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Early marginal bone loss around dental implants: a retrospective cohort

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THESIS

EARLY MARGINAL BONE LOSS AROUND DENTAL IMPLANTS:

A RETROSPECTIVE COHORT

by

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DEDICATION

I would like to dedicate this work to my parents, who have always pushed me to achieve higher education and inspired me to continue learning, and to my wife, who supports me daily and encourages me to be the best version of myself.

ACKNOWLEDGMENTS

Primarily, I thank Allah for giving me the patience, inspiration, and strength to accomplish this work. It is with immense gratitude that I acknowledge the support and help of my professor and research mentor, Dr. Albert Price, for guiding me on the path of clinical research and providing invaluable assistance throughout. His support has been instrumental in my journey. It gives me great pleasure to acknowledge the support and help of Professor. Serge Dibart and Dr. Jeremy R. Kernitsky for their unlimited support.

EARLY MARGINAL BONE LOSS AROUND DENTAL IMPLANTS: A RETROSPECTIVE COHORT

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ABSTRACT

Aim: To evaluate marginal bone loss around dental implants at the 2nd stage abutment surgery and retrospectively evaluate the association of pre-surgical variables.

Material and Methods: Eighty-seven subjects (41 Males and 46 females) were enrolled in this cohort. The subjects' ages ranged from 23 to 80 years. Two endosseous implant brands were utilized: Nobel Biocare and Straumann Bone Level . Clinical measurements (mesial, distal, buccal, and lingual) were recorded from the coronal margin of the implant platform to the bone margin with a periodontal probe (Williams periodontal probe, Hu-Friedy) at the time of implant placement and at the 2nd stage abutment surgery. The pre-surgical variables (medication intake, implant site, bone graft volume, membrane type, and smoking) were evaluated using Chi-square test.

Results: The marginal bone loss (MBL) difference was calculated. The Mean clinical MBL: Mesial = 0.71 mm, Distal = 0.56mm, Buccal/Labial = 0.65 mm, and Lingual/Palatal = 0.56 mm. The test showed no statistically significant difference between test and control subjects in each of the variables, with the exception of thyroid medication. A statistically significant (P value = 0.011) association was found between levothyroxine and MBL at the mesial measurement.

Conclusion: This limited cohort study suggests that medication-controlled hypothyroidism patients may experience an increased risk of marginal alveolar bone loss around dental implants at the 2nd stage abutment surgery. The final determination will be recalculated when the study population reaches the estimated requirement of 200 subjects.

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INTRODUCTION

Dental implants have become a cornerstone of modern restorative dentistry, offering patients a reliable and aesthetic solution for replacement of missing teeth. Despite advancements in implant design, surgical techniques, and biomaterials, the long-term success of dental implants remains a multifaceted challenge. One of the critical complications that clinicians encounter is marginal bone loss around dental implants, which can compromise implant stability, longevity, and treatment outcomes. While marginal bone loss can occur at any stage following implant placement, early detection and intervention are critical for mitigating adverse effects on implant stability and function. In the Branemark implant development era, early marginal bone loss was often observed after the first year of function, followed by minimal bone loss ($\leq$ 0.2 mm) annually. Six plausible post-op etiologic factors were hypothesized, including surgical trauma, occlusal overload, peri-implantitis, microgap, biologic width, and implant crest module (Oh et al., 2002). The current study investigated marginal bone loss prior to the implant being in function and before implant loading. Understanding the preoperative factors that may contribute to early marginal bone loss is essential for improving implant survival and success rates. This retrospective analysis investigated the preoperative factors associated with marginal bone loss in endosseous dental implants by examining a number of variables, including medication intake, implant site, previous bone graft history at the implant site, the membrane type used during any bone graft procedures, and smoking history.

A previous pilot study designed by Alrowais, which was limited to 23 patients, measured marginal bone loss at the second stage abutment surgery in the periodontal clinic at Boston University Goldman School of Dental Medicine (GSDM) (IRB H-33284, 2016). He reported 5 implant failures and individual bone loss ranging from 0-2mm. The Alrowis study included three

different implant systems utilized in the GSDM clinic at that time. The Biomet 3i design was a hex-platform Brannemark clone that positioned the implant abutment interface 1.0 mm below the platform peripheral bone level. The Nobel Replace Tri-Lobe Connection featured an internal connection that placed the abutment interface with the implant restorative margin at the crestal bone level. The third design, the ITI Straumann implant, had an internal cone attachment geometry with a coned abutment interface that resulted in a small horizontal separation or ledge at the implant/abutment interface from the bone margin, later referred to as a "platform switch" design (Alrowis 2016). The Straumann Bone Level Implant is best placed with the outer rim of the narrow 45° sloping edge (chamfer) at bone level.

