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"Marginal Bone Loss Around Dental Implants: A Radiographic Analysis"

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ABSTRACT

Background

Dental Implants have demonstrated high success and survival rates ranging from 94.6% to 100%. Crestal bone loss around dental implants during early wound healing may affect the risk of developing future marginal bone loss and peri-implant diseases.

Aim & Hypothesis

This retrospective case-control radiographic study aims to identify if a higher marginal bone loss (MBL) within 12 months of implant placement is associated with a higher risk of peri-implant MBL during the future function of the implant.

Materials and Methods:

Peri-apical radiographs of dental implants placed in the department of Periodontology between 2004 -2014 were included in our analysis. The implants have been in function for at least 2 years after prosthesis insertion. Linear measurements on the mesial and distal surfaces for each implant from the implant shoulder to the first bone to implant contact were performed. MBLwithin 12 months of implant placement (T1- implant placement, T2- healing abutment insertion, T3- crown/prosthesis insertion) were compared to those of more than 2 years after functional loading (T4). Radiographic bone loss was measured after calculating the distortion rate of radiographs using the known dimensions of the implant as reference values. Mixed effects linear regression analysis was performed for our collected data.

Results:

A total of 210 dental implants from 153 subjects were included in our analysis. The average function period of implants was 4.18 ± 0.15 years. Our results demonstrated that early MBL (from T1 to T3) was 0.59 mm ± 0.67 mm for implants with bone loss ≤2 mm at T4 and 1.12 mm ± 0.71 mm for implants with bone loss >2 mm at T4 ($p<0.001$). Previous history of periodontitis ($p = 0.045$), narrow implant diameter ($p = 0.039$), bone graft at the time of implant placement ($p = 0.03$) and implants placed in the mandible ($p = 0.02$) could also be associated with higher early MBL.

Conclusions:

Dental implants showing radiographic MBL >2 mm at least two years after functional loading (T4) have higher bone loss within 12 months after implant placement compared to those with bone loss ≤2 mm. Narrow diameter implants, implants placed in the mandible and simultaneous bone graft placement at the time of implant insertion seem to be associated with higher early MBL. Previous history of periodontitis might be associated with higher early MBL. Further studies are needed in order to understand better how early marginal bone loss of dental implants can increase or predict the risk of long-term progression of bone loss.

DEDICATION

To Ammi and Abbu

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LIST OF ABBREVIATIONS

RG – Radiographs

MBL – Marginal Bone Loss

SD – sulcus depth

JE – junctional epithelium

CT – connective tissue

fBIC- first bone to implant contact

IAJ – Implant Abutment Junction

ICT – Infiltrated Connective Tissue

T1 – Implant insertion

T2- Abutment connection

T3- Prosthesis insertion

T4- 2 years post loading

RBL – Rate of Bone Loss

LIST OF SYMBOLS

Mm: millimeters

≤ : less than equal to

> : greater than

~ : approximately

± : plus/minus

nm: nanometres

“Marginal Bone Loss Around Dental Implants:

A Radiographic Analysis

Dental Implants have been rapidly gaining popularity as an alternative to replacing missing teeth. Studies demonstrate success rates of 89.7% over 15 years and survival rates of up to 94.6% over 20 years [1]. Implant success can be measured using subjective and objective parameters. The criteria for a successful dental implant was first described by Albrektsson et al.[2] in 1986 as one that demonstrates absence of (a) mobility (b) peri-implant radiolucency (c) persistent and/or irreversible signs and symptoms of pain, infection, or exudate[2]. Furthermore, this criteria for success were revised and radiographic marginal bone loss (MBL) of less than 1.5 mm during the first year in function and 0.2 mm annual bone loss after the first year of function were added [3].

Marginal bone loss (MBL) during early healing around dental implants appears to be inevitable. There have been various theories proposed in the literature to explain this phenomenon. Albrektsson et al. [4] described marginal bone loss in the implant's first year of function as a normal remodeling process after bone injury caused by implant surgery [4]. The surgery leads to rupture of blood vessels and destruction of bone tissue evoking an acute inflammatory response eventually leading to a chronic inflammatory response where an envelope of bone tissue layer condenses around the implant leading to osseointegration [5]. Brunski et al. [6] described the repair process after implant surgery as one that involves remodeling where the damaged pre-existing bone will undergo at least one remodeling cycle which is around 4.25 months for humans. The bone may have to undergo several remodeling cycles especially in cases where major trauma has occurred during implant surgery [6].

Early bone loss around implants could depend on a series of treatment complications or due to poor implants, poor clinicians, and poor patients leading to aseptic loosening and not related to disease [4,5,7]. The foreign body response evoked post-surgery could lead to an early

dis-balance as a result of the above mentioned factors which could lead to the implant being embedded in soft tissue representing a primary clinical failure [5].

MBL around dental implants undergoes also a remodeling process from the establishment of the biologic width complex, recently also termed as "supra-crestal attached tissues", similar to the one found around teeth [8]. The average biologic width around non-submerged dental implants is 3.08 mm (SD-0.16 mm, JE-1.8 mm, CT-1.05 mm) [9]. The amount of bone remodeling following healing from surgical trauma and the establishment of biologic width is associated with various factors such as (i) apico-coronal border of implant smooth-rough surface (ii) implant- abutment junction (iii) depth of implant placement (iv) soft tissue thickness (v) flap elevation (vi) implant surface (vii) type of bone (viii) occlusal forces (ix) prosthetic abutment height and (x) type of prosthesis.

The location of the smooth/rough surface of the implants, relative to the alveolar crest, appears to play a key role on marginal bone remodeling. The movement of the border 1.0 mm more apically results in an increase of 0.73 mm of the biologic width [10,11]. Hammerle et al.[12] evaluated the effect of sub-crestal placement of the polished surface of non-submerged implants on marginal soft and hard tissue in 11 patients. At the control site, the junction between rough and polished border was located at the crest, whereas at test site, the apical border of the polished surface was placed about 1mm below the crest. The average crestal bone loss was 2.26 mm in the test group and 1.02 mm in the control group after one year of function. The study suggested that during the first year of function, the biologic seal is usually established 1 mm apically of the rough implant portion at the expense of the crestal bone independent of an initially increased counter sink depth [12]. The MBL and location of biologic width may be associated with thickness of soft tissue around implants, location of

the junction between rough and polished surfaces and location of micro gap in submerged implants [13].

In a study evaluating crestal bone changes around dental implants in a submerged and non-submerged positions in a canine mandible, the results demonstrated that the location of the implant-abutment interface (microgap) significantly affected crestal bone loss and first bone to implant contact (fBIC) compared to location of rough/smooth border of the implant. The surgical technique of submerging or not submerging the implant had no influence on crestal bone loss. The fBIC occurred at the level of the rough/smooth border of the implant in one piece implants whereas in those implants with an abutment connection, crestal bone loss was seen beyond the rough/smooth border of the implant, apical to the implant-abutment junction (IAJ) up to 2.0 mm [10]. A systematic review evaluating the impact of implant-abutment connection and positioning of the machined collar on crestal bone level changes concluded that a supra-crestal positioning of the machined collar exhibits less crestal bone loss and that a sub-crestal positioning of the IAJ for implants with a rough surface could help retain the bony coverage of the rough surface and is preferred over supra-crestal insertion [14]. For bone level implants, prior to abutment connection, a sub-crestal IAJ position offers slightly less MBL than supra- crestal and equi-crestal position. For tissue level implants, the rough/smooth surface margin should be ideally placed at the level of bone crest[15]. According to the Camlog Foundation consensus report, placing the smooth part of the implant below the alveolar crest may lead to bone loss, therefore the rough/smooth border should at best coincide with the adjacent alveolar bone [16].

There has been a debate regarding the effect of implant depth on marginal bone loss. Apico-coronal depth of implant placement appears to have conflicting results. In a prospective

randomized controlled trial evaluating 105 implants placed either supra crestal or sub crestal, the results indicated a non-significant effect on crestal remodeling between the two placements [17]. Ercoli et al. [18] studied 134 implants placed supra-crestal, sub-crestal and equi-crestal and found that a sub-crestal position would lead to greater odds of finding the implant in a sub-crestal position 12-18 months' post- surgery; however the linear measure of crestal bone loss did not differ when the implants were placed in the 3 positions [18].

Various studies have reported the effect of peri-implant soft tissue thickness on crestal bone stability. A beagle dog study by Berglundh et al. [19] found a greater amount of bone resorption around thin ridge mucosa (<2 mm) prior to abutment connection. They concluded that a minimum width of the peri-implant mucosa may be required, and that bone resorption may take place to allow a stable soft tissue attachment to form [19]. The previous finding was further confirmed in two prospective studies where implants were placed in thick (>2 mm) and thin (< 2 mm) tissues. A significantly greater crestal bone loss was observed if tissue thickness was 2.0 mm or less, up to 1.45 mm of crestal bone loss may occur [20,21].

Crestal bone level changes have also been observed following implant restoration. The position of the IAJ and related microgap poses a significant factor with regards to MBL. Studies have suggested that there is a strong inflammatory component associated with the microgap and there appears to be a contributory relationship between the degree of inflammation and magnitude of MBL [15,22]. Ericsson et al. [23] conducted a dog study and looked at the changes in peri-implant tissues after abutment connection. The findings of the study showed that the bone crest was consistently located 1 mm to 1.5 mm apical to the abutment/fixture level. He also found a 1 mm wide zone of normal non-infiltrated connective tissue (ICT) separated the apical portion of the abutment ICT and the bone crest, therefore

explaining the 1 mm bone loss observed after 1 year of implant function [23]. However, stress concentration at the coronal region of the implant was also considered a contributory factor to crestal remodeling [24].

The concept of platform switching (using a small diameter abutment over a wider diameter implant) was introduced to eliminate or minimize the above-mentioned effects. The biological basis of this concept was to increase the distance between the implant-abutment interface (microgap) and the bone surface by moving the microgap away from the crest and to increase the horizontal soft tissue dimension for the establishment of the biologic width, which may protect the bone crest [16,25]. In a meta-analysis comparing platform switching and platform matching, there was less MBL loss with platform switching than at implants with platform matching [26].

Aside from platform switching, the concept of internal abutment connection was also introduced to minimize the MBL for protection of the fastening screw from flexion associated with lateral forces, limiting micro leakage and screw loosening [27]. Studies have reported that MBL changes were significantly greater for the external connection compared to internal connection [28]. In the first year, MBL for implants with internal connections was limited (0.2 mm - 0.3mm) in comparison to implants with external connection that displayed up to 1.0 mm of average bone loss [29].

