choukroun et al. [11], and second-generation platelet concentrate is prepared by using a simplified regimen compared to PRP, no biochemical handling of blood or use of any gelling agent like calcium chloride and no risks associated with the use of bovine thrombin [12, 13]. Besides, PRF has a three-dimensional fibrin architecture [14], forming a scaffold to maintain growth factors, in which growth factors are released for more than 7 days [15].

The use of PRF in periodontal regeneration procedures may have potential benefits. A systematic review and meta-analysis [16] reported the effect of autologous platelet concentrate on the treatment of intrabony defects (IBD), but PRF was not evaluated. Castro et al. [17] reported a meta-analysis of 6 studies until 2016, but only three parameters including PD reduction, CAL gain, and bone fill were evaluated, and the evaluation is not detailed enough concerning intrabony defects. After that, more RCTs have been published, so it is necessary to evaluate the effect of PRF in the treatment of periodontal intrabony defects with detailed hard and soft tissue parameters.

The present systematic review and meta-analysis is primarily aimed at evaluating whether PRF could provide additional benefits for intrabony defect, by comparing the clinical and radiological parameters between periodontal surgery alone and periodontal surgery with using PRF in the treatment of intrabony defects.

2. Materials and Methods

2.1. Protocol and Registration. This study was conducted based on the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [18] and is reported following the Preferred Reporting Project Guidelines for Systematic Review and Meta-analysis (PRISMA) statement [19]. The protocol of this systematic review and meta-analysis was registered on the PROSPERO (CRD42020206056).

2.2. Eligibility Criteria. The inclusion criteria were set according to PICOS question: the participants (P) included systemically healthy adults who have suffered periodontal diseases with periodontal intrabony defects; the intervention (I) was periodontal surgery with the use of PRF; the comparison (C) was periodontal surgery without the use of PRF; the outcomes (O) contained radiographic parameters including IBD depth reduction and vertical bone fill (BF) % and clinical parameters including probing depth (PD), clinical attachment level (CAL), and gingival margin level (GML); the study (S) was only considered to be randomized controlled trials (RCTs) with blindness.

The exclusion criteria were as follows: (1) patients with systematic diseases or pregnancy or lactation for women; (2) smoker or using drugs known to affect the outcomes of periodontal therapy; (3) absent or uncompleted periodontal initial therapy before periodontal surgery; (4) one-wall defects included; (5) studies investigating any other oral surgical intervention like tooth extraction, implant therapy, treatment of jawbone defects, odontogenic cysts, and periapical surgery.

2.3. Information Sources and Search Strategy. Three electronic databases were searched without limits regarding publication date or status: MEDLINE via PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL). Only articles published in English were eligible. The last search was conducted on 16 November 2020. The search strategy was performed by combining (Mesh Terms OR Key Words) and using the following terms: "platelet concentrates" OR "platelet-rich fibrin" OR "PRF." In addition, OpenGrey (http://www.opengrey.eu) and Grey Literature Report (http://www.greylit.org) were used to supplement the search for grey literature by using the term "platelet-rich fibrin."

2.4. Study Selection and Data Collection Process. The titles and abstracts obtained from the first search were screened independently by the two reviewers (Liang Chen and Guoping Cheng). After the initial assessment, all full texts of the eligible articles were obtained and examined by both reviewers. Any disagreement in the final selection was resolved by open discussion between the two reviewers and by consulting a third author (Shu Meng).

Data from the studies included in the final selection were extracted independently by the two reviewers (Liang Chen and Guoping Cheng) and finally cross-checked. The extracted data information was as follows: (1) general characteristics: author, publication year, study design, duration, groups, country, and setting (university setting or private practice setting); (2) patient characteristics: number of patients and sites, sex, mean age of the patients, and smoking; (3) intrabony defect features: number of sites in each group, type of arch (maxilla, mandible, or both), tooth type, and walls of IBDs; (4) outcomes: probing depth (PD) reduction, clinical attachment level (CAL) gain, gingival margin level (GML) gain, IBD depth (alveolar bone crest to base of the defect) reduction, and vertical bone fill (BF) %.

2.5. Risk of Bias in Individual Studies and across Studies. The risk of bias was assessed by both reviewers (Liang Chen and Guoping Cheng) according to the Cochrane Handbook for Systematic Reviews of Interventions [18]. Seven quality criteria were verified: (1) random sequence generation

(selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective outcome reporting (reporting bias), and (7) other bias.

After the quality assessment, individual studies were categorized as being at low, high, or moderate risk of bias according to the following criteria: (1) low risk of bias: all domains were at low risk of bias; (2) high risk of bias: one or more domains were at high risk of bias; (3) moderate risk of bias: one or more domains were at unclear risk of bias and no high risk of bias. Heterogeneity across studies was characterized using Cochran-Q statistic and I^2 statistic tests.

2.6. Data Analysis. Data from the included studies were pooled to estimate the effect size, expressed as mean difference (MD) and 95% confidence interval (CI). When the homogeneity between the studies was good ($P \geq 0.10$ and $I^2 \leq 50\%$), the fixed-effects model was used for data merging. On the contrary, when $P < 0.10$ and $I^2 > 50\%$, the random-effects models were used. Data analyses were performed using the RevMan software [20].

3. Results

3.1. Study Selection. A total of 391 related articles (78 in PubMed, 227 in EMBASE, and 86 in Cochrane Central Register of Controlled Trials) were obtained, and none result was found in OpenGrey and Grey Literature Report. Then, 112 duplicate literatures were excluded, and 29 articles of the remaining 278 articles were screened by reading the titles and abstracts. After reading carefully the full text, 18 RCTs fulfilled the inclusion criteria and were selected for qualitative analysis, and 17 of them were included for meta-analysis as mean changes data could not be extracted from one study. A PRISMA flow diagram that depicts this selection process is displayed in Figure 1.

3.2. Study Characteristics. The general characteristics of the 18 studies included are displayed in Table 1. All the 18 studies were RCTs, of which 9 [13, 21–28] were split-mouth design and 9 [29–37] were parallel arm design. All the subjects were systematically healthy adults who suffered periodontitis with intrabony defects, except for one study [37] in which participants had periodontal-endodontic lesions with intrabony defects. And the type of intrabony defects is two-wall or three-wall. Further, all studies did not recruit smokers. In each study, periodontal initial therapy was performed before periodontal surgery. No study performed a minimally invasive surgery, and open flap debridement was used in all studies. The use of PRF as sole biomaterial or in combination with bone substitute grafting was used in the test group, while OFD alone or combined with bone substitute grafting was used in the control group. In terms of results assessment, there was no measurement calibration reported in two studies [13, 37]. Customized acrylic stents with grooves were used for measurement of clinical parameters using a periodontal probe, except for the two studies [13, 23] using a periodontal probe only. Intraoral standardized radiographs using the paralleling technique were used for radiological measurements except one study [24] using CBCT. Participants maintained proper oral hygiene during the follow-up period of 6-12 months in all studies. Additionally, all included studies were conducted in a university setting from India, Egypt, or Turkey.

3.3. Risk of Bias in Individual Studies. The risk of bias within selected studies is shown in Figure 2. All studies reported randomization of sequence generation with coin tossing or computer-generated tables. Concerning allocation concealment, all studies did not use methods such as opaque envelopes. However, one study [25] indicated clearly that it was randomized immediately before surgical operation, so neither the participants nor the researchers could predict the allocation results. It can be considered that the allocation concealment is sufficient allocation hiding in this study, and there is no adequate allocation hiding in the others except for this study. In terms of blinding, as it is a surgical operation, the personnel cannot be blind. All the included studies blinded the outcome assessment, one [25] of which did not blind the participants, and six studies [13, 22, 24, 27, 28, 36] did not state whether the participants were sufficiently blind. Incomplete outcome data were reported in three studies [25, 31, 35] with either imbalance in numbers or reasons for missing data across intervention groups. No selective reporting was found. Other bias was found in the studies of Rosamma et al. [13] and Ustaoğlu et al. [37] for no measurement calibration. According to the Cochrane Collaboration's tool for assessing the risk of bias, thirteen [21–24, 26–30, 32–34, 36] of the selected studies presented a moderate risk of bias, whereas five studies [13, 25, 31, 35, 37] exhibited a high risk of bias.

3.4. Synthesis of Results. Among the included 18 studies, 14 compared the effects of PRF with that of OFD alone. In terms of soft tissue parameter, one study [22] showed that there was no statistically significant difference in PD reduction between the control group and the experimental group, and no significant difference in CAL improvement among the three studies. Except that, remaining 13 studies showed that the use of PRF significantly improved CAL and reduced PD compared with the control group. Additionally, only 10 of the 14 studies reported the GML changes, and all studies showed that the GML changes of the PRF group were better than that of the control group except for one study [22]. In terms of hard tissue parameter, IBD depth reduction, and BF%, 12 studies [13, 22, 23, 29–37] that have reported the two data showed that the effect of the use of PRF was better than OFD only.