The Alrowais study and previous studies missed consideration of earlier events in the implant site history that may affect the quality and biologic responsiveness of the bone to the implant osteotomy and subsequent healing. This research expanded the patient base number acquired in the Alrowis study by soliciting the inclusion of any patients who have received dental implants under the supervision of the periodontal department. Our purpose was to isolate pre-operative bone or healing issues that might contribute to increased bone loss at the time of post-operative exposure. This study explored the complex etiology of marginal bone loss factors to identify predictive markers for implant marginal bone loss at the 2nd stage abutment surgery. The existing literature concentrated on marginal bone loss at immediate, early, and late implant loading protocols but not prior to implant loading/function. This study has the potential to create evidence-based treatment protocols and to optimize clinical decision-making in implant planning.

PATIENT-RELATED FACTORS

MEDICATION INTAKE

More than half (51.8%) of adults in the United States have at least 1 of 10 diagnosed chronic conditions (arthritis, cancer, chronic obstructive pulmonary disease, coronary heart disease, current asthma, diabetes, hepatitis, hypertension, stroke, and weak or failing kidneys), and twenty-seven percent have multiple chronic conditions (Boersma et al., 2020). The medication-related side effects on implant-related outcomes has been one of the primary explored subjects in the literature. A comprehensive assessment of the patient's medical background and current medications is essential for the success and prognosis of the planned endosseous implant since the patient's systemic status and medication intake may directly or indirectly affect bone metabolism.

Proton pump inhibitors (PPIs) have generated interest in implant dentistry due to the possible role of these medications on osseointegration. PPIs inhibit stomach acid production as a treatment for gastroesophageal reflux or gastric ulcers. Multiple studies have suggested that the intake of PPIs might be associated with an increased risk of dental implant failure (Chappuis et al., 2018; Chrcanovic et al., 2017). The most popular hypothesis assumes that the reduced stomach acidity impairs the intestinal absorption of dietary calcium (Chrcanovic et al., 2017). A cohort retrospective study by Wu and colleagues found that implant failure rates were 6.8% for people using PPIs compared to 3.2% for non-users. Hence, understanding the effect of PPIs on calcium reduction and the detrimental result on bone homeostasis highlights the clinical implications of the intake of PPIs (Chappuis et al., 2018).

Among other medications interfering with bone formation and turnover are selective serotonin reuptake inhibitors (SSRIs), used for the management of anxiety and depression. A cohort retrospective study found that patients using SSRIs were found to be 3 times more likely to experience early implant failure than nonusers (Altay et al., 2018). The study suggested that while SSRIs may increase osseointegration failure, the increase was not statistically significant. A recent cohort study suggests that SSRIs may lead to loss of bone mass by inhibiting the bone remodeling processes triggered by mechanical loading. This inappropriate response to mechanical loading may be a possible cause of "the after-loading failures" (Wu et al., 2014). Chrcanovic et al. 2017 also found that antidepressants and acid gastric reduction medication had a negative influence on implant longevity in patients experiencing multiple implant failures.

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption and have been widely used in the management of skeletal cancer metastases and for the treatment of primary and secondary osteoporosis. Bisphosphonates, whether IV or oral, have been investigated for their possible association with osteonecrosis of the jaw (Ruggiero et al., 2022). Oral bisphosphonates at the time of implant placement and during healing did not affect early implant success rates or crestal bone changes up to the time of stage-two surgery (Ruggiero et al., 2022). The implant location and the duration of drug therapy at the time of placement were not significant factors in bony changes (Memon et al., 2012).

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in dental practice for pain control. NSAIDs may interfere with bone homeostasis or osseointegration. However, studies investigating the effects of NSAIDs on bone homeostasis have not shown statistical significance.(Chappuis et al., 2018). Failure of osseointegration was more likely to occur in patients who used NSAIDs peri-operatively (44%) compared to patients who did not take

NSAIDs (38%). The NSAID group experienced higher cases of radiographic bone loss exceeding 30% of the overall height and cluster failures (Winnett et al., 2016). This suggests that the use of pre-operative NSAIDs may interfere with inflammatory bone metabolism, particularly in medically compromised populations, while having a minimal clinical effect in healthy individuals (Chappuis et al., 2018).