Furthermore, Galindo- Moreno et al. [30] proposed that shorter abutments (0-4 mm) demonstrated greater MBL than taller abutments which could be as a result of compression of the mucosa by the shorter abutment or formation of the biologic width [30]. However, further studies with longer follow-up periods are needed for conclusive evidence.

In a conventional implant surgery, a flap is most often elevated in order to assess the bone, anatomical landmarks, and to reduce risk of perforations and fenestrations. However, flap elevation is also associated with some amount of bone loss, post-operative peri-implant tissue loss, longer operative time, higher post- operative complications, slower postsurgical healing and increased patient discomfort. A meta-analysis by Chrcanovic et al.[31] found a non-significant effect of flapless technique on marginal bone loss. Similar findings were reported in a similar meta-analysis of Lemos et al [32].

Dental implants differ in terms of surfaces and designs and appear to have evolved with time. The original first-described osseointegrated dental implants consisted of a smooth machined surface [33]. Some implants involved acid etched surfaces in order to create micro-porosities on the implant surface. Implants with hydroxyapatite coating and plasma sprayed coatings appeared to undergo resorption and degradation ultimately causing the titanium particles to disintegrate. Other implant surface treatments include sand blasting, acid etch, anodic oxidation and laser treatments that gave rise to SLA, SLA active , TiUnite and LaserLok implant surfaces respectively[34].

In a study evaluating long-term clinical and radiographic data of Ti-Unite and turned implants placed in the same patient, a reduced rate of failure with Ti-Unite implants was observed [35]. Hydroxyapatite coated implants appear to have 0.5 mm of bone loss every year for the first 5 years followed by an accelerated pattern of annual marginal bone loss [7]. In a systematic review evaluating the effects of different implant surfaces and systems including Astra Tech (TiO Blast surface), Branemark (turned surface), IMZ and Straumann ITI (titanium plasma sprayed surface), Camlog (blasted and acid etched surface), Frialit (high temperature acid etched surface) on marginal bone-level alterations, between 1 and 3-year

examination, 87.1 % of ITI implants and 95.5% of Branemark implants exhibited a bone loss of < 0.4 mm. The MBL change from baseline to 3 years in function was 0.25 mm and 0.28 mm for Camlog and Frialit implants. Between ITI and IMZ implant, after 5 years' function, MBL change from baseline was 1.8 mm and 1.6 mm respectively. The MBL changes between Astra tech and Branemark system after 5 years were 0.29 and 0.2 mm. The results of the review concluded that no implant system is superior in marginal bone preservation [36].

Smooth implant collar surfaces have been associated with reduced plaque accumulation, but higher stress concentrations in the area of the crestal bone around the polished neck of the implants. The presence of a roughened collar or micro threads threads at the neck could reduce MBL due to increased interlocking of the implant and marginal bone. In a systematic review and meta - analysis evaluating machined, rough-surfaced and rough-surfaced micro threaded neck implant collar surfaces, marginal bone loss around rough surfaced micro-threaded neck implants was significantly lower than polished and rough-surfaced neck implants [37].

Hard tissue augmentation procedures are commonly employed to enhance bone volume, width and height for ideal implant placement. In a 5-year cross-sectional study, Benic et al. [38] observed machined implants with simultaneous GBR did not differ from implants placed in native bone with respect to marginal bone height, implant survival and peri-implant soft tissues [38]. These findings were consistent with subsequent studies, where marginal bone loss around implants placed in regenerated extraction sockets using porcine bone remained stable over time as seen with native bone [39,40]. However, in another study, implants placed in sites that received maxillary sinus augmentation demonstrated more MBL, primarily within the first 12 months after functional loading, than implants placed in native bone [41]. In a study

conducted by Jung et al.[42] evaluating the long-term outcome of implants placed with GBR using resorbable and non-resorbable membranes, no significant difference was seen between the two groups and bone levels around the implants [42]. However, the effects of different bone grafts (autografts, allograft, xenograft) and membranes (resorbable, non-resorbable) on the marginal bone around implants needs further evaluation.

The role of occlusal forces on peri-implant bone loss has been controversial and inconclusive. Various studies have been performed to understand the response of peri-implant bone to occlusal load. Frost et al. [43] introduced the hypothesis that bone adapts to certain strain from forces at a steady state; if the strain goes beyond the threshold capacity of the bone, it could lead to fatigue fracture that could eventually lead to marginal bone loss. These forces differ from person to person [43]. To avoid the high stress/strain in the surrounding bone in the adaptation period, Misch et al. [44] introduced the concept of progressive loading of oral implants [44]. A study conducted by Appleton et al. [45] demonstrated that progressively loaded implants had less marginal bone loss than conventionally loaded implants within a similar healing period [45]. Non-axial loads could result in high osteoclastic activity around implants leading to increased marginal bone loss. Miyata et al. [46-48] in a series of experiments, reported that minor occlusal overload did not result in marginal bone loss if applied alone, however, in combination with added ligatures to create experimental peri-implantitis, the summed-up bone loss was greater than with ligatures alone without occlusal overload[46-48]. However, Heitz-Mayfield [49] and colleagues did not find excessive occlusal load to lead to marginal bone loss [49]. Quirynen et al.[50] in a clinical study observing 69 patients with fixed prosthesis or overdentures with a 3-year follow up reported excessive MBL associated with parafunctional habits [50]. However, in a 5-year clinical study, patients with or without signs of occlusal wear presented with equivalent marginal bone levels [51].

The effect of factors such as age, gender, implant size and cantilever prosthesis on MBL around implant supported dentures was investigated in a study that included 126 implants for 36 months [52]. There appeared to be no association between MBL and implant length or diameter. MBL appeared to be more in older female patients and in patients who received cantilevers [52]. In a study by Halg et al.[53] cantilevers on fixed partial dentures did not demonstrate higher implant failure rate and bone loss around supporting implants compared with implants supporting conventional FDPs; however, more technical complications were observed in the cantilever group [53]. In a long term retrospective study, removable prosthesis tend to display more bone loss compared with FDP; none the less, there appears to be a lack of prospective studies to further clarify the effect of removable prosthesis on rate of MBL [54].

Apart from the MBL observed in the initial early remodeling phase associated with the host, implant and prosthetic factors, late MBL is also a key component that is associated with disease process. Peri-implant diseases consist of peri-implant mucositis leading to peri-implantitis. Peri-implant mucositis is a reversible inflammatory reaction in the soft tissues surrounding a functional implant whereas peri-implantitis is an inflammatory reaction associated with loss of supporting bone around an implant in function [55,56]. Different diagnostic parameters were proposed to aid with the identification and diagnosis of peri-implant diseases including increased probing depth over time of >5 mm, presence of BOP and suppuration, and radiographic bone loss of $\geq$ 2.5 mm and implant mobility [57 58]. However, there appears to be a lack of consistent definition in the diagnostic criteria of peri-implant diseases. Recently, as proposed by the 2017 World Workshop on the Classification of Periodontal and Peri-implant diseases, the case definition for peri-implant mucositis entails visual signs of peri-implant inflammation, presence of profuse bleeding and/or suppuration

on probing, increase in probing depths compared to baseline and absence of bone loss beyond crestal bone level changes resulting from initial remodeling. The diagnosis of peri-implantitis should be what is mentioned above along with progressive bone loss in relation to radiographic bone level assessment at 1 year following the delivery of the implant-supported prosthetics reconstructions or in the absence of initial radiographs and probing depths, radiographic evidence of bone level ≥ 3 mm and/or probing depths ≥ 6 mm in conjunction with profuse BoP[56].

Zitzmann et al.[59] reported the prevalence of peri-impantitis, cross sectional studies (including 662 and 216 subjects) reported that peri-implant mucositis occurred in 80% of the subjects and in 50% of the implant sites. Peri-implantitis was identified in 28% and ≥ 56% of subjects and in 12% and 43% respectively of implant sites that were in function for an average of 10 years [59]. A meta-analysis by Derks and Tomasi [60], estimated a prevalence of 14-30% of peri-implantitis. There also appeared to be a positive relationship between prevalence of peri-implantitis and function time and a negative relationship between peri-implantitis and threshold for bone loss [60]. However, the lack of consistency in case definitions affected the reported severity of the diseases thereby affecting the results of the prevalence.

The pattern of bone loss associated with peri-implantitis is characterized by a non-linear progression with the rate of loss increasing over time, with a similar pattern within the same subject [61,62]. Different patterns of bone loss were observed such as (i) low rate of MBL over time (ii) an initial period of slow followed by a rapid loss of bone support (iii) a high rate of initial bone loss followed by almost no bone level change and (iv) a continuous high rate of bone loss leading to a complete loss of bone support [62].

The risk indicators associated with peri-implantitis reported by the consensus report of the sixth European Workshop on Periodontology are poor oral hygiene, history of periodontitis and cigarette smoking [63]. In the 2017 World Workshop, Schwarz et al. [64] described history of periodontitis and poor plaque control/ lack of regular maintenance therapy as possible risk indicators for peri-implantitis [64]. Experimental studies in animals and humans demonstrated that prolonged plaque accumulation around implants leads to a more severe and stronger inflammatory response when compared with that around natural teeth. Tissue destruction at peri-implantitis sites appears to be faster and more extensive than around periodontitis sites [65]. However, the exact disease process and pathway of bacteria around dental implants has not been studied. There is limited evidence on the association of smoking, diabetes, alcohol consumption, genetic traits, and implant surface with peri-implantitis. Further research needs to be performed to determine the association of lack of keratinized mucosa, excess cement, genetic factors, iatrogenic factors, systemic conditions, occlusal overload and titanium particles with peri-implantitis [64,66].

Initial MBL around dental implants is usually associated with the physiologic remodeling associated with surgical trauma, foreign body reaction and establishment of biologic width which could extend approximately up to 1 year after functional loading. This bone loss usually amounts to 1.5 mm - 2 mm in both a horizontal and vertical direction [67-69]. Late marginal bone loss could be associated with pathologic bone loss due to presence of inflammation leading to peri-implantitis. The average bone loss around affected implants after 1 year of function was noted to be 1.68 mm and 32% of the implants appeared to demonstrate bone loss of >2 mm [61]. In a systematic review by Derks and Tomasi [60] , the average bone loss in patients implants exhibiting peri-implantitis was >2 mm [60].

Initial crestal bone loss around dental implants may have a key role in the increased risk of developing peri-implant diseases. Although several studies have previously focused on the investigation of the amount of MBL, what is considered "physiological MBL" during the early stages of wound healing is still unclear. Also unclear is how it affects the long- term stability of the bone around implants, the success of implants, and which are the possible risk indicators at the implant and subject level that could affect this initial MBL. The long-term maintenance of peri-implant bone has been associated with the amount of MBL that occurs in the early stages of wound healing only in one study so far. Galindo-Moreno et al. [70] investigated the association of clinical variables on the development of MBL and also made an attempt to establish a threshold for discriminating between low and high bone loser types and the validity of using 2 mm as a threshold to differentiate between normal and pathological bone loss. They concluded that if the MBL is higher than 0.44 mm at 6 months post loading, MBL progression tends to be significantly higher, with an increased risk of implant failure. They also mention that a new success criterion should be developed based on MBL rates rather than raw MBL data [70].