Four of the 18 studies compared the effects of BG combined with PRF and bone grafting without PRF. Agarwal et al. [21] reported when 12 months after operation, the BG combined with PRF group exhibited statistically significantly greater changes compared with the BG group in PD reduction, CAL gain, GML gain, IBD depth reduction, and bone fill%. Bodhare et al. [24] reported when 6 months after operation, BG combined with PRF is found to be significantly greater in the gain in CAL and IBD depth reduction and more effective in PD reduction although not significant, as

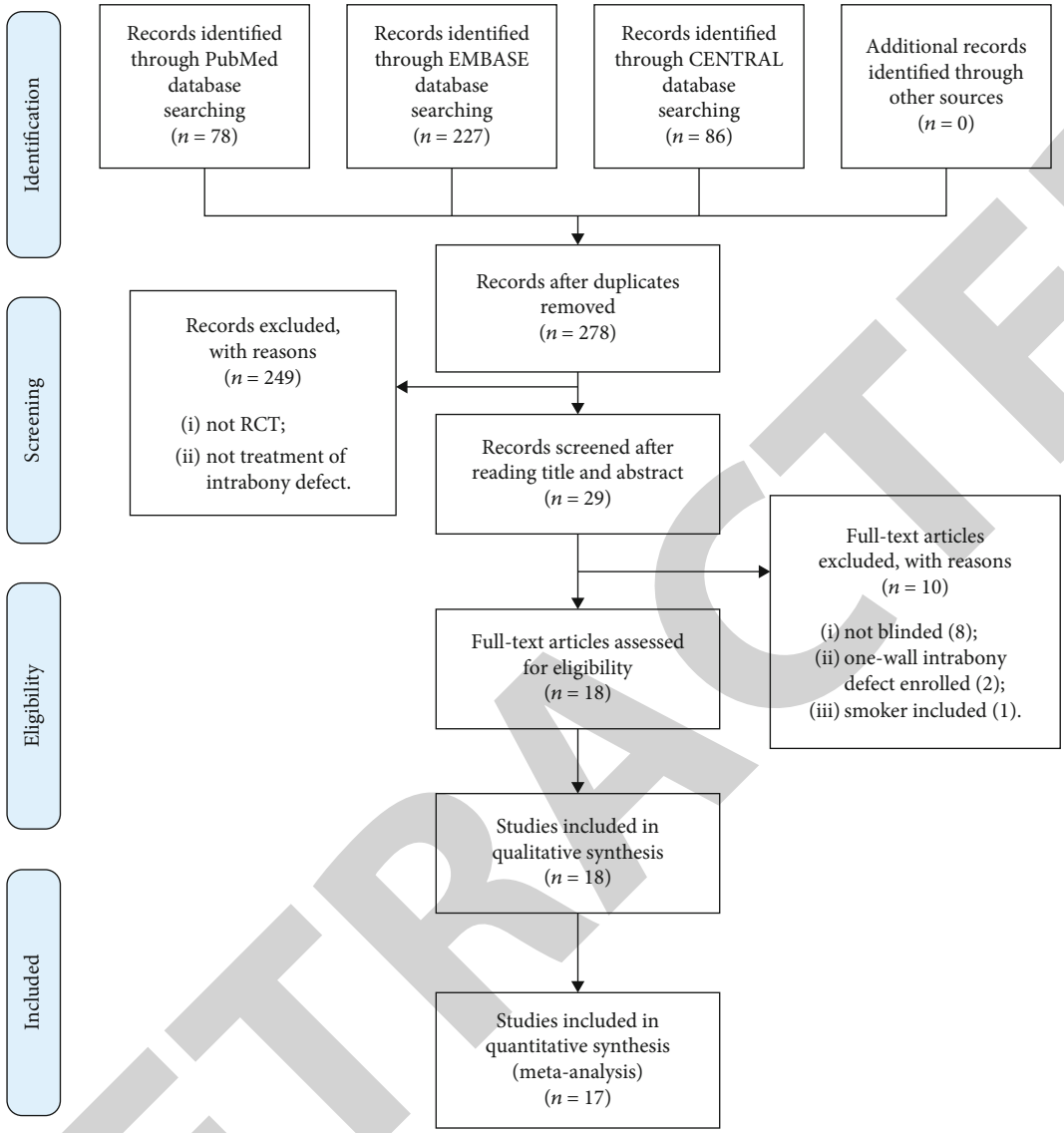


Figure 1: PRISMA flowchart for study selection.

compared to treatment with BG alone in periodontal intrabony defects. No significant clinical differences between BG group and BG combined with PRF group during six months or nine months were reported in the research by Gamal et al. [25]. In the six-month study of Sezgin et al. [27], gain in CAL was significantly greater in the test group than in the control group, whereas no intergroup differences were observed in PD reduction, GML changes, and IBD depth reduction.

Moreover, two articles have assessed the effect of PRF for wound healing. In the research of Patel et al. [26], at 7 days after surgery, all 13 sites in the test group (OFD+PRF) showed perfect healing (i.e., score 1 of wound healing index [100%]), and in the control group, only five sites showed perfect healing (i.e., score 1 of wound healing index [38%]). The difference between test and control groups at 7 days was significant ($P = 0.003$). At the end of 14 days, all sites in the test group and nine sites in the control group showed perfect healing with a score 1 of WHI (70%) with no statically significant difference ($P = 0.21$). In the study of Rosamma et al. [13], after 7 days, visual analog scale was used to assess the patient experience and the initial soft tissue healing with the two treatment modalities. The result showed that, compared to OFD alone, the use of PRF significantly reduced the postoperative pain and discomfort after periodontal surgery and significantly accelerated periodontal wound healing.

As mean change data could not be extracted from the study of Gamal et al. [25], a total of 17 RCTs were quantitatively analyzed. The primary outcomes were IBD depth reduction and bone fill%, and the secondary outcomes were the changes in PD, CAL, and GML. PRF as the only implant substances or combined with bone graft substitute, other bone stimulating substances such as ALN, ATV, MF, and RSV were not included in this analysis. In this meta-analysis, two comparisons are set up as follows.

3.4.1. OFD+PRF vs. OFD Alone. In the primary outcomes (Figure 3), the heterogeneity was high in IBD depth reduction ($I^2 = 93\%$) and BF% ($I^2 = 92\%$), so a random-effects

Table 1: General characteristics of the included studies.

Author (year)	Study design, blinded (duration)	Population			Intervention (number of surgical sites)	
		No. of participant baseline (end)	Age (mean/range)	Gender	Control	Test
Agarwal et al. (2016) [21]	Split-mouth, double blinded (12 months)	32 (30)	52 ± 7 (?)	14F/18M	OFD+DFDBA +saline (30)	OFD+DFDBA+PRF (30)
Ajwani et al. (2015) [22]	Split-mouth, single blinded (9 months)	20 (20)	30.5 (?)	10F/10M	OFD (20)	OFD+PRF (20)
Bajaj et al. (2017) [23]	Split-mouth, double blinded (9 months)	19 (17)	29.7 (20-30)	9F/10M	OFD (27)	OFD+PRF (27)
Bodhare et al. (2019) [24]	Split-mouth, single blinded (6 months)	20 (20)	35.9 (27-45)	9F/11M	OFD +bioactive glass (20)	OFD+bioactive glass+PRF (20)
Gamal et al. (2016) [25]	Split-mouth, single blinded (9 months)	30 (29)	39.6 ± 3.9 (28-51)	9F/21M	OFD +xenograft (9)	T1: OFD+xenograft+PRF (10); T2: OFD+xenograft+PRGF (10)
Kanoriya et al. (2016) [29]	Parallel, triple blinded (9 months)	108 (90)	39 (30-50)	55F/53M	OFD (30)	T1: OFD+PRF (30); T2: OFD+PRF +1% ALN (30)
Martande et al. (2016) [30]	Parallel, double blinded (9 months)	96 (90)	37.6 (?)	48F/48M	OFD (30)	T1: OFD+PRF (30); T2: OFD+PRF +1.2% ATV (30)
Patel et al. (2017) [26]	Split-mouth, double blinded (12 months)	13 (13)	44 ± 9 (?)	9F/4M	OFD (13)	OFD+PRF (13)
Pradeep et al. (2012) [34]	Parallel, double blinded (9 months)	54 (50)	36.8 (?)	27F/27M	OFD (30)	T1: OFD+PRF (30); T2: OFD+PRP (30)
Pradeep et al. (2015) [33]	Parallel, triple blinded (9 months)	126 (120)	41 (30-50)	60F/60M	OFD (30)	T1: PRF (30); T2: 1% MF (30); T3: OFD+PRF+1% MF (30)
Pradeep et al. (2016) [32]	Parallel, triple blinded (9 months)	90 (90)	35 (25-45)	45F/45M	OFD (30)	T1: OFD+PRF (30); T2: OFD+PRF +1.2% RSV (30)
Pradeep et al. (2017) [31]	Parallel, double blinded (9 months)	62 (57)	39.7 (?)	28F/34M	OFD (29)	T1: OFD+PRF (29); T2: OFD+PRF +HA (32)
Rosamma et al. (2012) [13]	Split-mouth, single blinded (12 months)	15 (15)	29.47 ± 7.65 (17-44)	9F/6M	OFD (15)	OFD+PRF (15)
Sezgin et al. (2017) [27]	Split-mouth, single blinded (6 months)	21 (15)	? (38-61)	7F/8M	OFD+ABBM (15)	ABBM+PRF (15)
Sharma et al. (2011) [35]	Parallel, double blinded (9 months)	42 (35)	35.34 ± 6.45 (30-50)	18F/24M	OFD (28)	OFD+PRF (28)
Thorat et al. (2011) [36]	Parallel, single blinded (9 months)	40 (32)	31.12 ± 2.06 (25-45)	18F/22M	OFD (16)	OFD+PRF (16)
Thorat et al. (2017) [28]	Split-mouth, single blinded (12 months)	18 (15)	25 ± 1.5 (?)	10F/8M	OFD (15)	OFD+PRF (15)
Ustaoğlu et al. (2020) [37]	Parallel, double blinded (9 months)	45 (45)	40 ± 8.37 (26-59)	22F/23M	OFD (15)	T1: OFD+PRF (15); T2: OFD +GTR (15)