Anti-hypertensive (AHTN) medications have a positive effect on endosseous implant longevity and survival rate (Chappuis et al., 2018). Ultimately, patient specific factors, such as medication or (poly)medication, interfere with the immune system and bone turnover and may, alone or in combination with other factors, contribute to bone loss of osseointegrated implants (Bosshardt et al., 2017).

SMOKING

Tobacco product use is the primary cause of preventable diseases and deaths in the United States. As of 2021, nearly 46 million U.S. adults, which is about 18.7%, use tobacco products. Cigarettes are the most commonly used tobacco product, with 11.5% of adults reporting using them, followed by e-cigarettes with 4.5%. In the period between 2020 and 2021, there was a decrease in the prevalence of cigarette smoking, while the use of e-cigarettes increased (Cornelius et al., 2023). Extensive research has been conducted on the impact of smoking on endosseous implant osseointegration, success rates, survival, and marginal bone level. A 10-year prospective study concluded that marginal bone level around implants at 10 years was significantly negatively associated with smoking along with general health, implant location, full-mouth probing attachment level, and change over time in full-mouth probing pocket depth (Karoussis et al., 2004). DeLuca and Zarb presented a 20-year study of two hundred thirty-five patients with seven hundred sixty-seven Branemark implants and reported no difference in bone

loss in the first year of clinical loading, but a higher incidence of marginal bone loss occurred in the smoking group in subsequent years (DeLuca & Zarb, 2006; Qian et al., 2012). Nicotine suppresses the gene expression of enzymes that are critical for the regulation of osteoblast proliferation, differentiation, and apoptosis, leading to significant defects on bone formation and remodeling (Deng et al., 2008). A later systematic review and meta-analysis concluded that smoking significantly increased failure rate, the risk of postoperative infections as well as marginal bone loss (Chrcanovic et al., 2015). Supporting data from another study showed that marginal bone loss and implant success are negatively affected by tobacco smoking (Galindo-Moreno et al., 2015). The data on the effects of waterpipe smoking**,** cigar and pipe smokers**,** and electronic cigarettes on peri-implant hard and soft tissue is currently limited.

IMPLANT SITE RELATED FACTORS

POST EXTRACTION DIMENSIONAL CHANGES

Tooth extraction is one of the most common treatments for non-restorable teeth, and its role in buccal bone loss is well established. Several human studies have reported the dimensional changes that occur in the alveolar ridge after tooth extraction, using various methodologies, including clinical, cast model, and radiographic examinations (Araújo et al., 2015). Up to 50% reduction of the original ridge width will occur, with bone resorption greater at the buccal aspect than at its lingual/palatal counterpart. A larger amount of alveolar bone reduction takes place in the molar regions (Araújo et al., 2015). Although most of the dimensional changes that comprise socket healing occur during the first 3 months, bone fill was observed between 3 and 6 months post-extraction, and the reorganization of the alveolar ridge may continue for up to 1 year post-extraction (Schropp et al., 2003). The rate of socket healing may be influenced by biological

differences among individuals, as well as the size of the alveolar socket and the extent of surgical trauma that occurs during the extraction procedure (Araújo et al., 2015).

BONE GRAFTING TECHNIQUE AND MEMBRANE USE

Various techniques have been proposed to reduce the loss of alveolar ridge that occurs after tooth extraction. These techniques include partial extraction protocols, orthodontic extrusion, and alveolar ridge preservation therapy, which involves filling the socket with biomaterials, such as bone graft particles, with or without the application of a sealing material. Alveolar bone preservation through socket preservation technique using a bone graft can be an effective therapy to prevent bone loss both horizontally and vertically after the extraction of non-molar teeth. Flap elevation, using a membrane, and a xenograft or allograft could further improve the outcome, particularly in preserving midbuccal and midlingual height (Avila-Ortiz et al., 2014). Ridge augmentation is indicated when the width, height, or a combination of both is insufficient to place implants in an optimal position. Alveolar ridge reconstructing procedures are used for horizontal and vertical ridge augmentation. These techniques include but are not limited to, the use of barrier membranes for guided bone regeneration, particulate grafting materials, onlay block grafting techniques, distraction osteogenesis, ridge split techniques, and, in severe defects, a combination staged approach of these techniques (McAllister & Haghighat, 2007). For molar ridge preservation, bone grafts did not significantly impact ridge width but significantly decreased buccal vertical height reduction compared with natural healing after extraction (Walker et al., 2017). During the alveolar ridge preservation procedure, the use of membranes requires soft tissue coverage for optimal treatment outcomes. Exposure of membranes may compromise results, with e-PTFE or non-resorbable membranes being more problematic than collagen membranes. There is no evidence to support the superiority of one grafting technique