AIM AND HYPOTHESIS

The **primary aim** of this study is to identify the MBL threshold that occurs during the early stages of wound healing after implant placement that can be associated with a higher risk of peri-implant bone loss during the future function of the implant.

A **secondary objective** of this study is to identify possible risk indicators that could increase the MBL that occurs during the early stages of wound healing after implant placement and during the future function of the implant.

Our **hypothesis** is that implants that demonstrate radiographic MBL of >2 mm, 2 years after functional loading, have higher bone loss within 12 months of implant placement compared to implants showing MBL of ≤2 mm.

MATERIALS AND METHODS

Study Design

This study was a retrospective case-control study analysing MBL on peri-apical radiographs of dental implants placed in the Department of Periodontology at Tufts University School of Dental Medicine from January 1, 2004 to December 31, 2014.

Up to 8,000 records were reviewed for the purposes of this study.

The inclusion and exclusion criteria for the implants were listed as below:

Inclusion criteria

- Single/multiple implants placed in maxilla or mandible
- Single unit or multi-unit implant-supported restorations.
- Patients with periapical radiographs that permit analysis of marginal bone loss around implants that have been restored prosthetically. (For our primary analysis we used the most recent radiograph within 12 months after implant placement and the most recent available 2 years after loading from the axiUm records of each patient). (All other radiographs that happened between the above periods and were available in axiUm records were collected for secondary analysis of early wound healing process after implant placement.)

Exclusion criteria:

- Implants without any periapical radiographs within 12 months after implant placement.
- Implants without any periapical radiographs 2 years after implant loading.

- Implants with radiographs that do not permit analysis of MBL around implants (for instance radiographs with a very high distortion or a poor diagnostic quality).

Radiographic analysis:

Periapical radiographs were used that already existed in patients' records in axiUm and MBL was compared around implants that happened during 12 months after implant placement and at least 2 years after functional loading. Panoramic radiographs were excluded due to high distortion rate. Bitewings were excluded due to inability to identify extent of first bone-implant contact (fBIC) and failure to measure entire length of implant. For secondary analysis, any radiographs that were also available during the wound healing stages (healing abutment connection, prosthesis installation) were collected. Therefore, radiographic and patient data from records through July 11, 2017 were included in this study.

Linear bone measurements were made on the mesial and distal surfaces of each implant from reproducible reference points, the implant shoulder, for the determination of bone loss. A horizontal line was drawn through the shoulder of the implant, and the distance from this line to the first bone-to-implant contact was measured at the mesial and distal site of the implant. Radiographic bone loss was determined after calculating the distortion rate of radiographs using the known dimensions of the implant as reference values (Figure 1).

The **different time points of during wound healing** during which radiographic analysis was conducted were the following:

T1- Implant placement

T2- Healing abutment connection

T3- Prosthesis insertion

T4- 2 years after functional loading (prosthesis insertion)

All information from clinical records regarding subject-related factors, implant-related factors and prosthesis installation were used.

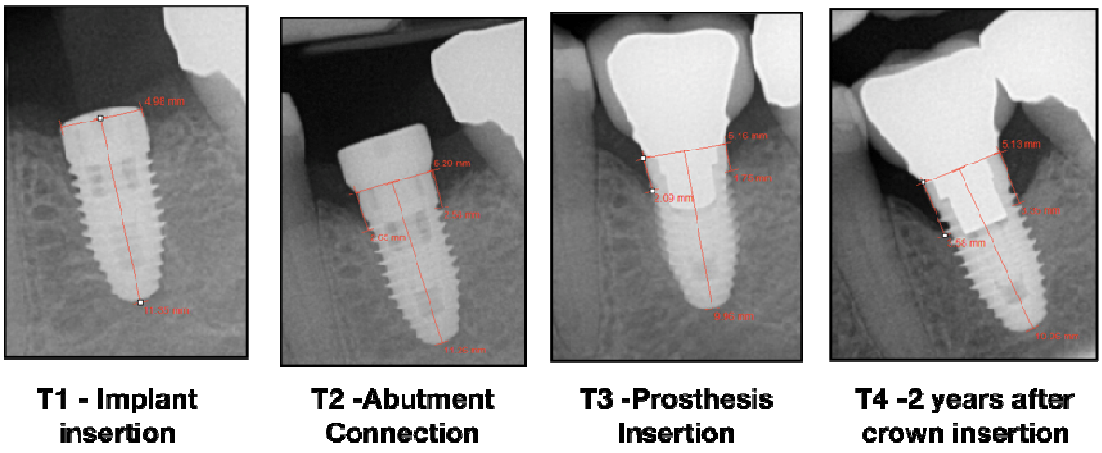

Figure 1: **Measurements recorded for dental implants on peri-apical radiographs.** Linear measurements were recorded from implant shoulder to first alveolar bone crest to implant contact at mesial and distal surfaces.

Data collection from clinical records (for secondary analysis):

All available information from axiUm patients' records regarding both subject- and implant-related factors that could be possible risk indicators for MBL were collected. This information was collected at the time of implant placement, at the time that the radiograph was available within 12 months after implant placement and at the time that the radiograph was available 2 years after implant loading (Table 1).

Table 1: Data recorded for subject-factors and implant-factors

Subject Factors	Implant Factors
Age	Implant site: Maxilla Mandible
Gender: Male Female	Implant site: Anterior Posterior
Systemic disease: Hypertension Diabetes Hypercholesteremia	Timing of Implant placement: Immediate Delayed
Medications: Fish oil Vitamin D Statin	Abutment connection: One stage Two stage
H/o radiation: Yes No	Implant prosthesis connection: Internal hex External hex
H/o periodontitis: Yes No	Prosthesis retention: Screw retained Cement retained
Bisphosphonate use: Yes No	Bone Regeneration: Yes No
Steroid use: Yes No	Membrane: Resorbable Non - resorbable
H/o previous implant failure: Yes No	Depth of implant placement: Supra-crestal Crestal Sub-crestal
H/o of smoking: Current Former None	Type of prosthesis: Fixed Removable
	Prosthesis Unit: Single-unit Multi-unit
	Healing abutment
	Cover screw exposure: Yes No
	Tooth – implant distance
	Implant Diameter/Length

STATISTICAL ANALYSIS

Sample Size Calculation:

Power calculations were performed using nQuery Advisor (version 7.0). To compare differences in MBL during the healing period between implants with high MBL (MBL ≥ 2 mm) and low MBL (MBL <2 mm) a sample size was calculated using the following assumptions: a type I error of 5%; a type II error of 1%; a MBL of 1.21 mm (SD = 1.064) for the high MBL group; a mean MBL of 0.253 mm (SD = 0.342) for the low MBL group. A minimum sample size was determined to be 27 implants per group for a total of 54 implants.

To obtain a more representative sample of implants in the study, we reviewed up to 8,000 records, provided from the IT Department of TUSDM after IRB approval. This sample of implants provided greater than 99% power for the analysis.

Data Analysis:

Descriptive statistics (means and standard deviations for continuous items, counts and percentages for categorical data) were calculated for overall implant level and subject level as well as between T4 MBL groups of ≤ 2 mm and >2 mm. Generalized estimating equation for implant level and chi square test for subject level were used to perform analysis. Differences in bone level healing were assessed with a mixed effects linear regression model. A multivariate mixed effects linear regression with backwards selection was used to identify significant covariates. Confounding factors were adjusted with a multivariable mixed effects model. All p-values less than 0.05 were considered statistically significant. The statistical software Stata (version 13.1) was used for the analysis.

RESULTS

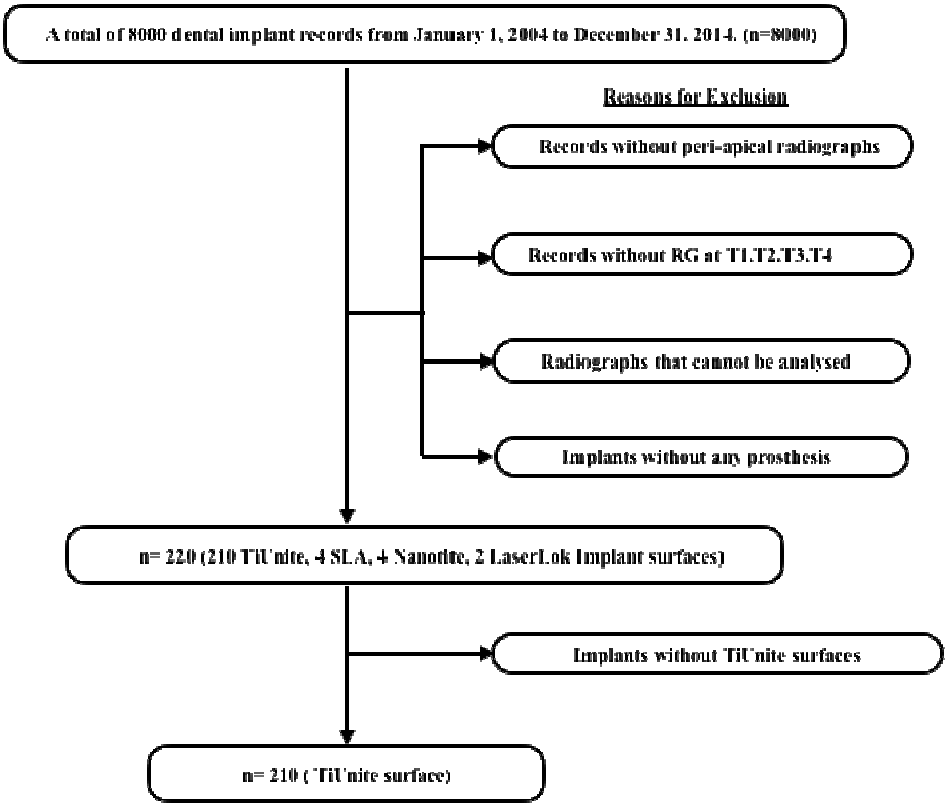

Figure 2: Flow chart depicting the screening process
T1 – implant insertion, T2 – abutment connection, T3 – prosthesis insertion and T4 – 2 years post loading.