OFD: open flap debridement; PRF: platelet-rich fibrin; DFDBA: demineralized freeze-dried bone allograft; PRGF: platelets rich in growth factors; ALN: alendronate; ATV: atorvastatin; PRP: platelet-rich plasma; MF: metformin; RSV: rosuvastatin; HA: hydroxyapatite; ABBM: anorganic bovine bone mineral; GTR: guided tissue regeneration.

model was used. A statistically significantly greater in IBD depth reduction (mean difference: 1.81 mm; 95% CI: 1.53 to 2.08) with additional PRF in OFD was found. Similarly, a statistically significant beneficial effect of BF% (mean difference: 39.56%; 95% CI: 36.73 to 42.38) was found in the OFD+PRF group.

In the secondary outcomes (Figure 4), the meta-analysis showed that the clinical parameters of OFD+PRF group were better than those of OFD alone group. There are statistically significant differences in PD reduction (mean difference: 1.18 mm; 95% CI: 0.94 to 1.42), CAL gain (mean difference: 1.25 mm; 95% CI: 0.93 to 1.57), and GML gain (mean difference: 0.42 mm; 95% CI: 0.32 to 0.53), with high heterogeneity across the studies (I^2 = 87%, 90% and 92%, respectively).

3.4.2. B +PRF vs. BG Alone. There were only three studies [21, 24, 27] in this comparison (Figure 5). No evidence of heterogeneity was found (I^2 = 0.0%) across the studies in IBD depth reduction, PD reduction, and CAL gain, so a fixed-effects model was applied. Random-effects model was used in GML gain with a high heterogeneity (I^2 = 52%). Only one article reported BF% data, so meta-analysis was only conducted in IBD depth of primary outcomes. The results show that a greater IBD depth reduction for the BG+PRF group

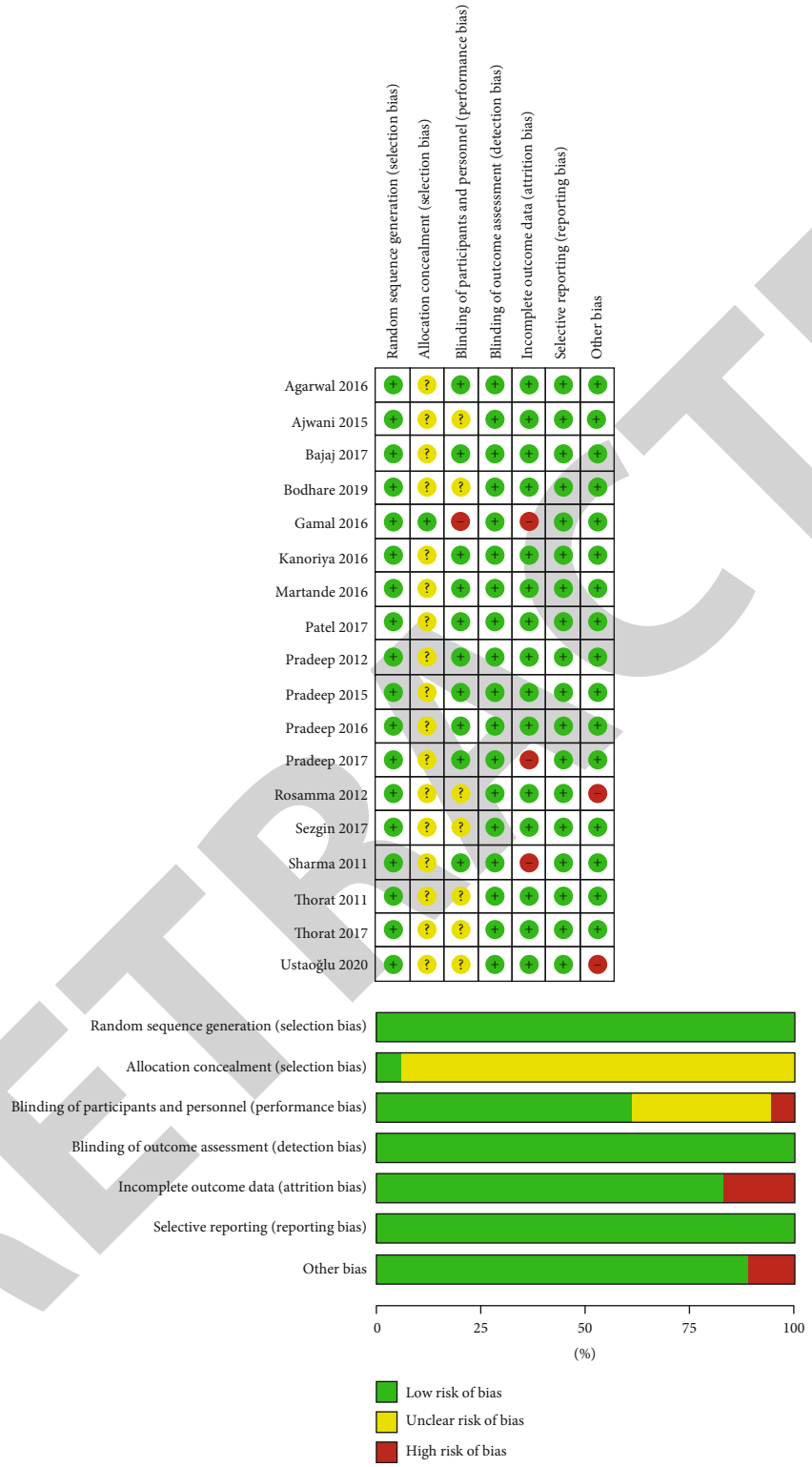


Figure 2: Risk of bias summary of the included studies.

was found than BG alone group, and the difference was statistically significant (mean difference: 0.92 mm; 95% CI: 0.66 to 1.18).

As for the secondary outcomes, compared with the BG alone group, the BG+PRF group showed more statistically significant advantages in PD reduction (mean difference: 0.52 mm,;95% CI: 0.21 to 0.82), CAL gain (mean difference: 1.09 mm; 95% CI: 0.77 to 1.41), and GML gain (mean difference: 0.69 mm; 95% CI: 0.31 to 1.06).

3.5. Risk of Bias across Studies. The publication bias was evaluated by the visual symmetry of the funnel plot (Figure 6).