over another (Darby et al., 2009). There is no conclusive evidence to support the claim that ridge preservation procedures will prevent the need of additional alveolar bone augmentation procedures before endosseous implant placement (Darby et al., 2009). For horizontal ridge augmentation, a systematic review failed to identify one specific protocol, procedure, or material to be superior (Jepsen et al., 2019). In a systematic review and meta-analysis of vertical ridge augmentation techniques, no definite conclusions could be drawn regarding the superiority of any particular vertical ridge augmentation technique (Urban et al., 2019).

IMPLANT SITE

The implant site as a prognostic factor has been investigated in the literature. In Branemark's original studies and Zarb's studies confirmed that the dental implant failure rate is higher in the maxilla than in the mandible, with the area of lowest failure rate being the anterior mandible and the highest being the posterior maxilla. A more recent cohort study consisting of a consecutive series of patients who had dental implants placed by one surgeon over a 21-year period reinforced the idea that implants placed in the maxilla had almost twice the failure rate of those placed in the mandible. The order of failure rates from lowest to highest in this study was the anterior mandible, posterior mandible, anterior maxilla, and posterior maxilla (Moy et al., 2005).

MATERIALS AND METHODS

STUDY DESIGN

This study was conducted in compliance with the protocol IRB H-41757 with applicable regulatory requirements, and Boston Medical Center (BMC)/Boston University (BU) Medical Campus Human Research Protection policies and procedures. This cohort included 87 patients aged between 18 to 80 years, of either gender, who have undergone a two-stage endosseous

implant procedure before their abutment surgery. Endosseous implant brands in the cohort study are Nobel Biocare (Nobel Biocare AB, Göteborg, Sweden) and Straumann Bone Level (Institute Straumann AG, Waldenburg, Switzerland). The patients were selected from a list of patients from the graduate periodontal department at the Goldman School of Dental Medicine. The protocol avoided influencing treatment decisions prior to abutment surgery by approaching patients for inclusion after the implant was placed. Exclusion criteria included patients who have had a sinus lift at the implant site or who were taking the following medications: bisphosphonates, gabapentin, glucocorticoids, methotrexate, or estrogen supplements, as these medications are known to affect bone healing. Implants in third molars and mandibular incisor sites were excluded. Implants placed simultaneously at sites of the maxillary central incisors were excluded. Non-English-speaking subjects, pregnant women and employees, students, or trainees under the direct supervision of the principal investigator are also excluded. More than 1 implant may be measured in a single patient if the second site is in a different quadrant or at least 10 mm away. A research study ID# will be assigned to the patient at the time of consent and recorded to identify their clinical research file.

CLINICAL PROCEDURE

The abutment surgery was a normal standard of care procedure done under local anesthetic. Clinical measurements were recorded from the coronal margin of the implant platform to the bone margin with a periodontal probe. Mesial, lingual, buccal, and distal measurements were recorded at the time of placement with the same periodontal probe (Williams periodontal probe, Hu-Friedy). There was no intervention or change to the planned treatment sequence or materials. The total patient contact time for this research measurement was less than 15 minutes. We

retrospectively reviewed the patient records for specific variables that might influence the vitality and responsiveness of the bone at the site. (see Fig. 3 and 4)

If the implant was placed sub-crestal, the pre-operative measurement was given a positive (+) value, if the bone level was below the implant platform at the time of placement the measurement was given a (-) value. These measurements were then repeated at the abutment or uncovering stage 3-6 months later. There were 118 implants from 87 patients. The data sheets shown in Figures 1, 3, and 4 were used to record the measurements and associated variables.

CRF-PATIENT RESEARCH ID#: _____

Measurements recorded at the time of abutment surgery:

Positions measured will be: Mesial___mm Distal ___mm Buccal___mm Lingual___mm

Figure 1. Clinical measurements from the coronal margin of the implant platform to the bone margin using a periodontal probe (Williams periodontal probe, Hu-Friedy).