Our research protocol was previously reviewed and approved by our Health Sciences Institutional Review Board (IRB #12632) (Figure 2). A total of 8000 records of dental implants of patients was provided from Tufts IT department for the Department of Periodontology at Tufts University School of Dental Medicine from December 2004 to January 2014. Records were excluded on the basis of missing radiographs at 4 time points (T 1, T2, T3, T4), non-periapical radiographs, radiographs that could not be analyzed and implants that did not have any prosthesis insertion. 220 implants were selected out of which

10 were excluded on the basis of implant surface (4 SLA, 4 Nanotite, 2 LaserLok) due to insufficient sample size with other implant surfaces to conduct a statistically significant comparison and to establish a homogenous sample. A sample size of 210 implants and 153 subjects was included in our final analysis. The implants were further separated into two groups depending on the amount of MBL demonstrated at T4; T4 ≤2 mm and >2 mm.

Overall descriptive statistics at subject-level:

There was a total of 153 subjects in our analysis. The average age of the subjects was 65.16 years ± 1.044years. There was a total of 92 (60.1%) males and 61(39.9%) female subjects. 117(76.5%) subjects were non- smokers, 12(7.8%) were current smokers and 24 (15.7%) were former smokers. 75(49.0%) subjects had a history of treated periodontitis and 78 (51.0%) did not have a history of periodontitis (Table 2).

Table 2: Overall subject-level descriptive statistics

Co-variates	Frequency	Percent (%)
Age	65.16 years	SD ±1.04
Gender:		
Male	92	60.1%
Female	61	39.9%
Smoking Status:		
None	117	76.5%
Current	12	7.8%
Former	24	15.7%
History of Periodontitis:		
Yes	75	49.0%
No	78	51.0%
Total	153	100%

Overall descriptive statistics at implant-level:

A total sample size of 210 implants with only TiUnite surface were selected. 138 (65.7%) implants were placed in the maxilla and 72 (34.3%) were in the mandible. The majority of dental implants were posterior (149-70.95%). 121 implants (57.6%) were placed in regenerated bone and 89 (42.4%) implants were placed in native bone. 69 (32.9%) implants were placed with simultaneous graft placement and 141(67.1%) implants had no bone graft. 110 (52.4%) implants were screw-retained and 100 (47.6%) implants were cement-retained. 46 (21.9%) implants were narrow diameter, 81(38.6%) regular diameter, 79 (37.6%) wide and 4 (1.9%) extra wide diameter implants. The average duration of function of the implants was 4.18 years ± 0.15 years (Table 3).

Table 3: Overall implant-level descriptive statistics:

Co-variates	Frequency (n)	Percent (%)
Implant Location		
Maxilla	138	65.7%
Mandible	72	34.3%
Implant Location		
Anterior	61	29.05%
Posterior	149	70.95%
Regenerated Bone:		
Yes	121	57.6%
No	89	42.4%
Graft at time of implant placement		
Yes	69	32.9%
No	141	67.1%
Prosthesis connection		
Screw-retained	110	52.4%
Cement-retained	100	47.6%
Implant Diameter:		
Narrow	46	21.9%
Standard	81	38.6%
Wide	79	37.6%
Extra-Wide	4	1.9%
Total	210	100%
Duration of Function	4.18 years	SD ± 0.148

Descriptive statistics at subject-level based on T4 groups:

Chi square analysis and generalized estimating equations revealed no statistically significant difference between descriptive statistics at subject-level and implant-level based on T4 groups of ≤ 2 mm at T4 and >2 mm (Table 4 & 5).

Table 4: Descriptive statistics based on T4 groups at subject-level:

	T4 ≤2mm		T4>2mm	
Co-Variates	**Frequency**	**Percent**	**Frequency**	**Percent**
Age	66.58 years	SD ± 1.41	63.29 years	SD ± 1.57
Gender: Male Female	 52 31	 62.7% 37.3%	 40 30	 57.1% 42.9%
Smoking Status: None Current Former	 66 7 10	 79.5% 8.5% 12.0%	 49 7 14	 70.0% 10.0% 20.0%
History of Periodontitis: Yes No	 37 46	 44.6% 55.4%	 37 33	 52.9% 47.1%
Total	83	100%	70	100%

** No statistically significant difference between the two groups

Table 5: Descriptive Statistics based on T4 groups at implant-level:

	T4 ≤2mm		T4>2mm	
Co-variates	**Frequency**	**Percent**	**Frequency**	**Percent**
Implant Location:				
Maxilla	81	69.23%	57	61.29%
Mandible	36	30.77%	36	38.71%
Implant Location:				
Anterior	30	25.64%	31	33.33%
Posterior	87	74.36%	62	66.67%
Regenerated Bone:				
Yes	66	53.7%	57	59.4%
No	57	46.3%	39	40.6%
Graft at the time of implant placement:				
Yes	42	34.1%	31	32.3%
No	81	65.9%	65	67.7%
Prosthesis connection:				
Screw retained	64	52.0%	49	51.0%
Cement retained	59	48.0%	47	49.0%
Implant Diameter:				
Narrow	24	19.5%	24	25.0%
Standard	49	39.8%	36	37.5%
Wide	48	39.0%	34	35.4%
Extra Wide	2	1.5%	2	2.1%
Total	117	100%	93	100%
Duration of function	4.15 years	SD ± 2.37	4.21 years	SD ± 1.86

** No statistically significant difference between the two groups

Difference in the average mesial bone level, distal bone level and overall bone level from T1, T2, and T3 between the two t4 groups (≤2 mm and >2 mm)

The following section describe the results for MBL between T1, T2 and T3 (early stages of wound healing) and implants that demonstrated MBL of ≤2 mm at and >2 mm at T4 for mesial, distal and overall bone levels after adjusting for age, gender, smoking status/history, periodontitis, anterior/posterior, maxilla/mandible, implant diameter, screw/cement retained, native/regenerated, and implant + bone graft and implant without bone graft. Our results demonstrated that the mesial MBL (from T1, T2, and T3) was higher for implants that

demonstrated MBL of >2 mm at T4 (1.04 mm ± 0.80 mm) compared to implants that demonstrated MBL of ≤2 mm at T4 (0.57 mm ± 0.69 mm). The difference was statistically significant after adjustment and non-adjustment of co-variates (p <0.001) (Table 6).

Table 6: Mixed effects model to evaluate difference between groups T4≤2 mm and T4>2 mm and marginal bone loss from T1, T2 and T3 at mesial bone level:

Mesial bone level	N	Mean bone loss at T4 (mm)	SD	Mean Bone Loss Progression (T1-T3) (mm)	SD	Min	Max	p-value
T4 ≤ 2mm	119	0.96	0.70	0.57	0.69	-1.80	2.50	<0.001
T4 >2mm	91	2.88	1.12	1.04	0.80	-2.17	3.49	
Total	210	1.79	1.31	0.78	0.77	-2.17	3.49	

At distal MBL, implants that had MBL of ≤2 mm and >2 mm at T4 demonstrated mean MBL of 0.60 mm ± 0.73 mm and 1.17 mm ± 0.78 mm respectively from T1 – T3 with a statistically significant difference between the two groups (p <0.001) after adjustment and non-adjustment of covariates (Table 8). Our results demonstrated that the distal MBL (from T1, T2, and T3) was higher for implants that demonstrated MBL of >2 mm at T4 compared to implants that demonstrated MBL of ≤2 mm at T4.

Table 7: Mixed effects model to evaluate difference between groups T4≤2 mm and T4>2 mm and marginal bone loss from T1, T2 and T3 at distal bone level:

Distal bone level	N	Mean bone loss at T4 (mm)	SD	Mean Bone Loss Progression (T1-T3)(mm)	SD	Min	Max	p-value
T4 ≤ 2mm	114	1.13	0.67	0.60	0.73	-2.11	3.23	<0.001
T4 >2mm	96	2.86	1.04	1.18	0.78	-0.61	3.38	
Total	210	1.92	1.21	0.86	0.80	-2.11	3.38	

Overall MBL also showed statistically significant difference between the two groups with an overall MBL of 0.59 mm ± 0.67 mm and 1.12 mm ± 0.71 mm from T1-T3 for implants that had MBL of ≤2 mm and >2 mm at T4 respectively, after adjustment and non-adjustment of co-variates ($p<0.001$)(Table 9). Our results demonstrated that the overall MBL (from T1, T2, and T3) was higher for implants that demonstrated MBL of >2 mm at T4 compared to implants that demonstrated MBL of ≤2 mm at T4.

Table 8: Mixed effects model to evaluate difference between groups T4≤2 mm and T4>2 mm and marginal bone loss from T1, T2 and T3 at overall bone level:

Overall bone level	N	Mean bone loss at T4 (mm)	SD	Mean Bone Loss Progression (T1-T3)(mm)	SD	Min	Max	p-value
T4 ≤ 2mm	117	1.08	0.63	0.59	0.67	-1.96	2.87	<0.001
T4 >2mm	93	2.83	1.02	1.12	0.71	-0.59	3.43	
Total	210	1.86	1.20	0.82	0.73	-1.96	3.43	

Pattern of Marginal Bone Loss

Figure 3 below illustrates in a bar chart the findings reported in the tables above (Tables 7, 8, 9). We can observe that groups with MBL of >2mm at T4 appear to have higher MBL at T1 – T3 for mesial, distal and overall MBL.