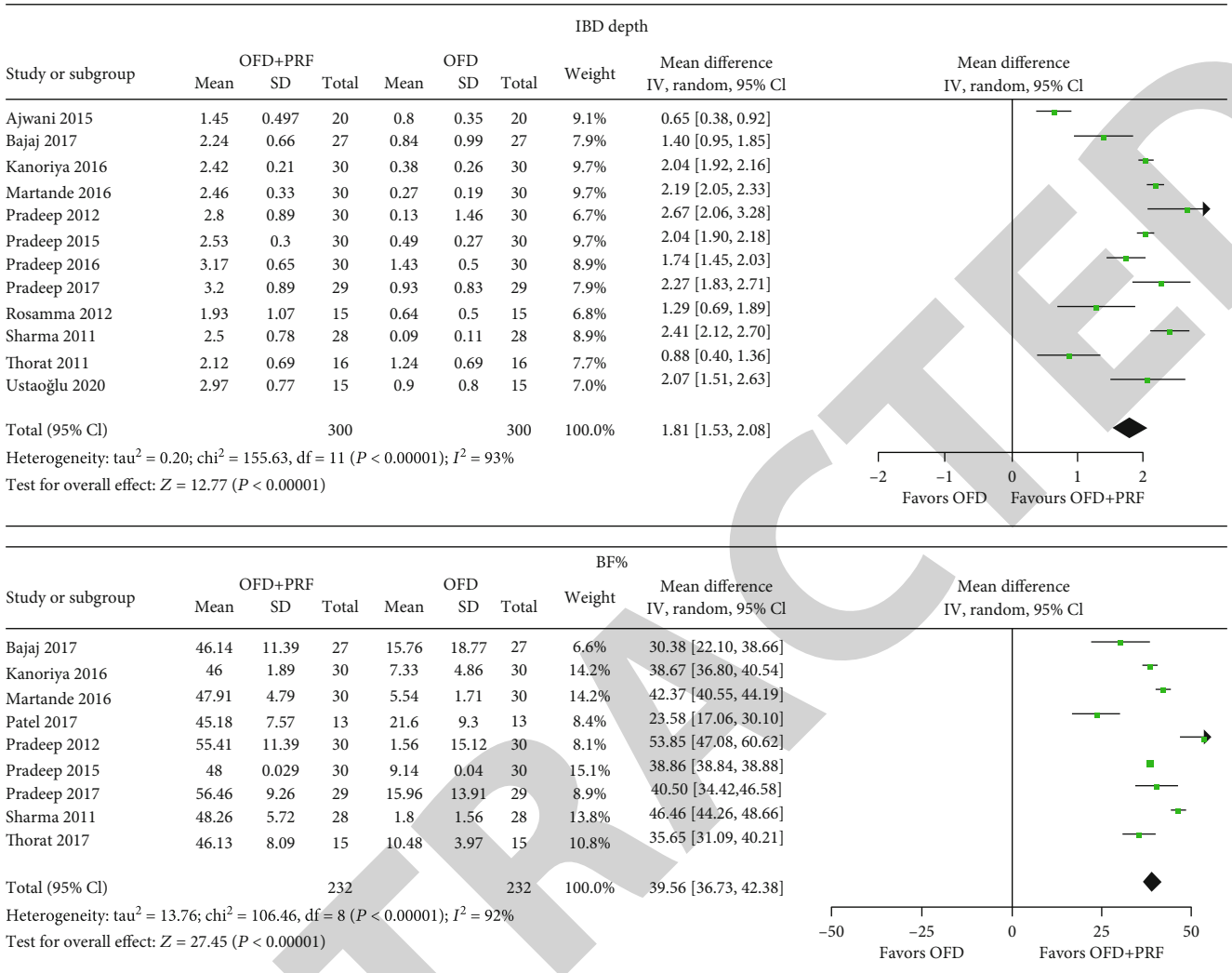


Figure 3: Forest plots for IBD depth reduction and BF% in the group OFD+PRF vs. OFD alone.

The studies with large sample size and high accuracy were distributed at the top of the funnel plot and concentrated in the vertical line, while other studies were evenly distributed on both sides. The shape of funnel plot was approximately symmetrical, indicating no obvious publication bias.

4. Discussion

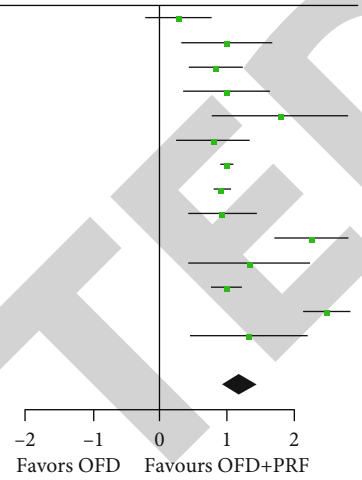
4.1. Summary of Evidence. This systematic review and meta-analysis focused on evaluating the effectiveness of surgical treatment of periodontal bone defects with PRF, including clinical and radiological parameters. Clinical scenarios involving implants were beyond the scope of this review. The results of this meta-analysis revealed that OFD combined with PRF is more effective than OFD procedures alone, radiographically in IBD depth reduction by 1.81 mm (95%CI = 1.53, 2.08) and vertical bone fill% by 39.56% (95%CI = 36.73, 42.38), as well as clinically in PD reduction by 0.52 mm (95%CI = 0.21, 0.82), CAL gain by 1.25 mm (95%CI = 0.93, 1.57), and GML gain by 0.42 mm (95%CI = 0.32, 0.53). In addition, BG combined with PRF found to be more effective than BG procedure alone radiographically in IBD depth reduction by 0.92 mm (95%CI = 0.66, 1.18), as well as clinically in PD reduction by 0.52 mm (95%CI = 0.21, 0.82), CAL gain by 1.09 mm (95%CI = 0.77, 1.41), and GML gain by 0.69 mm (95%CI = 0.31, 1.06). Furthermore, the qualitative analysis showed that, after 7 days, better wound healing occurred with the use of PRF.

Only one meta-analysis has been reported to evaluate the additional effect of PRF in the treatment of intrabony defects before. The meta-analysis of Castro et al. [17] only compared OFD+PRF to OFD alone, including a total of 6 studies until 2016. Comparing to OFD alone, OFD +PRF showed greater improvement in IBD depth reduction by 1.65 mm (95%CI = 0.99, 2.31), PD reduction by 1.1 mm (95%CI : 0.62, 1.58), and CAL gain by 1.24 mm (95%CI : 0.59, 1.89). It was indicated that OFD+PRF is more effective than OFD alone, which is in accordance with our results. A meta-analysis [38] showed that OFD +1% alendronate+PRF was even better than OFD+PRF. However, GML and BF% changes were not assessed in the study of Castro et al. Interestingly, our study revealed that PRF has certain benefits for GML gain in both OFD and

PD

Study or subgroup	OFD+PRF Mean	SD	Total	OFD Mean	SD	Total	Weight	Mean difference IV, random, 95% Cl
Ajwani 2015	1.9	0.738	20	1.6	0.843	20	7.4%	0.30 [−0.19, 0.79]
Bajaj 2017	3.14	1.26	27	2.14	1.26	27	5.8%	1.00 [0.33, 1.67]
Kanoriya 2016	3.7	0.91	30	2.86	0.68	30	8.2%	0.84 [0.43, 1.25]
Martande 2016	3.76	1.12	30	2.76	1.43	30	6.0%	1.00 [0.35, 1.65]
Patel 2017	4.2	1.69	13	2.4	0.84	13	3.6%	1.80 [0.77, 2.83]
Pradeep 2012	3.77	1.19	30	2.97	0.93	30	7.0%	0.80 [0.26, 1.34]
Pradeep 2015	4	0.18	30	3	0.18	30	10.6%	1.00 [0.91, 1.09]
Pradeep 2016	4.03	0.18	30	3.1	0.3	30	105%	0.93 [0.80, 1.06]
Pradeep 2017	3.9	1.09	29	2.97	0.93	29	7.1%	0.93 [0.41, 1.45]
Rosamma 2012	4.67	0.9	15	2.4	0.63	15	6.8%	2.27 [1.71, 2.83]
Sharma 2011	4.55	1.87	28	3.21	1.64	28	4.1%	1.34 [0.42, 2.26]
Thorat 2011	4.56	0.37	16	3.56	0.27	16	9.8%	1.00 [0.78, 1.22]
Thorat 2017	4	0.63	15	1.5	0.34	15	8.6%	2.50 [2.14, 2.86]
Ustaoğlu 2020	4.69	1.34	15	3.36	1.12	15	4.4%	1.33 [0.45, 2.21]
Total (95% Cl)			328			328	100.0%	1.18 [0.94, 1.42]

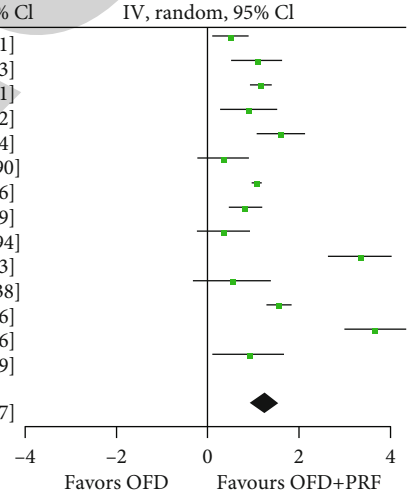
Heterogeneity: tau^2 = 0.14; chi^2 = 98.51, df = 13 (P < 0.00001); I^2 = 87%
Test for overall effect: Z = 9.68 (P < 0.00001)



CAL

Study or subgroup	OFD+PRF Mean	SD	Total	OFD Mean	SD	Total	Weight	Mean difference IV, random, 95% Cl
Ajwani 2015	1.8	0.632	20	1.3	0.675	20	7.4%	0.50 [0.09, 0.91]
Bajaj 2017	2.66	1.07	27	1.59	1.01	27	5.8%	1.07 [0.51, 1.63]
Kanoriya 2016	4.2	0.66	30	3.03	0.18	30	8.5%	1.17 [0.93, 1.41]
Martande 2016	3.4	1.13	30	2.5	1.33	30	6.7%	0.90 [0.28, 1.52]
Patel 2017	3.7	0.37	13	2.1	0.74	13	7.1%	1.60 [1.06, 2.14]
Pradeep 2012	3.17	1.29	30	2.83	0.91	30	7.0%	0.34 [−0.22, 0.90]
Pradeep 2015	4.03	0.18	30	2.96	0.18	30	8.9%	1.07 [0.98, 1.16]
Pradeep 2016	3.3	0.65	30	2.47	0.77	30	8.0%	0.83 [0.47, 1.19]
Pradeep 2017	3.03	1.16	29	2.67	1.09	29	6.9%	0.36 [−0.22, 0.94]
Rosamma 2012	4.73	0.88	15	1.4	1.06	15	6.3%	3.33 [2.63, 4.03]
Sharma 2011	3.31	1.76	28	2.77	1.44	28	5.5%	0.54 [−0.30, 1.38]
Thorat 2011	3.69	0.44	16	2.13	0.43	16	8.3%	1.56 [1.26, 1.86]
Thorat 2017	4	0.63	15	0.33	1.21	15	6.3%	3.67 [2.98, 4.36]
Ustaoğlu 2020	4.19	1.05	15	3.3	1.17	15	5.8%	0.89 [0.09, 1.69]
Total (95% Cl)			328			328	100.0%	1.25 [0.93, 1.57]