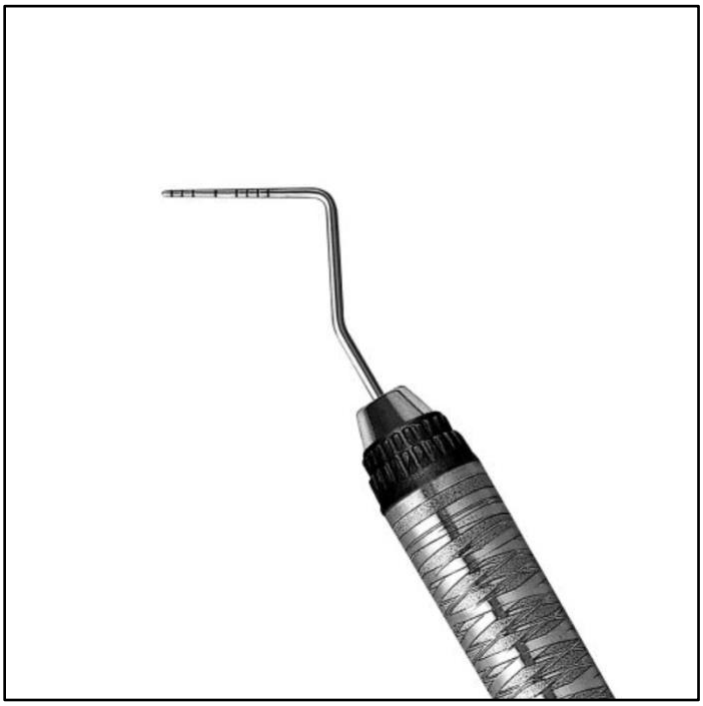

Figure 2. Periodontal probe (Williams periodontal probe, Hu-Friedy)

RETROSPECTIVE RECORD REVIEW: Variables with potential effect on bone status measured at abutment surgery.

1. Age: ____ years
2. Sex: M ___F___
3. Race: (As recorded on the patient record) _____
4. Medications: (Taken at least 1x/day) _____

   (In record, not excluded in section 11.2.)

5. Tooth sites: Molar site? yes___no____

   (#1,16,17,32 and 23-26 are excluded)

6. Abscess prior to extraction: yes___ no___
7. Extraction technique: Date: __/__/___
   a. Regular forceps/elevation only: yes___no___
   b. Surgical/resection yes___no___
8. Bone grafts used and volume:
   a. Socket graft (volume_____) Date: __/__/__ yes___no___
   b. Site graft (volume_____) Date: __/__/__ yes___no___
9. Implant surgery variables:
   a. Bone augmentation at implant site:(volume_____) yes___ no___
   b. Insertion torque above 45Ncm: yes___no___
10. Healing times:
    a. Implant date -Extraction date: I (__/__/__) - E (__/__/__)=_____days
    b. Abutment date-Implant date: A (__/__/__) - I (__/__/__) = ____days
    c. Graft (#8 above)-Implant date: I (__/__/__) - G(__/__/__) = ____days
11. Smoking yes___no___

Figure 3. Study variables sample data sheet.

VARIABLE OF INTEREST

1. Medications: (Taken at least 1x/day) _____

3. Tooth sites: Molar site? yes___no___

(#1,16,17,32 and 23-26 are excluded)

4. Bone graft variables:

a. Socket graft (volume_____) Date: __ /__ / __ yes___no___

b. Site graft (volume_____) Date: __ /__ / __ yes___no___

c. Membrane type (Resorbable, Non-resorbable)

5. Smoking status yes___ no___

Figure 4. Patient list of variables reported in the current study.

STATISTICAL DATA ANALYSIS

The measurements were divided into two categories: a test and a control sample. Marginal Bone Loss (MBL) >1mm was counted as a test, and MBL $\leq$ 1 was counted as a control. In this study, the examiners measured the MBL to the closest mm using the Williams periodontal probe, as mentioned earlier. The variables of interest were:

1. Medication intake.
2. Implant Site
    a. Molar vs non-Molar
    b. Maxilla vs Mandible

3. Bone Graft Variables
    a. Graft Volume (≤0.5 cc vs > 0.5 cc)
    b. Membrane type used (Resorbable vs non-Resorbable)
4. Smoking Status

The mean difference in marginal bone level around each implant from the time of implant placement to the time of abutment surgery was calculated. The difference was calculated for the four different locations: mesial, distal, buccal/labial, and lingual/palatal of each implant. Chia square test was conducted to examine the association between MBL at the four points and each variable: Medication, implant site, graft volume, membrane type, and patient smoking status. The null hypothesis was that there was no association between the variables.