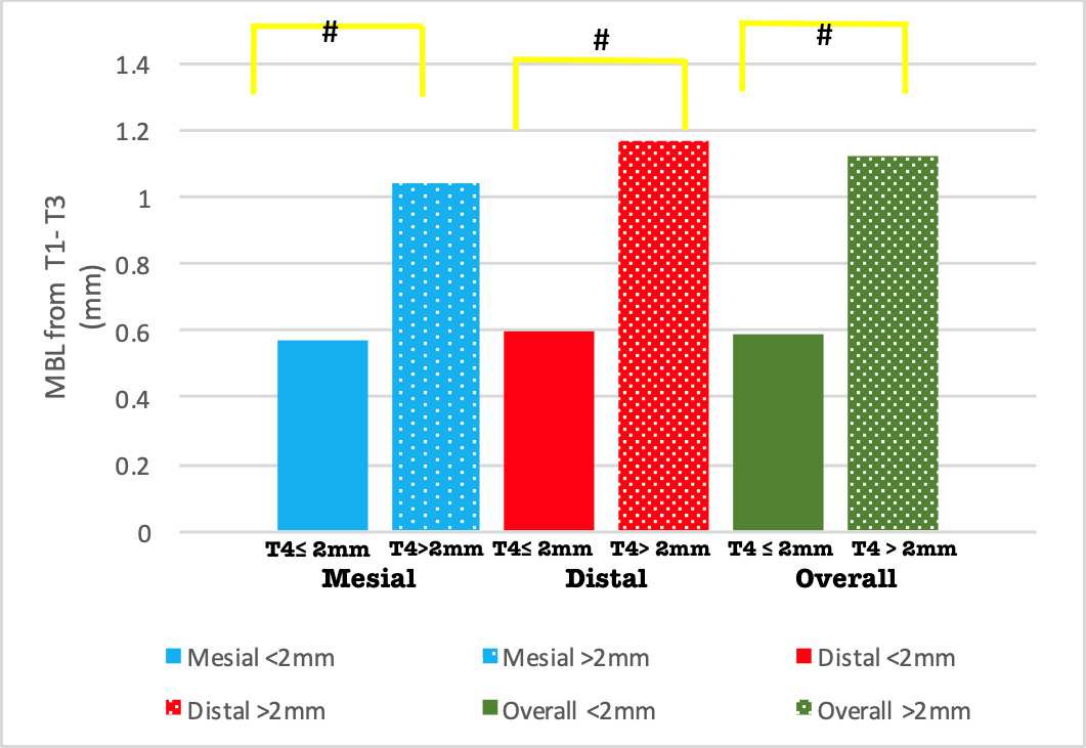

Figure 3: Depicts relationship between MBL at T4 for ≤2mm and >2mm and MBL from T1- T3 for mesial, distal and overall MBL.
- p value <0.001

Figure 4 below further depicts the trend of MBL from the time of implant insertion up to 2 years post-loading of the implant. The highest amount of MBL is observed from healing abutment insertion (T2) to implant-supported prosthesis insertion (T3) followed by a relatively stable MBL up to 2 years post implant function (T4).

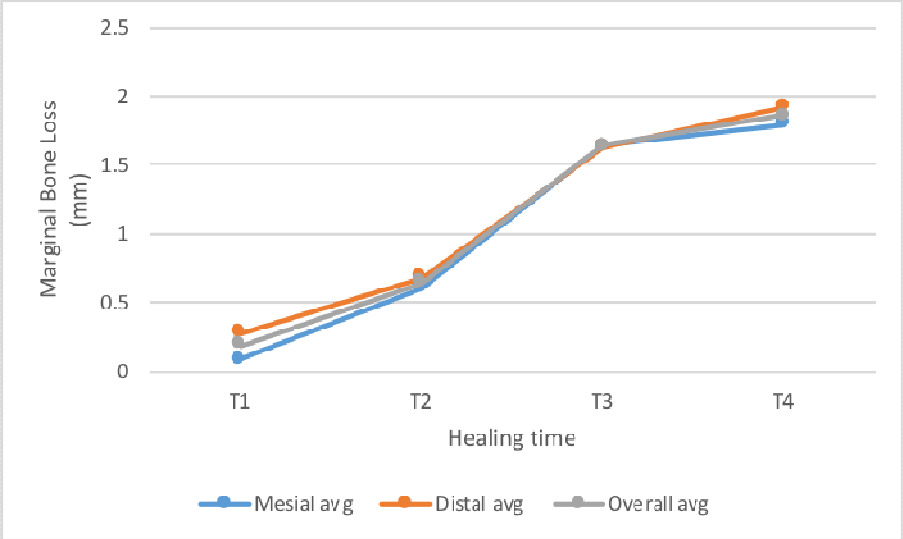

Figure 4: Pattern of MBL from T1 to T4 during different healing times: T1, T2, T3, T4

Figures 5 - 7 below depict the pattern of MBL for the two T4 groups (>2 mm and ≤2 mm of MBL from T1 to T4) at the mesial, distal and overall MBL. A linear accelerating pattern of MBL for the T4>2 mm group was observed at all time points of healing. The pattern of bone loss for the T4 group with ≤2 mm of MBL demonstrated a lower rate and a decreased amount of MBL compared to the >2 mm T4 group from T1 – T3, followed by a reduction in MBL at T4.

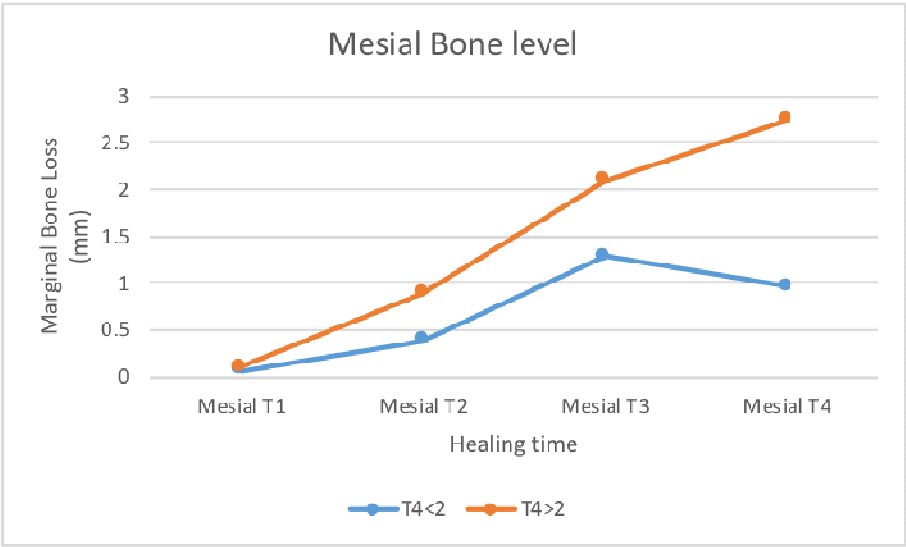

Figure 5: Pattern of MBL from T1 to T4 in relationship with the healing times: T1, T2, T3, T4 (based on the two T4 groups for mesial bone level).

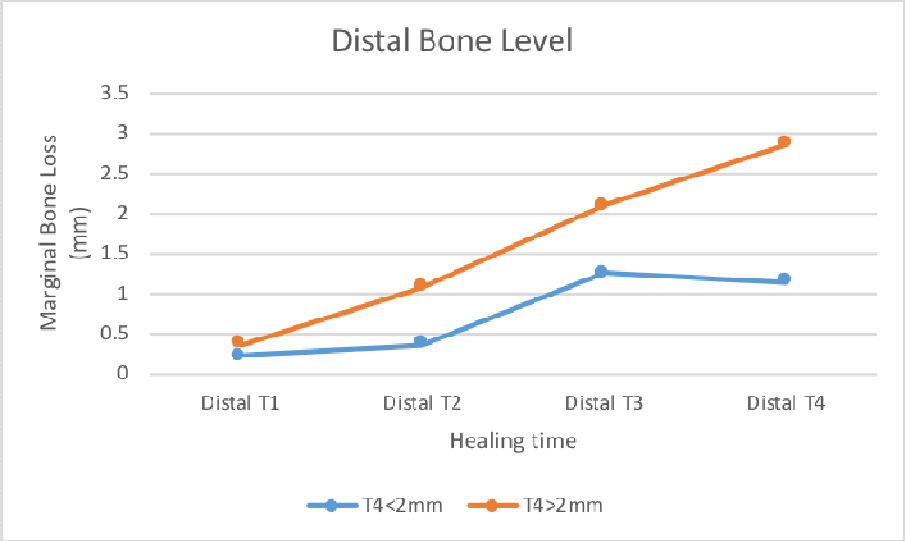

Figure 6: Pattern of MBL from T1 to T4 in relationship with the healing times: T1, T2, T3, T4 (based on the two T4 groups for distal bone level).

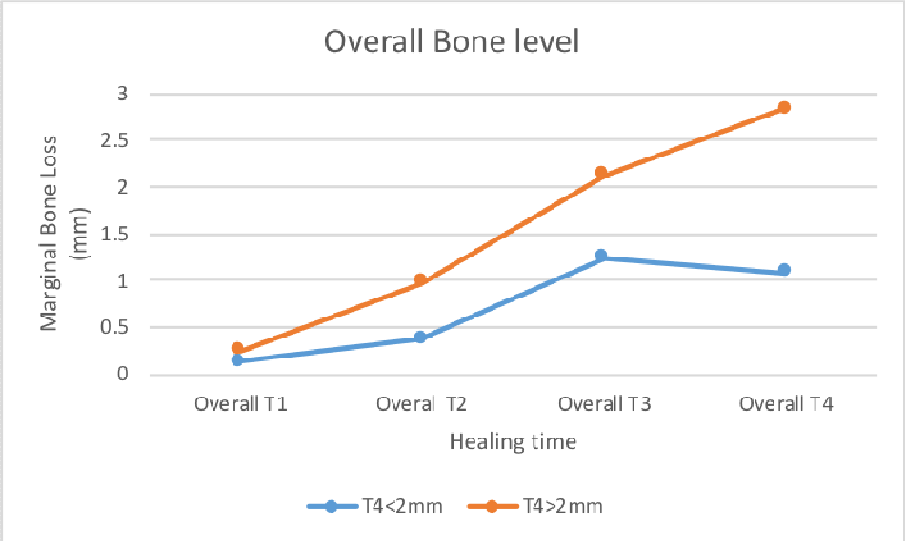

Figure 7: Pattern of MBL from T1 to T4 in relationship with the healing times: T1, T2, T3, T4 (based on the two T4 groups for overall bone level).

Association of Risk Indicators with Marginal Bone Loss:

For mesial MBL, implant location (maxilla vs mandible) and implant diameter (regular and wide) had a statistically significant p-value after adjustment ($p = 0.009$) and non-adjustment ($p= 0.001$) of co-variates. At distal MBL, history of periodontitis had a significant p-value without adjustment ($p = 0.004$) and implant/graft group after adjustment ($p=0.009$). For the overall bone level group, implant location (maxilla vs mandible) with and without adjustment ($p = 0.019$ and $p = 0.017$), and history of periodontitis without adjustment ($p = 0.045$) had a statistically significant p-value. Implant with simultaneous graft group with adjustment ($p = 0.03$), wide diameter implant compared to narrow one after adjustment ($p = 0.039$) and regular diameter implant compared to narrow one without adjustment ($p=0.043$) also demonstrated a statistically significant difference (Table 9).