Heterogeneity: tau^2 = 0.30; chi^2 = 131.54, df = 13 (P < 0.00001); I^2 = 90%
Test for overall effect: Z = 7.62 (P < 0.00001)



GML

Study or subgroup	OFD+PRF Mean	SD	Total	OFD Mean	SD	Total	Weight	Mean difference IV, random, 95% Cl
Ajwani 2015	−0.3	0.483	20	−0.3	0.675	20	5.6%	0.00 [−0.36, 0.36]
Kanoriya 2016	0.24	0.056	30	−0.06	0.07	30	18.6%	0.30 [0.27, 0.33]
Martande 2016	0.22	0.1	30	0.06	0.02	30	18.5%	0.16 [0.12, 0.20]
Pradeep 2012	0.2	0.71	30	−0.27	0.58	30	6.4%	0.47 [0.14, 0.80]
Pradeep 2015	0.27	0.07	30	−0.06	0.04	30	18.7%	0.33 [0.30, 0.36]
Pradeep 2017	0.47	0.73	29	−0.17	0.53	29	6.4%	0.64 [0.31, 0.97]
Rosamma 2012	0.07	0.26	15	−1.13	0.74	15	4.9%	1.20 [0.80, 1.60]
Sharma 2011	0.1	0.08	28	−0.67	0.46	28	12.3%	0.77 [0.60, 0.94]
Thorat 2011	−0.31	0.95	16	−1.31	1.01	16	2.0%	1.00 [0.32, 1.68]
Thorat 2017	0.32	0.5	15	−0.16	0.4	15	6.5%	0.48 [0.16, 0.80]
Total (95% Cl)			243			243	100.0%	0.42 [0.32, 0.53]

Heterogeneity: tau^2 = 0.01; chi^2 = 119.59, df = 9 (P < 0.00001); I^2 = 92%
Test for overall effect: Z = 8.13 (P < 0.00001)

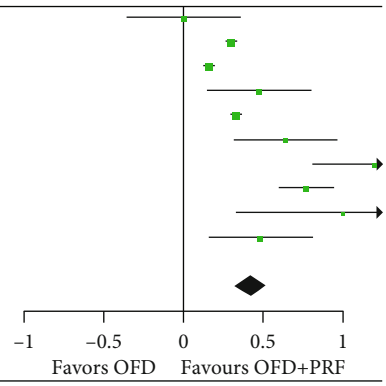


Figure 4: Forest plots for PD reduction, CAL gain, and GML gain in the group OFD+PRF vs. OFD alone.

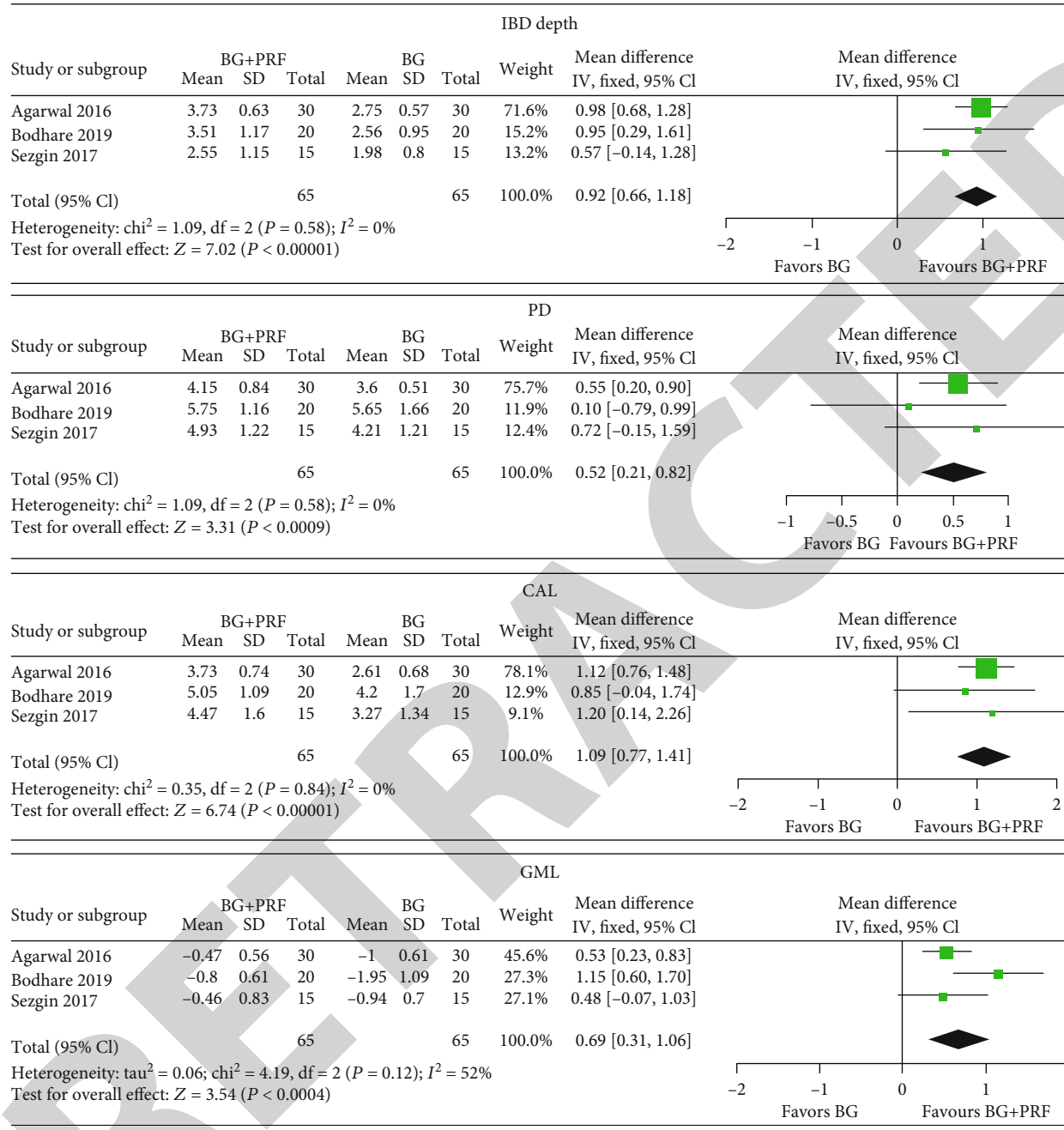


Figure 5: Forest plots for IBD depth reduction, PD reduction, CAL gain, and GML gain in the group B +PRF vs. BG alone.

BG surgery. Besides, we found that the combination of bone grafting with PRF will further generate statistically better changes of soft and hard tissue than BG alone.

The use of PRF is also beneficial to other oral tissue regeneration. Based on recent systematic reviews and meta-analysis, OFD+PRF demonstrated better results than OFD alone in grade II furcation treatment [39]. In terms of gingival recession, Moraschini and Barboza Edos [40] have reported in 2016 that the use of PRF membranes did not improve the root coverage, keratinized mucosa width, or CAL of Miller classes I and II gingival recessions compared with the other treatment modalities. On the contrary, the meta-analysis of Li et al. [41] and Panda et al. [42] suggested that PRF when used in addition to coronally advanced flap (CAF) showed favorable results for the treatment of gingival recession defects. Moreover, He et al. [43] reported that local application of PRF after lower third molar extraction was a valid method for relieving pain and 3-day postoperative swelling and reducing the incidence of alveolar osteitis.

4.2. Limitations. In order to adhere to high methodological standards and to maximize the clinical applicability of the results reported in this review, stringent inclusion criteria were adopted. In terms of study design, split-mouth design and parallel design were included in this review, because recent evidence showed that both of them are equally

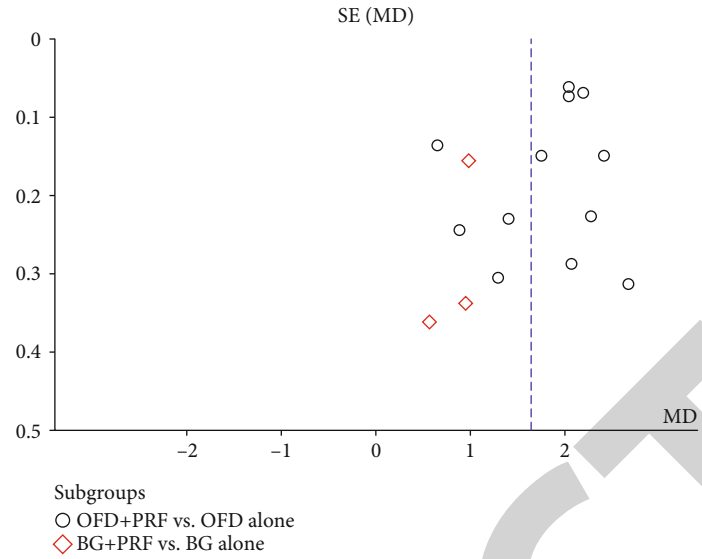


Figure 6: Funnel plot analysis of the studies. SE: standard error; MD: mean difference.

effective [44]. In regard of participants, studies including smokers are excluded, because smoking is a clear risk factor of periodontal diseases [45] and significantly affects the outcome of periodontal regeneration surgery [4, 46]. The type of intrabony defects was limited in only two or three walls, because the number of remaining bony walls was found to be correlated positively with regeneration potential in grafting procedures [47], and one-wall defect is a risk factor for failure (odds ratio [OR] ≥ 10.4) [48]. In the blind method, we require that outcome assessments must be blinded. On the one hand, due to surgery procedures, operation physicians could not be blinded; on the other hand, the final measurement is done manually regardless of clinical or radiographical measurement, and the results will be greatly affected by the accessors. Thus, blinding for the outcome assessment was of great importance, and studies without blind method were excluded. Although screening programs were stringent, there was still no risk of low bias in this review, and at least one ambiguous bias risk emerged in all studies, mainly in the domain of allocation concealment and blinding of participants.