RESULTS

Eighty-seven subjects (41 Males and 46 females) participated in this cohort study. The subjects' ages ranged from 23 to 80 years (Mean = 53.7). One hundred and eighteen implants were evaluated. The mean, median, mode, and standard deviation of the MBL difference between the time of implant placement and the time of abutment surgery were recorded in Table (1).

	Mean	**Median**	**Mode**	**Standard Deviation**
Mesial	0.71	0.50	0	1.16
Distal	0.56	0.50	0	1.00
Buccal	0.65	1.00	0	1.49
Lingual	0.56	0.50	1.00	0.98

Table (1). Marginal bone level difference at the time of implant placement compared to the bone level at the time of 2nd stage abutment surgery.

MEDICATION INTAKE

Of the 87 subjects, 50 were taking at least one type of medication. A Chi-square test was used to determine the association between MBL and the use of levothyroxine, statins, anti-hypertensive, and anti-depressant medications. The association between the use of multiple medications (36 subjects) and MBL using the Chi-square test. The results of the medication intake variable are in Table (2).

Medications	Mesial			Distal			Buccal /Labial			Lingual / Palatal		
	Control	Test	P-value	Control	Test	P-value	Control	Test	P-value	Control	Test	P-value
Levothyroxine												
Yes	4	5		6	3		5	4		7	2	
NA	88	21	**0.0116**	93	16	0.14	86	23	0.10	93	16	0.54
Statins												
Yes	19	4		20	3		18	5		18	5	
NA	72	23	0.48	78	17	0.57	72	23	0.80	81	14	0.41
Anti-hypertensive												
Yes	24	6		26	4		26	4		26	4	
NA	67	21	0.66	72	16	0.54	64	24	0.12	73	15	0.63
Anti-depressants												
Yes	8	2		7	3		7	3		8	2	
NA	83	25	0.82	91	17	0.25	83	25	0.62	91	17	0.72
Multiple Medications												
Yes	33	9		34	8		34	8		35	7	
NA	58	18	0.78	64	12	0.65	56	20	0.37	64	12	0.90

Table (2). Marginal bone level differences with medication intake variables tested by a Chi-square test.

The Chi-square test showed no difference between test subjects and control subjects in all the medication intake variables, with the exception of levothyroxine. For levothyroxine, the association of MBL mesially and the medication intake was statistically significant (P value = 0.011).

IMPLANT SITE VARIABLES

A total of 118 implants were included; 64 implants were placed in the maxilla, while 54 were placed in the mandible. Implant sites were categorized into molar and non-molar. Fifty-three implants were placed in a molar site, and 65 implants were placed in a non-molar site. A Chi-square test investigated the association between MBL and the implant site variables: (molar vs non-molar) and (maxilla vs mandible). The test showed no statistically significant difference, as demonstrated in Table (3).

BONE GRAFT VARIABLES

GRAFT VOLUME

Fifty-one Implants were placed in previously grafted sites, while the rest of the 67 implants were placed in a pristine (non-grafted) site. Grafted sites were categorized based on graft volume in cubic centimeters (cc) at the time of the bone grafting procedure. Graft volumes were divided into > 0.5 cc and ≤ 0.5 cc. A Chi-square test was conducted to investigate the association between MBL and graft volume. There was no association between MBL and graft volume. The results are shown in Table (3).

Study Variables	Mesial			Distal			Buccal/Labial			Lingual/Palatal		
	Control (n)	Test (n)	P-value	Control (n)	Test (n)	P-value	Control (n)	Test (n)	P-value	Control (n)	Test (n)	P-value
Implant Site (A)												
Molar	39	14	0.40	45	8	0.62	41	12	0.95	47	6	0.20
Non-Molar	52	13		53	12		50	15		52	13	
Implant Site (B)												
Maxilla	53	11	0.10	53	11	0.94	51	13	0.46	53	11	0.94
Mandible	38	16		45	9		40	14		45	9	
Bone Graft Volume												
> 0.5 cc	9	4	0.15	10	3	0.55	11	2	0.53	11	2	0.97
≤ 0.5 cc	30	8		32	6		29	9		32	6	
Membrane type												
Resorbable	35	9	0.19	35	9	0.18	36	8	0.14	36	8	0.21
Non-Resorbable	4	3		7	0		4	3		7	0	
Smoking												
Yes	11	1	0.20	11	1	0.40	7	5	0.12	11	1	0.43
No	80	26		87	19		83	23		88	18	

Table (3). Statistical analysis of the study variables: implant site, bone graft volume, membrane type, and smoking by the Chi-square test.