Table 9: Association of Risk Indicators with Marginal Bone Loss

	Mesial bone level		Distal bone level		Overall bone level	
	Adjusted	**Non-adjusted**	**Adjusted**	**Non-adjusted**	**Adjusted**	**Non-adjusted**
T4 ≤2mm vs T4 >2mm	**≤ 0.001**	**≤ 0.001**	**≤ 0.001**	**≤ 0.001**	**≤ 0.001**	**≤ 0.001**
Age	0.758	0.935	0.347	0.630	0.283	0.761
Gender	0.236	0.366	0.946	0.890	0.424	0.670
Periodontitis	0.164	0.092	0.078	**0.038**	0.146	**0.045**
Smoking status	ab-0.590 ac-0.478 bc-0.372	ab- 0.597 ac- 0.391 bc- 0.316	ab-0.878 ac-0.747 bc-0.741	ab -0.825 ac- 0.626 bc-0.893	ab- 0.499 ac- 0.931 bc- 0.540	ab- 0.755 ac- 0.482 bc- 0.467
Maxilla vs mandible	**0.009**	**0.01**	0.060	0.066	**0.019**	**0.017**
Ant/ post	0.296	0.731	0.151	0.388	0.115	0.624
Prosthesis retention	0.856	0.650	0.466	0.470	0.765	0.892
Native vs regenerated bone	0.716	0.824	0.381	0.529	0.412	0.689
Implant/bone graft	0.533	0.722	**0.009**	0.112	**0.031**	0.283
Implant diameter	de- 0.052 **df– 0.008** dg- 0.242 ef- 0.222 eg- 0.645 fg- 0.923	**de- 0.012** **df- 0.013** dg- 0.576 ef- 0.97 eg- 0.725 fg- 0.733	de- 0.326 df- 0.439 dg- 0.368 ef- 0.860 eg- 0.579 fg- 0.538	de- 0.242 df-0.817 dg-0.745 ef- 0.216 eg- 0.925 fg- 0.804	de-0.095 **df- 0.039** dg- 0.256 ef-0.459 eg- 0.583 fg- 0.729	**de 0.043** df- 0.129 dg- 0.627 ef - 0.504 eg- 0.817 fg - 0.959

p-values reported after adjusting for co-variates and after not adjusting for co-variates. Significant p-values are highlighted in bold. Smoking status key: a = non- smoker, b= current c = former.

Implant diameter key: d= narrow, e= Regular, f= Wide g= extra wide

Reference groups: Implant Diameter – narrow, and smoking status- non-smoker

Association of Marginal Bone Loss with implant-level and subject-level factors:

The effect of subject-level factors such as age, gender, smoking history (current, former, none) and history of treated periodontitis and implant-level factors such as implant location, prosthesis retention, native vs regenerated bone, implant diameter and bone graft at the time of implant placement and its effect on MBL from T1-T3 was analyzed for mesial, distal and overall marginal bone levels using a mixed effects model. Access to a large database of EHR allowed us to collect data for a variety of factors. However, in order to avoid losing statistical power and the effect of co-linearity between co-variates, specific important factors only were selected for analysis. For subject-level, age and gender were selected to establish demographics of the patient and history of periodontitis and smoking were selected to confirm the findings of previous studies [71,72]. For implant-level factors we chose implant location (anterior / posterior, maxilla / mandible), native vs regenerated bone, implant diameter, bone graft at the time of implant placement and prosthesis retention (screw vs cement retained) in order to cover important aspects that can affect early stages of wound healing (i.e. location of placement, choice of size, quality of bone and finally the type of retention that could affect MBL after prosthesis insertion). Further analysis will be performed on the remaining subject-level and implant-level factors in future studies.

Association of Marginal Bone loss with subject-level factors:

The mean distal bone loss from T1- T3 in patients who had a history of periodontitis demonstrated higher MBL of 0.97 mm ± 0.86 mm compared to 0.75 mm ± 0.72 mm in those with a negative history of periodontitis without adjusting for covariates. The difference was statistically significant ($p < 0.038$) (Table 10). The overall average bone loss from T1-T3 in patients with a history of periodontitis 0.92 mm ± 0.76 mm was significantly higher than patients without a history of periodontitis 0.72 mm ± 0.69 mm without adjustment of co-

variates (p = 0.045) (Table 11). The statistical significance was lost after adjustment was done (p= 0.078). All other subject level factors demonstrated no statistically significant effect on bone loss after adjustment and non-adjustment of co-variates.

Table 10: Mixed effects model to evaluate difference in the average distal bone level from T1, T2 and T3 in subjects with history of periodontitis

History of Periodontitis	N	Mean	SD	min	max	p-value (non-adjusted)	p-value (adjusted)
No	102	0.75	0.72	-2.11	3.16	0.038	0.078
Yes	108	0.97	0.86	-1.63	3.38		
Total	210	0.86	0.80	-2.11	3.38		

Table 11: Mixed effects model to evaluate difference in the average overall bone level from T1, T2 and T3 in subjects with history of periodontitis

History of Periodontitis	N	Mean	SD	min	max	p-value (non-adjusted)	p-value (adjusted)
No	102	0.72	0.69	-1.96	2.63	0.045	0.078
Yes	108	0.92	0.76	-1.20	3.44		
Total	210	0.82	0.73	-1.96	3.44		

Association of Marginal Bone loss with implant-level factors:

The effect of implant factors- implant location, bone graft before and at the time of implant placement, implants placed in native bone vs regenerated bone, type of prosthesis retention (screw or cement retained) and implant diameter on marginal bone loss around dental implants was evaluated. There was a statistically significant difference between mesial marginal bone levels from T1-T3 and implant location i.e. maxilla and mandible (p = 0.009). Implants placed in the mandible demonstrated a higher mean bone loss 0.95 mm ± 0.64 mm than implants placed in maxilla 0.68 mm ± 0.82 mm both after adjustment and non-

adjustment of co-variates. (p = 0.009) and (p=0.01) (Table 12). A statistically significant difference was observed between mesial marginal bone levels from T1-T3 and between narrow and wide diameter implants(p<0.008). Narrow diameter implants demonstrated higher marginal bone loss from T1-T3, (1.05 mm ± 0.97 mm) compared to regular (0.68 mm ± 0.73 mm) and wide diameter implants (0.70 mm ± 0.67 mm). These differences were statistically significant (p=0.012) and (p=0.013) (Table 13).

For distal marginal bone loss from T1-T3, there was a statistically significant difference between implants that were placed with simultaneous graft (1.0 mm ± 0.87 mm) demonstrating higher MBL than implants without bone graft (0.79 mm ± 0.76 mm) (p < 0.009). However, the statistical significance was lost when adjustment was performed (p = 0.112) (Table 14).

When the effect of implants factors on overall marginal bone loss was analysed, implants placed in the mandible demonstrated higher overall marginal bone loss 0.98 mm ± 0.63 mm than those placed in the maxilla 0.73 mm ± 0.76 mm (p < 0.02 with and without adjustment) (Table 15). Narrow diameter implants demonstrated statistically higher (1.02 mm ± 0.94 mm) marginal bone loss from T1-T3 compared to regular diameter implants (0.70 mm ± 0.68 mm) after co-variates were not adjusted (p = 0.043). Narrow diameter implants also demonstrated higher MBL compared to wide diameter implants (0.82 mm ± 0.64 mm) (p = 0.04) after adjusting for co-variates (Table 16). All other diameters were not statistically significant. Also, implants with simultaneous graft placement demonstrated a statistically significant higher amount of MBL that implants without graft (0.92 mm ± 0.86 mm vs 0.78 mm ± 0.66 mm) (p = 0.03 after adjustment) (Table 17).

All other implant factors did not reach statistical significance for mesial, distal and overall marginal bone loss from T1-T3 when covariates were adjusted.

Table 12: Mixed effects model to evaluate difference in the average mesial bone level from T1, T2 and T3 between the maxilla and mandible.

Location	N	Mean	SD	min	max	p-value (non-adjusted)	p-value (adjusted)
Maxilla	138	0.68	0.82	-2.17	3.49	0.011	0.009
Mandible	72	0.95	0.64	0	2.55		
Total	210	0.82	0.77	-2.17	3.49		

Table 13: Mixed effects model to evaluate difference in the average mesial bone level from T1, T2 and T3 between the implant diameters.

Implant Diameter	N	Mean	SD	min	max	p-value (non-adjusted)	p-value (adjusted)
Narrow	46	1.05	0.97	-1.80	3.49	0.012	0.052
Regular	81	0.68[a]	0.73	-1.13	2.55		
Wide	79	0.70[b]	0.67	-2.17	2.10	0.013	0.008
Extra wide	4	0.84	0.43	0.40	1.42		
Total	210	0.77	0.77	-2.17	3.49		

** a= Narrow vs Regular b = Narrow vs wide

Table 14: Mixed effects model to evaluate difference in the average distal bone level from T1, T2 and T3 between implant/bone graft group

Implant + Graft	N	Mean	SD	min	max	p-value (non-adjusted)	p-value (adjusted)
No	141	0.79	0.76	-2.11	3.16	0.112	0.009
Yes	69	1.00	0.88	-1.04	3.38		
Total	210	0.86	0.80	-2.11	3.38		

Table 15: Mixed effects model to evaluate difference in overall bone level from T1, T2 and T3 between the maxilla and mandible

Location	N	Mean	SD	min	max	p-value (non-adjusted)	p-value (adjusted)
Maxilla	138	0.73	0.77	-1.96	3.44	0.017	0.019
Mandible	72	0.99	0.63	0	2.63		
Total	210	0.82	0.73	-1.96	3.44		

Table 16: Mixed effects model to evaluate difference in overall bone level from T1, T2 and T3 between implant diameters

Implant Diameter	N	Mean	SD	min	max	p-value (non adjusted)	p-value (adjusted)
Narrow	46	1.03	0.94	-1.96	3.44	0.043	
Regular	81	0.70[a]	0.68	-1.08	2.87		
Wide	79	0.82[b]	0.64	-1.20	2.63		0.039
Extra wide	4	0.83	0.34	0.60	1.34		
Total	210	0.82	0.73	-1.96	3.44		

a = Narrow Vs regular b= Narrow Vs Wide

Table 17: Mixed effects model to evaluate difference in overall bone level from T1, T2 and T3 between implant/bone graft group.

Implant + Graft	N	Mean	SD	min	max	p-value (non adjusted)	p-value (adjusted)
No	141	0.78	0.66	-1.96	2.63	0.283	0.031
Yes	69	0.91	0.86	-1.20	3.44		
Total	210	0.82	0.73	-1.96	3.44		

DISCUSSION

The primary hypothesis of our study was that dental implants that demonstrated radiographic MBL of > 2 mm, two years after functional loading, demonstrated higher MBL within 12 months after implant placement compared to implants showing radiographic MBL of ≤ 2 mm. This hypothesis was confirmed for mesial, distal, and overall average MBL. The group of implants demonstrating MBL of > 2 mm appeared to have twice the amount of bone loss within first 12 months of implant insertion than the group with MBL of ≤ 2 mm. This is a critical finding as it confirms the theory that the rate and pattern of bone remodelling within the first 12 months is crucial for the future stability of the dental implant.