In the quantitative analysis of the effect of PRF on periodontal surgery, the heterogeneity among the studies was as high as the meta-analysis of Castro et al. [17], Tarallo et al. [39], Panda et al. [42], Li et al. [38], and Li et al. [41]. Heterogeneity may come from different clinical research methodology and implementation processes. (1) Different preparation and usage methods of PRF: the preparation of PRF entirely depends on the speed of blood collection and immediate centrifugation [49]. In the ten [13, 22, 24, 26, 29, 31–35] of 17 studies, blood was collected in sterile glass test tubes and immediately centrifuged at 3000 rpm for 10 min, while three [21, 28, 36] at 400 g for 12 min, one [27] at 2700 rpm for 12 min, one [30] at 3000 rpm for 12 to 14 min, one [37] in titanium tubes at 2800 rpm for 12 min, and one study [23] are unknown. In terms of usage, PRF was filled into the intrabony defects and used as a membrane to cover the defect in 15 studies, while only filled in the other two studies [13, 26]. (2) Great difference of teeth sites: six studies [23, 29–31, 34, 35] reported maxillary/mandibular single-rooted teeth or multirooted teeth, two [24, 33] reported maxillary/-mandibular molar teeth, two [32, 36] only mandibular molar teeth, one [28] reported molar teeth without maxillary/mandibular types, one [37] only single-rooted teeth, one [27] reported maxillary/mandibular anterior teeth or premolars or molars, and four [13, 21, 22, 26] not mentioned. Most of the studies did not contain teeth with furcation involvement, but Bodhare et al. [24] reported intrabony defects with furcation involvement and three studies [13, 26, 32] not mentioned. (3) Baseline comparison between groups: there should be no difference in the baseline between groups, but seven studies [22, 24, 28, 31, 34, 35, 37] did not compare baseline differences between groups, although they have listed baseline data. (4) Blinding of participants: six studies [13, 22, 24, 27, 28, 36] did not state if participants were blinded, and these results might be affected duo to the Hawthorne effect.

In the comparison of OFD+PRF and OFD alone, although the heterogeneity was high, forest plot of IBD depth reduction and BF% revealed that the studies are located on the right side of the vertical line, which indicated that all studies have affirmed the additional benefits of PRF, but the size of the benefits was not completely accurate because of the high heterogeneity. Therefore, there was ample evidence that OFD+PRF is superior to OFD alone. On the other hand, in the comparison of BG+PRF and BG alone, PRF also showed benefits in primary outcomes, but the benefit was smaller than that of PRF in the use of OFD. Although there was no heterogeneity, the evidence is not completely reliable due to the small number of studies.

The ease of preparation and cost-effectiveness of PRF offers a huge advantage, but the mechanical properties of PRF are poor. A study [50] to evaluate the mechanical properties of PRF found that PRF obviously lacked rigidity and

degraded quickly, and the degradation rate after one week was about 36% of the initial mass. Because the epithelial barrier is needed to guide periodontal regeneration for at least 4 to 6 weeks [51], and the bone defects need longer maintenance time, so PRF cannot be used as a simple filling material or barrier membrane. PRF is more suitable to be used as an addition of periodontal regeneration surgery. At present, OFD is no longer regarded as periodontal regeneration surgery, and different combinations of strategies are gradually used for periodontal regeneration. Periodontal regeneration with many different regenerative materials, including barrier membranes, grafts, active biological compounds, and combinations of those, demonstrated significant clinical improvements in intrabony defects, far beyond those achieved with debridement only [4].

In summary, based on the evidence and limitations in this review, it is suggested that more RCT studies are still required to explore whether PRF can enhance the regeneration effect of GTR or BG or combination of other modalities in the periodontal regenerative surgery. In the RCTs, it is recommended to carry out detailed design as follows to reduce bias as much as possible: adopt standardized PRF preparation process and surgical procedures, strictly recruit patients, use correct method of randomization and adequate allocation concealment, blinding of patients and outcome assessors, calibrate measurement results, and strengthen patient plaque control after operation.

5. Conclusion

In conclusion, current systematic review and meta-analysis has revealed that the use of PRF was significantly effective in the treatment of periodontal intrabony defects. The major findings suggest the following points:

(1) In all the included studies, open flap debridement (OFD) combined with PRF was significantly better than OFD alone in intrabony defect depth reduction and bone fill % changes, but the size of the benefits was uncertain due to the high heterogeneity of the studies. In terms of PD reduction, CAL gain, and gingival margin level gain, the additional use of PRF seemed to be more effective compared to OFD alone

(2) The combination of bone grafting (BG) and PRF will further increase the therapeutic effect of BG in intrabony defect depth reduction, PD reduction, CAL gain, and gingival margin level gain. The benefit of BG+PRF seemed to be less than OFD+PRF. But the small number of studies suggests a low degree of confidence and certainty in treatment effects

(3) PRF seems to promote early wound healing in 1 week after periodontal surgery

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgments

This study was supported by the National Natural Foundation of China (No. 82071121).

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Hindawi
BioMed Research International
Volume 2021, Article ID 6660052, 7 pages
https://doi.org/10.1155/2021/6660052

Research Article

Effects of Implant Surface Debridement and Systemic Antibiotics on the Clinical and Microbiological Variables of Periimplantitis

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Received 9 December 2020; Revised 9 January 2021; Accepted 16 January 2021; Published 23 January 2021

Academic Editor: Marwa Madi

Objective. To investigate the role of implant surface debridement alone and in conjunction with systemic antibiotics on the clinical and microbiological variables of periimplantitis. *Materials and Methods*. Data of forty-six patients with at least one dental implant having bleeding-on-probing (BoP), probing pocket depth (PPD) of more than 5 mm, and radiographic bone loss of more than 3 mm were retrieved from clinical records. Data was recorded for dental implant with the deepest PPD, BoP, and bone loss from each patient. "Group-A" received implant surface debridement alone, while "group-B" additionally received systemic antibiotics. Clinical and microbiological data of patients were compared before and after the treatment. *Results*. At the implant level, a significant reduction of PPD, mucosal recession (MR), and BoP was achieved for all patients. Group B achieved significant improvement in MR and BoP compared to group A at implant level. PPD, MR, and plaque scores showed improvement at implant site level. At 3 months recall visit, 44% of group A and 52% of group B implants required surgical treatment. The presence and proportions of studied bacteria of both groups did not differ significantly at the recall visit when compared to the initial visit. However, P. intermedia and P. micros showed a significant reduction in group A at the recall visit. *Conclusions*. Implant surface debridement improved the clinical parameters of periimplantitis. In addition, adjunctive use of systemic antibiotics increased mucosal recession and improved bleeding on probing in periimplantitis.

1. Introduction

Periimplantitis is a chronic, inflammatory disease characterized by gradual breakdown of the soft and hard tissues around a dental implant [1, 2]. Without proper management, periimplantitis can cause mobility and eventual loss of the affected dental implant. Periimplantitis may affect 6.6%-34% of all the dental implants over a period of 14 years [3, 4].

The etiology of periimplantitis is multifactorial in nature; however, bacteria play a vital role in disease initiation and progression [5]. Significant differences have been reported in the microbiota associated with diseased implants compared to healthy dental implants [6, 7]. In contrast to healthy implants which mainly have a biofilm composed of Gram-positive cocci [6, 8], the biofilm associated with periimplantitis is characterized by the predominance of anaerobic bacteria. Prevotella intermedia/nigrescens, Porphyromonas gingivalis, and Aggregatibacter actinomycetemcomitans are some of the most common bacteria associated with periimplantitis [9, 10]. Multiple similarities could be drawn between

periimplantitis and periodontitis including similar bacterial species associated with both diseases [9]. However, microbial species unique to periimplantitis have also been reported in the literature [6, 11–16].

Studies on the treatment outcome of periimplantitis are scarce, and evidence of a single effective treatment modality for periimplantitis is inconclusive [17]. Antibiotics along with implant surface cleaning/debridement have been reported to improve the clinical and microbiological parameters in periimplantitis [18]. The effects of adjunctive antibiotic treatment remained significant even after one-year posttreatment when compared to baseline. This study did not have a control group which makes the utility of adjunctive antibiotics use uncertain in the treatment of periimplantitis. As far as we know, the role of systemic antibiotics in addition to implant surface debridement has not been studied before. Therefore, we aimed to investigate the role of implant surface debridement alone and in conjunction with systemic antibiotics on the clinical and bacteriological variables of periimplantitis.