MEMBRANE TYPE (RESORBABLE VS NON RESORBABLE)

This study investigated the possible association between MBL and resorbable and non-resorbable membranes. The Chi-square test showed no statistical significance, indicating no association between MBL and membrane type as demonstrated in Table (3).

SMOKING

Nine of the 87 subjects were cigarette smokers. Twelve of the 118 implants were placed in a smoker subject. A Chi-square was conducted and failed to show any association between MBL and smoking. The results are shown in Table (3).

DISCUSSION

This is the first retrospective cohort study designed to investigate the complex etiology of the MBL around dental implants at the 2nd stage of implant abutment surgery. The previous publications investigated the marginal bone loss at immediate, early, and late implant placement protocols and not prior to implant loading/function.

The current cohort of 87 patients with 118 implants failed to reject the null hypothesis, which states that there is no association between any of the study variables (implant site, graft volume, membrane type, smoking status, and medication intake) and MBL except for one of the medication intake variables (levothyroxine). Statins showed no association with MBL around the dental implant. Despite the limited evidence of the effect of statins on dental implant bone levels, animal studies have shown positive results on implant osteointegration, increased bone formation and density, and enhanced bone-to-implant contact (Tahamtan et al., 2020). Randomized clinical

trials will be needed to assess the role of statins in improving osseointegration around dental implants.

The current study showed no association between anti-hypertension medications and MBL at the 2nd stage abutment surgery. The results of our study need to be cautiously interpreted as all the antihypertensive medication classes (thiazide-type diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers) were investigated as one category due to the limited number of subjects. Our study also did not find any significant association between MBL and the use of antidepressant medication. The sample size of subjects taking antidepressants in this cohort was too small (only 10 out of 87) to draw reliable conclusions. Based on the literature, antidepressants, such as SSRIs have been associated with a higher risk of failure of osseointegrated implants (Wu et al., 2014). Randomized clinical trials taking the type, dose, and duration of SSRIs intake are required to validate SSRI study outcomes and better understand SSRIs intake on osseointegration. Multiple medication intake also had no significant effect. Levothyroxine intake had no significant effect on MBL around implants at the distal, buccal, and lingual. Although, there was a significant MBL found on the mesial site. In a study, Medically controlled hypothyroid female patients had more crestal implant bone loss in the first year of loading, especially if additional medications for other disorders were taken (Attard & Zarb, 2002). MBL appeared to taper off after the first year of loading. Although hypothyroidism is associated with bone mineralization abnormalities, hypothyroidism patients treated with thyroid hormone (levothyroxine) may not experience an increased risk of crestal alveolar bone loss after dental implant treatment (Ursomanno et al., 2021).

No statistically significant association was found between implant sites (molar vs. non-molar), (maxilla vs mandible) or the bone graft volume variable.

The study showed no association between cigarette smoking and MBL around dental implants despite the fact that the negative effect of tobacco smoking on MBL and implant success has been verified (Chung et al., 2007; Karoussis et al., 2004; Qian et al., 2012). Our findings may be related to the number of cigarettes consumed per day and the number of implants placed in the maxilla (4) or mandible (8), as all the smoking subjects smoked 10 cigarettes or less per day. Heavy smokers (>10 cigarettes/day) that have implants placed in the maxilla have more MBL than moderate smokers ($\leq$ 10 cigarettes/day) (Nitzan et al., 2005). In smokers, maxillary implants failed 1.6 times more often than mandibular implants (Lambert et al., 2000).

CONCLUSION

The current limited cohort study evaluation suggests that medication-controlled hypothyroidism patients may have an increased risk of marginal alveolar bone loss around dental implants at the 2nd stage abutment surgery. Final determination will be recalculated when the study population reaches the estimated requirement of 200 subjects.

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