There is a lack of consensus in what is considered to be acceptable early MBL of dental implants. Adell at al. [68] observed MBL of around 1-1.5 mm in the first year after implant-supported prosthesis insertion followed by 0.05 - 1 mm MBL annually after the first year [68]. Roos et al. [73] demonstrated not more than 1.0 mm of MBL after first year of function followed by not more than 0.2 mm of annual bone loss thereafter. Johannson and Ekfeldt demonstrated an MBL of 0.4 mm at the first year and annual following 0.1 mm MBL rate. Hobo et al reported MBL of 1-1.5 mm after first year of implant placement [73].

However, it is important to mention that the implants used in these previous studies were mainly machined surface Branemark implants. Those implants are no longer used in clinical practice and therefore the MBL threshold levels determined then might not be applicable around the more modern implants that have been introduced with different surface treatments. In our study, the implants that were included were pre-dominantly TiUnite surface in order to obtain a homogeneous sample for analysis. Anodic oxidation is reported to

effectively increase the thickness of the TiO2 layer from 17-200 nm in conventional titanium implants to 600-1000 nm also creating a nanoscale surface characteristic which propagates adhesion, proliferation and extracellular matrix deposition of human gingival fibroblasts. Human studies have demonstrated a significantly greater BIC around anodized implants in both maxilla and mandible compared to machined titanium implants [74]. However, due to insufficient sample size of implants with different surface characteristics, the MBL around different implant surfaces could not be analysed in our study. Furthermore, the implants included in the study were implants with an internal connection, therefore the effect of micro-gap on the marginal bone levels could not be analysed.

The results of our study were consistent with the findings of a study conducted by Galindo-Moreno et al. [70] that found that implants with increased MBL rates at early stages (healing and immediate post-loading periods) are likely to reach MBL values of >2 mm at 18 months. MBL rates at 6 months around an implant of more than 0.44 mm are an indication of peri-implant bone loss progression [70]. In addition, in a recent study, Acharya et al.[75] performed an exploratory analysis of factors that influence annual rates of peri-implant MBL. They concluded that the preloading rate of bone loss (RBL) was strongly predictive of later bone levels and the models for RBL placement-loading and MBL placement-review were very similar. Together these data indicated an "early bone loser type" who is more predisposed to worse MBL after prosthesis insertion and function [75].

Another important finding in our study was that when analysing MBL from implant insertion (T1) until 2 years post-loading (T4), the most significant increase in the MBL appeared to occur during the period between healing abutment connection (T2) and prosthesis insertion (T3). There appeared to be a slow rate of MBL from implant insertion (T1) to healing

abutment insertion followed by a rapid rate of MBL until prosthesis is loaded (approximately 1 mm) followed by a relatively steady/low rate of MBL after loading.
This was true for implants that were placed in a two-staged approach. Furthermore, for mesial, distal and overall bone level based on T4 levels, the >2mm group demonstrated a linear accelerating pattern of bone loss from T1 to T4 whereas, the ≤2mm group demonstrated a significantly lower rate of MBL with a similar pattern of MBL up to T3, followed by a steady rate and in some cases a reduction in MBL from T3 to T4.

In this study, we observed 210 implants from 153 subjects consisting of purely TiUnite surface implants. For our primary analysis, the MBL was calculated at four time points; T1- Implant insertion, T2- healing abutment connection, T3- implant-supported prosthesis insertion and T4- 2 years post-functional loading. The early stages of wound healing constituted the first 12 months after implant placement viz. from the time of implant placement (T1) until prosthesis insertion (T3). There are numerous factors that have been reported in literature that could attribute to the physiological bone remodelling around dental implants after implant insertion (T1) such as remodelling due to surgical trauma, biologic width formation, metallic leakage from the dental implant or foreign body reaction evoked by the implant [5].

The connection of a healing abutment to an implant (T2) could further affect the MBL due to the position of the implant abutment junction creating a microgap that could serve as a reservoir for bacterial proliferation in the peri-implant tissue and bone. The presence of a microgap could lead to a mismatch during functioning of the implant and abutment leading to microwear also known as micromotion. This micromotion could lead to wear and reduction in the precise adaptation leading to an increase in microgap contributing to microleakage[76].

According to the trend in MBL in our study, the highest amount of MBL seemed to occur between T2 – T3, i.e. between healing abutment connection to implant prosthesis insertion. This could be explained first by the biologic width formation at the time of abutment insertion. As demonstrated by Hermann et al. [77] bone remodelling occurs rapidly during the early healing phase of implant placement for non-submerged implants and after abutment connection for submerged implants [77]. Another factor that could contribute to the higher rate of MBL from T2 – T3 could be the abutment connection and disconnection rate until the final prosthesis has been loaded, a phenomenon frequently observed in clinical practice. In 1997, Abrahammson et al. [78] conducted an experiment on 5 beagle dogs to evaluate the effect of abutment removal and subsequent reconnection. Their findings confirmed that abutment dis/re- connection compromised the mucosal barrier and resulted in a more apically positioned zone of connective tissue integration leading to additional marginal resorption to allow for a connective tissue barrier of proper dimension to form [78]. The findings of a recent meta-analysis further confirmed that abutment disconnection/reconnection may affect peri-implant MBL by 0.19 mm and greater [76,79]. The number of abutment connections and disconnections appear to play a significant effect on the peri-implant bone loss with the greatest mean differences in MBL with abutment disconnection of more than three-four times. Further randomized controlled trials and human studies need to be performed to validate this theory. Furthermore, poor plaque control and patient compliance or prolonged periods of healing abutment retention till a final prosthesis is inserted could also contribute to a high MBL.

Occlusal stress and occlusal overload after prosthesis insertion (T3) has been proposed in literature as the cause of MBL; however, it lacks conclusive evidence. In our study though,

the MBL after loading appears to be relatively stable and with a low rate of progression as compared to the time-period between abutment connection and prosthesis insertion.

As a secondary analysis, the association of selected subject-level factors and implant-level factors such as age, gender, smoking status and history of periodontitis, location (maxilla or mandible/ anterior or posterior), implants placed in native or regenerated bone, bone graft at the time of implant placement, implant diameter and type of prosthesis retention (screw or cement retained crown) with MBL were evaluated, in order to reduce the chance of co-linearity. Further studies will be performed assessing the remaining factors for which data were collected.

At a subject-level, history of periodontitis demonstrated a statistically significant difference at distal and overall MBL when covariates were not adjusted. Implants placed in patients with a history of periodontitis demonstrate higher MBL than those without. This finding is in accordance with the study by Heitz-Meyfield et al.[72], where patients with a history of periodontitis reported a higher risk of peri-implant bone loss and implant failure with an odds ratio of 3.1 to 4.7 [72]. The study also reported smoking to be a significant risk factor for adverse implant outcome; however, smoking was not a significant factor for MBL in our study. These findings were also consistent with the results of a meta-analysis [80].

In our study, age and gender did not demonstrate a significant effect on early MBL around dental implants. In a systematic review by Bryant et al.[81] an increase in age did not appear to affect stability of crestal bone levels around dental implants. They included studies that show 0.2-0.3 mm of bone loss in 80-90 year- old individuals after one year of function. They also made an association of an effect of age on osseointegration if it is combined with other

ailments and medical conditions such as diabetes, osteoporosis etc. This was contrary to the findings of Negri et al. [82] where female patients in the age group of 50-60 years demonstrated peak of MBL. They hypothesize the cause to be due to decrease in bone mass density with increase in age as well as correlation with menopause onset and hormonal changes that occur during that age period in females [82]. Mumcu et al. also found no differences in MBL between males and females in the first 24 months [52]. In our study however, there was no significant effect of gender on MBL.

Several studies have reported smoking to be a risk factor for implant placement. In a study by Nitzan et al. [71] smokers exhibited more MBL 0.15mm than non-smokers (0.047 mm). They also reported that smoking had a greater effect on MBL in the maxilla than in the mandible [71]. These findings were consistent with another study by Penarrocha et al. [83] where MBL assessed in panoramic radiographs, peri-apical radiographs and digital radiographs demonstrated higher MBL in smokers who smoked 11-20 cigarettes per day, especially in implants in the maxilla [83]. These findings were inconsistent with the findings in our study where no statistically significant association was found in smokers versus non-smokers and former smokers and MBL. However, the number of smokers in our study were only 12 without a significant power to make valid conclusions about the effect of smoking.

Upon analysing the association of implant factors: implant location, implant diameter and bone graft at the time of implant placement had a statistically significant association with MBL. In our study implants placed in the mandible showed a significantly higher MBL than those placed in the maxilla for mesial, distal and overall average MBL. Narrow diameter implants showed a statistically significantly higher amount of early marginal bone loss for mesial and overall average bone levels. This is consistent with the findings of a retrospective

radiographic study, where narrow diameter implants appeared to have been associated with more early MBL than regular diameter ones [84]. A three dimensional finite element analysis revealed that higher stress values and concentration areas were observed around narrow diameter implants as compared to wider diameter implants [85]. However, Ormanier et al. [86] in another 3D finite element analysis found that narrow diameter implants in combination with low density bone and compromised peri-implant bone thickness could adversely affect marginal bone stability [86].

In certain cases, bone graft at the time of implant placement could be required due to deficient buccal bone. In our study, implants placed with bone graft demonstrated higher MBL with distal and overall bone levels. This could be due to the resorption of the bone graft that ultimately happens. However, the resorption rate of the graft could depend on the source of bone graft; autogenous, allogenic or xenograft. Further analysis needs to be performed to verify association between source of bone graft and the rate of MBL. Another possible explanation could be that the residual bone graft particles that are not incorporated to the bone where the implant is osseointegrated might act as "foreign body" materials, triggering peri-implant inflammation and crestal bone resorption. However, implants placed in regenerated bone did not demonstrate a statistically significant difference of MBL compared to implants placed in native bone in our study. This is consistent with the findings of Barone et al. [39] where implants placed in augmented sites demonstrated similar survival rates and MBL in native and regenerated bone [39].

Regarding implant location, implants placed in the mandible demonstrated significantly higher MBL than implants placed in the maxilla in our study. Our findings were consistent with the data recorded in a study conducted by Ajanovic et al. [87] after one year of loading, the

mean bone loss around mandibular implants was 0.701 mm and around maxillary implants was 0.627 mm; however, their results did not reach a statistical significance. In their study, implants placed in the anterior area demonstrated higher bone loss than implants placed in the posterior one [87]. Our study did not find any statistically significant difference between the two locations.

A systematic review by Bryant et al. [81] reported that regardless of jaw site, mean crestal bone levels surrounding Branemark implants were relatively stable over time. Additionally, implants in the maxilla and the mandible demonstrated bone loss of 0.08 mm and 0.05 mm respectively with no significant difference. They also concluded that implant success will not necessarily be compromised by jaw sites with low bone density [81]. Further studies with long term follow up needs to be conducted to further confirm the findings of our study in regards with jaw site.