2. Materials and Methods

In this retrospective study, the patient database of the Ace Dental and Implant Center (a privately-owned clinic in Peshawar, Pakistan) was searched for periimplantitis patients based on the following criteria as suggested by Renvert et al. [19].

(1) Bleeding/suppuration on probing (BoP)

(2) Probing pocket depths (PPD) of more than 5 mm

(3) Radiographic bone loss of more than 3 mm (periapical radiographs were used to measure bone loss from the first implant thread to crestal bone)

The inclusion criteria were as follows:

(1) Patients with minimum one titanium dental implant diagnosed with periimplantitis

(2) Dental implants must be in use for minimum period of 1 year or more and

(3) Patients older than 18 years

Patients were excluded from the study if:

(1) Systemic antibiotics were used in the 3 months before treatment or

(2) Nonsteroidal anti-inflammatory drugs were used in the past four weeks

(3) Patients with diabetes and other chronic systemic disease were also excluded

Sample size was calculated using G∗ Power software version 3.1.9.4 at an effect size of 0.39, alpha = 0.05, and power of the study = 0.80. A total of 46 patient records were obtained from the database.

2.1. Data Collection. The following data was obtained at the initial visit (before starting the treatment): (1) age (in years), (2) sex, (3) presence of chronic systemic disease [3, 20], (4) dental status (edentulous, dentate, and number of remaining teeth), (6) present or past smoking history, and (7) history of periodontitis. Moreover, implants having the greatest probing measurements were selected as target implants, and while deepest pockets were selected as target implant sites.

The following clinical measurements were obtained for all teeth/implants present at the initial and at the recall visits (3 months after the initial visit): (1) plaque scores (measured by the modified plaque index proposed by Van der Weijden et al. [21]), (2) bleeding/suppuration on probing, (3) PPD in mm, (4) clinical attachment level (CAL), and (6) mucosal recession was calculated by subtracting PPD from CAL (MR = CAL − PPD). A single operator made all the measurements around the target dental implant using a Marquis CP-12 probe (Hu-Friedy, Chicago, Illinois, USA).

Data on the use and type of systemic antibiotics during periimplantitis treatment was retrieved from the patient database. Data of patients who received a standard antibiotic regimen (amoxicillin 500 mg three times a day plus metronidazole 400 mg twice a day for 5 days) was selected for the study. Submucosal plaque samples had been previously obtained by using sterile paper points from the deepest implant sites at the initial visit as well as 3 months recall visit. Microbiological data was obtained from the laboratory records.

Data was made fully anonymous by assigning a serial number to each record, and ethical approval (EC Ref. No. RCD-19-04-018) was obtained from the institutional ethical committee of Rehman College of Dentistry, Peshawar.

2.2. Initial Visit. Data of all periimplantitis patients referred to the Ace Dental and Implant Center, University Town Peshawar, for treatment of periimplant infection was evaluated. Past medical and dental histories were recorded at the initial visit. Patients were divided into two groups, group A ($n = 25$) who had received implant surface debridement along with a standard regimen of antibiotics (amoxicillin 500 mg three times a day plus metronidazole 400 mg twice a day for 5 days), while group B included patients who only received implant surface debridement without the use of systemic antibiotics.

2.3. Microbiological Analysis. Sterile paperpoints were used to obtain submucosal plaque from the periimplant pocket with the greatest PPD measurement [22]. Subsequently, paperpoints were transferred to 5 ml sterile tubes with standard reduced transport fluid (a ditheithreitol poised mineral salt solution) [23]. Within 2 hours of collection, all samples were carried to the Veterinary Research Institute (VRI), Peshawar, for microbiological culture.

Selected bacterial species were anaerobically cultured according to the standard methods [24] Serial dilutions of the previously obtained submucosal plaque samples were cultured on 5% horse blood agar plates (Oxoid no.2, Basingstoke, UK) supplemented with hemin (5 mg/l) and menadione (1 mg/l). Trypticase soy-serum-bacitracin-vancomycin

(TSBV) plates were used as culture medium for the A. actinomycetemcomitans growth. Incubation of blood agar culture plates was carried out in an anaerobic environment (80%N2, 10%H2, and at 10%CO2) at a temperature of 37°C. TSBV plates were incubated and were carried out at 5%CO2 for up to two weeks. Bacterial colonies were counted three times on agar plates using a magnifying glass, and the average was taken to calculate colony forming units per ml (CFU/ml). The presence and relative proportions of target bacteria were noted. Colony morphology, Gram-staining & microscopy, anaerobic growth, fermentation of glucose, and indole were used to identify bacterial species.

2.4. Implant Surface Debridement. Before commencement of the nonsurgical treatment, patients were provided a commercially available 0.12% chlorhexidine mouthwash to rinse for one minute. Local anesthesia was administered to the affected implant (medicaine 2%, 1 : 100000 epinephrine), and debridement of implant surface was carried out with an ultrasonic scaler having specialized tip for implant surface (WoodPecker; Guilin Zhuomuniao Medical Devices, Guilin, China). Patients having gingivitis or periodontitis were also treated. A generic mouthwash containing 0.12% chlorhexidine was prescribed, and patients were instructed to use it three times a day for 30 days [25]. Standard oral hygiene instructions (OHI) were given to all patients.

2.5. Recall Visit. After 3 months of the initial visit, patients were again examined by the same clinician (MI), and clinical measurements were recorded. Patients were referred for periimplant surgery if indicated.

2.6. Statistical Analysis. GraphPad Prism software (version 5.00 for Windows, San Diego California, USA) was used for data analysis. To compare continuous and categorical variables, Wilcoxon signed ranks and McNemar tests were used, respectively. Differences were considered significant at a p value of ≤5.

3. Results

Table 1 presents general features of patients included in the study. Forty-six (46) patients, ages ranging from 42 to 71 years (55.7 ± 15), were included in the study. The participants comprised of 34 males and 12 females. Group A included 25 patients who received a standard regimen of systemic antibiotics as mentioned earlier in the materials and methods part, while 21 patients received implant surface debridement alone.

3.1. Clinical Parameters at the Target Implant Site. Table 2(a) presents a comparison of the clinical parameters between initial and recall visits. The studied clinical parameters did not differ significantly between the two groups at the initial visit. PPD of the target sites decreased significantly ($p < 0.001$) in both groups at recall visit in comparison to the initial visit. The mean PPD of group B was significantly lower than group A ($p = 0.003$), when both groups were compared at the recall visit. Measurements of the CAL significant changed only in group B ($p = 0.002$), while it was not significant in group A ($p = 0.12$). For both groups, values of MR were significantly higher at the recall visit in comparison to the initial visit (group B, $p = 0.002$; group A, $p = 0.01$). In addition, the mean MR values were significantly greater in group A ($p = 0.005$) in comparison to group B at the recall visit. Significant reduction of BoP was also observed for both the groups at the recall visit compared to the initial visit (group B, $p = 0.03$; group A, $p = 0.011$). The deepest periimplant pockets showed the greatest PPD and MR changes in both groups.

Plaque scores and suppuration on probing did not change significantly for both groups at the recall visit.

Table 1: Characteristics of the patients at the initial visit ($N = 46$).

Age (mean ± SD)	42-71 (55.7 ± 15)	
Gender	Male	34 (74)
	Female	12 (26)
Dental status (N, %)	Edentulous	14 (30)
	Dentate	32 (70)
Smoking habits	Smoker	4 (8)
	Nonsmoker	31 (67)
	Past-smoker	5 (11)
	Not known	6 (13)
Past history of periodontitis	Yes	17 (37)
	No	24 (52)
	Unknown	5 (11)

3.2. Clinical Parameters of the Target Implants. Both groups showed significantly lower PPD values around the target implants at the recall visit (group B: $p = 0.003$ and group A: $p = 0.04$) when compared to the initial visit (Table 2(b)). CAL showed no significant change for both groups at the recall visit when compared to the initial visit. Only group B showed a significant increase in MR in comparison with the initial visit ($p = 0.001$) and in comparison, with group A ($p = 0.012$). Moreover, BoP in the group B showed a significant change at recall visit when compared to; initial visit ($p = 0.001$) and to group A ($p = 0.02$). Suppuration on probing showed no significant change, while plaque scores decreased significantly when compared to the initial visit for both groups (group B: $p = 0.04$ and group A: $p = 0.01$). In group B, 44% of patients needed surgery, while in group A, 52% of the target implants were referred for periimplant surgery at the recall visit.

3.3. Microbiological Parameters. Table 3 presents microbiological data of the implants. Differences between the mean proportions and prevalence of studied bacterial species of the two groups at the initial visit were not significant. Similarly, group A did not show significant changes in the prevalence or proportions of the bacterial species between initial and recall visits. Interestingly, the prevalence of P. intermedia and P. micros in group A was significantly lower at recall visit ($p = 0.002$ and $p = 0.001$, respectively) compared to the initial visit. Moreover, a reduction in proportions of P. intermedia was observed ($p = 0.04$) in the group A at the recall visit.

Table 2: Clinical measurements of target implant site (a) and target implant (b) at initial visit and three-month recall visit of patients group A (with antibiotics, $N = 25$) and group B patients (without antibiotics, $N = 21$).

	Initial visit	Recall visit	p value initial vs. recall visit	p value evaluation group B vs. group A
A. Target implant site				
PPD (mm ± SD)				
Total	7.3 (1.7)	5.3 (1.4)	<0.001	
Group B	7.5(1.6)	4.6 (1.2)	<0.001	
Group A	7.6 (1.4)	5.2 (1.3)	<0.001	0.003
CAL (mm ± SD)				
Total	11.2 (2.0)	10.3 (1.4)	0.001	
Group B	12.0 (1.8)	10.4 (1.6)	0.003	
Group A	11.0 (1.7)	10.6 (1.7)	0.12	0.3
MR (mm ± SD)				
Total	4.3 (1.9)	5.2 (2.2)	0.001	
Group B	4.5 (2.0)	6.3 (1.6)	0.002	
Group A	3.8 (1.4)	4.5 (2.3)	0.01	0.005
BoP (%)				
Total	100	84	0.004	
Group B	100	86	0.03	
Group A	100	78	0.011	0.4
Suppuration on probing (%)				
Total	23	9	0.20	
Group B	27	8	0.09	
Group A	19	8	0.33	0.2
Plaque scores (%)				
Total	33	24	0.2	
Group B	36	38	0.59	
Group A	30	10	0.07	0.1
B. Target implant				
PPD (mm ± SEM)				
Total	5.6 (1.2)	4.7 (1.1)	<0.001	
Group B	5.4 (0.9)	4.3 (0.6)	0.003	
Group A	5.5 (1.5)	4.8 (1.3)	0.04	0.07
CAL (mm ± SEM)				
Total	11.1 (2.2)	10.3 (2.2)	0.34	
Group B	12.1 (2.3)	10.7 (2.0)	0.2	
Group A	9.6 (2.1)	9.9 (2.2)	0.6	0.32
MR (mm ± SEM)				
Total group	4.8 (2.1)	5.4 (2.5)	0.001	
Group B	5.9 (2.1)	6.6 (1.8)	0.001	
Group A	4.6 (1.6)	4.7 (2.3)	0.17	0.012
BoP				
Total	5.1 (1.2)	3.7 (1.8)	<0.001	
Group B	5.2 (1.1)	3.0 (1.9)	0.001	
Group A	5.0 (1.4)	4.1 (1.6)	0.08	0.02
Suppuration on probing				
Total group	1.0 (1.6)	0.3 (1.2)	0.05	
Group B	0.8 (1.1)	0.4 (1.4)	0.23	
Group A	0.9 (1.9)	0.3 (1.1)	0.17	0.8

Table 2: Continued.

	Initial visit	Recall visit	p value initial vs. recall visit	p value evaluation group B vs. group A
Plaque scores				
Total	2.6 (2.3)	0.8 (1.3)	0.01	
Group B	2.4 (2.1)	1.2 (1.5)	0.04	
Group A	2.7 (2.5)	0. (0.7)	0.01	0.1

Group B: implant surface debridement alone; Group A: implant surface debridement with adjunctive systemic antibiotics.

Table 3: Prevalence and proportions (±SD) of the studied bacteria at the target implant site as at initial and recall visits ($N = 46$).

		Bacterial species						
		Group B ($N = 25$)			Group A ($N = 21$)		Recall visit group B vs. group A	
		Initial visit	Recall visit		Initial visit	Recall visit		
A. actinomycetemcomitans	Prevalence N (%)	0 (0)	0 (0)	ns†	0 (0)	0 (0)	ns	ns
	Mean (±SD) proportion	0 (0)	0 (0)	ns	0 (0)	0 (0)	ns	ns
P. gingivalis	Prevalence N (%)	4 (16)	0 (0)	ns	6 (28.5)	5 (24)	ns	0.06
	Mean (±SD) proportion	1.6 (4.3)	0 (0)	ns	5.3 (14.5)	36.1(17.5)	ns	ns
P. intermedia	Prevalence N (%)	6 (24)	2 (8)	ns	8 (38)	4 (19)	0.002	ns
	Mean (±SD) proportion	1.8 (3.2)	3.8 (2.8)	ns	2.6 (4.1)	1.5 (2.3)	0.04	ns
T. forsythia	Prevalence N (%)	9 (36)	6 (24)	ns	7 (33)	5 (24)	ns	ns
	Mean (±SD) proportion	2.3 (4.4)	3.6 (5.1)	ns	1.4 (3.4)	3.6 (3.4)	ns	ns
P. micros	Prevalence N (%)	18 (72)	14 (56)	ns	17 (81)	10 (47.6)	0.001	ns
	Mean (±SD) proportion	19.2 (22.4)	12.1 (14.3)	ns	19.8 (24.1)	8.2 (9.5)	ns	ns
F. nucleatum	Prevalence N (%)	15 (60)	14 (56)	ns	15 (71)	13 (62)	ns	ns
	Mean (±SD) proportion	3.1 (5.3)	3.4 (6.3)	ns	2.1 (7.2)	1.9 (4.5)	ns	ns
C. rectus	Prevalence N (%)	2 (8)	2 (8)	ns	1 (4.8)	1 (4.8)	ns	ns
	Mean (±SD) proportion	4.4 (2.2)	2.28 (0)	ns	2.0 (0)	1.5 (2.6)	ns	ns
Total CFU count		5.4×10^6 (5.9×10^6)		ns	3.8×10^6 (2.8×10^6)		ns	

Group B: implant surface debridement alone; Group A: implant surface debridement with adjunctive systemic antibiotics; †ns: not significant.

No significant differences could be detected in the bacterial loads (average CFU/ml) of the two groups at the target implant level. The growth of A. actinomycetemcomitans could not be confirmed in any of the patient samples.

4. Discussion

The present study evaluated the effects of adjunctive systemic antibiotics and implant surface debridement on the clinical and microbiological parameters of periimplantitis. The use of antibiotics improved the mean PPD, MR, and BoP in periimplantitis. Moreover, significant improvements were observed in PPD and MR with implant surface debridement combined with systemic antibiotics at the implant sites with the greatest PPD measurements, and MR and BoP at implant level in comparison to implant surface debridement only.

Limited studies are available on the effectiveness of implant surface debridement alone and in combination with systemic antibiotics; therefore, more research is needed to elucidate its role in the evidence-based management of periimplantitis [26]. One uncontrolled cohort study has reported improvement in the clinical parameters of periimplantitis with implant surface debridement combined with systemic antibiotics [18]. A literature review including 16 studies has suggested that nonsurgical treatment alone has no or minimal effects on improving the clinical parameters of periimplantitis [27]. However, they observed improvement in BoP and PPD with mechanical debridement combined with systemic antibiotics. These findings are in line with the current study.

Another literature review has reported that nonsurgical treatment/implant surface debridement has limited or no value in periimplantitis treatment and all affected implants invariably need surgical treatment over a period of time [28]. In contrast, we found that more than 50% of patients did not need surgery at the recall visit regardless of antibiotics use. Since we only followed the patients for three months, the proportions of patients requiring surgical treatment might increase with a longer follow-up time.

The absence of pus has been previously suggested to correlate with the success of periimplantitis treatment [29]. Implants having pus at the initial visit consistently needed surgical management after three months of debridement as described by Thierbach et al. [29], while those showing no pus on probing at the beginning did not need surgery. This finding could not be verified in our results.

Moreover, *P. gingivalis* was completely eradicated in group B (with antibiotics) at the recall visit in contrast to

group A (no antibiotics) where the prevalence and proportions of *P. gingivalis* were unaffected. Previous reports suggest that the combined effects of amoxicillin and metronidazole are effective against *P. gingivalis*, which substantiates our findings [24]. Intriguingly, a lower frequency of *P. intermedia* and *P. micros* was found only in group A. Effectiveness of implant surface debridement alone in decreasing the prevalence and proportions of *P. intermedia* and *P. micros* in periodontal disease has been previously reported [30].

Multiple aspects of periimplantitis are like chronic periodontitis, both are opportunistic infections, triggered by the existence of bacteria and an aberrant response from the host immune system [2]. Due to the close similarities, periimplantitis is usually treated in a similar manner to periodontitis, consisting of mechanical debridement and use of local and systemic antibacterial agents [2]. Recent studies, however, suggest that important differences could exist between the microbiota associated with periimplantitis compared to periodontitis [31, 32]. Large-scale microbiological studies using open-ended microbial detection techniques are required to further elucidate the role of specific microbial species in the etiology and pathogenesis of periimplantitis. In addition, the behavior of biofilm on implant surface and its interaction with host immune system in the presence of implant biomaterial also need further investigation [33].

5. Conclusions

In the current study, adjunct use of systemic antibiotics did not demonstrate an additional advantage in reducing periimplant bacterial species and total bacterial loads. Implant surface debridement alone is effective in improving the clinical parameters of periimplantitis. In addition, adjunctive use of systemic antibiotics significantly reduced pocket probing depths, increased mucosal recession, and decreased bleeding on probing in periimplantitis.

Data Availability

Details are presented within the article in the form of tables and text in results. Other data will be made available upon request.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

We thank the technical and support staff of the microbiology laboratory of the Veterinary Research Institute, Peshawar, for their help with laboratory work throughout the research project.

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