In another study looking at Ti Unite Surface (Nobel Biocare implants) implant location; maxilla or mandible, and in anterior or posterior region of the jaw did not have an effect on early MBL. However, Henry et al. [88] demonstrated higher implant failure rate in implants placed in the maxilla than in the mandible for both completely and partially edentulous arches. Also, more than 50% of the failed implants were also placed in type 3 to type 4 bone (posterior maxilla) [88]. The author attributes the failure due to a combination of poor bone density and quality along with improper surgical handling as well as fixture length.

Cement-retained crowns have been documented to exhibit higher MBL due to the excess cement that could possibly attract microbes and potentially change the microflora to one consistent with periodontitis [7]. This was contrary to the findings of Koller et al. [89] where

cement-retained crowns exhibited 1.55 mm of MBL and screw-retained crowns exhibited 1.30 mm of MBL after approximately 5 years of functional loading. However, Nissan et al. [90] found a higher rate of MBL around screw-retained (1.4 mm) crowns than cement-retained (0.6 mm) crowns [89]. In our study, there was no statistically significant difference between cement-retained crowns and screw-retained crowns on early MBL. Furthermore, the effect of splinted and non-splinted crowns on early MBL needs to be evaluated in future studies.

A significant strength of our study was the large sample size with an increased power. Having access to a large patient EHR database helped us in recording multiple implant-level and subject-level factors as recorded in the patients' EHR . The large data collected can be used to generate new hypothesis for further studies. Although only a limited number of factors were analysed in this study, further studies will be performed to evaluate the remaining factors.

One of the limitations of the study could be its retrospective study design. There could have been a chance of selection bias by grouping the implants in groups of >2 mm and <2 mm at T4 on the basis of radiographs, since the peri-apical radiographs were not standardized and that could have led to an error in identifying the correct positon of fBIC, especially in anterior radiographs due to inconsistent angulation. Also, bucco-lingual measurements could not be evaluated.

In addition, due to the increased number of co-variates, the statistical significance may be lost when adjusting for co-variates. The presence of several confounding factors could also have led to a reduced statistical significance of the implant- and subject-level factors. Retrospective studies are observational studies only that cannot determine a cause and effect

relationship between factors and their outcome. Therefore, in order to further elucidate the relationship between the aforementioned factors, prospective cohort or randomized controlled trials need to be performed. Also, the exact cause and nature of wound healing process after implant placement needs to further be studied.

Peri-apical radiographs are associated with an over-estimation of bone defects [91], which could have affected the accuracy of the mesial and distal bone levels. However, we were adjusting MBL measurement by calculating the distortion of the radiographs referring to the actual length of the implants. Also, the lack of standardization of radiographs could have skewed the measurements. However, measurements on peri-apical radiographs are more accurate than on panoramic ones due to the higher distortion rate [91]. According to Albrektsson et al. [92] peri-apical radiographs are an important clinical tool to be used at implants placement, loading and thereafter [92].

Another possible limitation is the possibility of reporting bias. Some of the factors that were evaluated such as history of smoking and history of periodontitis were reported by the patients and observations of the clinician. Since the clinicians were mainly residents at a post-graduate program ranging from first to third year, there could have been a chance of bias in reporting history of periodontitis. Also, the severity of periodontal disease was not recorded or evaluated. Also, patients could have been untruthful about their smoking status as a lot of them are aware that smoking could affect the surgeon's decision to perform surgery. Also, a large sample size of our study were non-smokers, therefore it is difficult to reach conclusive results in regards to the association of smoking on early MBL. In addition, the implants were placed in an academic environment by post-graduate students of different clinical experiences and level. The surgeries could have taken longer than an average dental implant surgery in

private practice performed by an experienced operator. The lack of surgical experience and longer surgical times keeping the flap elevated and bone exposed could have had an effect on the outcome of the wound healing process after implant placement. Future studies from dental implants placed in clinical practices are needed in order to compare or validate our results.

The information acquired from this study has several clinical implications. Patients who have undergone recent implant surgery should be monitored frequently. Oral hygiene instructions need to be reviewed at each appointment and clinicians should expose peri-apical radiographs in order to observe and compare the MBL periodically during the first 12 months after implant placement. A clear protocol for radiographic examination and type of radiographs that are needed for patients with implants is urgently needed. In case an accelerated early MBL is detected stringent and more intense periodontal maintenance protocols are indicated. Clinicians need to pay increased attention while implants are only at the phase with healing abutments waiting for the prosthesis insertion since MBL can occur at an accelerated pace. Furthermore, this study may help clinicians determine the timing of treatment.

Within the limitations of the study, the rate of MBL within the first 12 months of implant placement and during the early stages of wound healing may be associated with a higher risk of peri-implant bone loss during the future function of the implant. Further studies need to be performed in order to evaluate the association of the remaining subject-level and implant-level factors and its effect on and to understand how early MBL can increase or predict the risk of long-term progression of bone loss. Future prospective cohort studies or randomized controlled trials are needed.

CONCLUSIONS

1. Dental implants showing radiographic marginal bone loss >2 mm at least two years after functional load have higher bone loss within 12 months after implant placement compared to those with bone loss ≤ 2 mm.

2. History of periodontitis might be associated with a higher marginal bone loss in early stages of wound healing.

3. Implants placed in the mandible are associated with a higher early marginal bone loss than implants placed in the maxilla.

4. Implants requiring a simultaneous bone graft placement demonstrate a higher marginal bone loss in the early stages of wound healing.

5. Narrow diameter implants are associated with higher early marginal bone loss as compared to regular and wide diameter implants.

APPENDIX A

Table 1: Data recorded for subject-factors and implant-factors

Subject Factors	Implant Factors
Age	Implant site: Maxilla Mandible
Gender: Male Female	Implant site: Anterior Posterior
Systemic disease: Hypertension Diabetes Hypercholesteremia	Timing of Implant placement: Immediate Delayed
Medications: Fish oil Vitamin D Statin	Abutment connection: One stage Two stage
H/o radiation: Yes No	Implant prosthesis connection: Internal hex External hex
H/o periodontitis: Yes No	Prosthesis retention: Screw retained Cement retained
Bisphosphonate use: Yes No	Bone Regeneration: Yes No
Steroid use: Yes No	Membrane: Resorbable Non - resorbable
H/o previous implant failure: Yes No	Depth of implant placement: Supra-crestal Crestal Sub-crestal
H/o of smoking: Current Former None	Type of prosthesis: Fixed Removable
	Prosthesis Unit: Single-unit Multi-unit
	Healing abutment
	Cover screw exposure: Yes No
	Tooth – implant distance
	Implant Diameter/Length

Table 2: Overall subject level descriptive statistics:

Co-variates	Frequency	Percent (%)
Age	65.16 years	SD ±1.04
Gender: Male Female	 92 61	 60.1% 39.9%
Smoking Status: None Current Former	 117 12 24	 76.5% 7.8% 15.7%
History of Periodontitis: Yes No	 75 78	 49.0% 51.0%
Total	153	100%

Table 3: Overall implant level descriptive statistics:

Co-variates	Frequency (n)	Percent (%)
Implant Location: Maxilla Mandible	 138 72	 65.7% 34.3%
Implant Location: Anterior Posterior	 61 149	 29.05% 70.95%
Regenerated Bone: Yes No	 121 89	 57.6% 42.4%
Graft at time of implant placement: Yes No	 69 141	 32.9% 67.1%
Prosthesis connection: Screw-retained Cement-retained	 110 100	 52.4% 47.6%
Implant Diameter: Narrow Standard Wide Extra-Wide	 46 81 79 4	 21.9% 38.6% 37.6% 1.9%
Total	210	100%
Duration of Function	4.18 years	SD ± 0.148

Table 4: Descriptive statistics based on T4 groups at subject-level:

	T4 ≤2mm		T4>2mm	
Co-Variates	**Frequency**	**Percent**	**Frequency**	**Percent**
Age	66.58 years	SD ± 1.41	63.29 years	SD ± 1.57
Gender:				
Male	52	62.7%	40	57.1%
Female	31	37.3%	30	42.9%
Smoking Status:				
None	66	79.5%	49	70.0%
Current	7	8.5%	7	10.0%
Former	10	12.0%	14	20.0%
History of Periodontitis:				
Yes	37	44.6%	37	52.9%
No	46	55.4%	33	47.1%
Total	83	100%	70	100%

Table 5: Descriptive Statistics based on T4 groups at implant-level:

	T4 ≤2mm		T4>2mm	
Co-variates	**Frequency**	**Percent**	**Frequency**	**Percent**
Implant Location:				
Maxilla	81	69.23%	57	61.29%
Mandible	36	30.77%	36	38.71%
Implant Location:				
Anterior	30	25.64%	31	33.33%
Posterior	87	74.36%	62	66.67%
Regenerated Bone:				
Yes	66	53.7%	57	59.4%
No	57	46.3%	39	40.6%
Graft at the time of implant placement:				
Yes	42	34.1%	31	32.3%
No	81	65.9%	65	67.7%
Prosthesis connection:				
Screw retained	64	52.0%	49	51.0%
Cement retained	59	48.0%	47	49.0%
Implant Diameter:				
Narrow	24	19.5%	24	25.0%
Standard	49	39.8%	36	37.5%
Wide	48	39.0%	34	35.4%
Extra Wide	2	1.5%	2	2.1%
Total	117	100%	93	100%
Duration of function	4.15 years	SD ± 2.37	4.21 years	SD ± 1.86

Table 6: Mixed effects model to evaluate difference between groups T4≤2 mm and T4>2 mm and marginal bone loss from T1, T2 and T3 at mesial bone level:

Mesial bone level	N	Mean bone loss at T4 (mm)	SD	Mean Bone Loss Progression (T1-T3) (mm)	SD	Min	Max	p-value
T4 ≤ 2mm	119	0.96	0.70	0.57	0.69	-1.80	2.50	< 0.001
T4 >2mm	91	2.88	1.12	1.02	0.80	-2.17	3.49	
Total	210	1.79	1.31	0.78	0.77	-2.17	3.49	

Table 7: Mixed effects model to evaluate difference between groups T4≤2 mm and T4>2 mm and marginal bone loss from T1, T2 and T3 at distal bone level:

Distal bone level	N	Mean bone loss at T4 (mm)	SD	Mean Bone Loss Progression (T1-T3)(mm)	SD	Min	Max	p-value
T4 ≤ 2mm	114	1.13	0.6	0.60	0.73	-2.11	3.23	< 0.001
T4 >2mm	96	2.86	1.0	1.17	0.78	-0.61	3.38	
Total	210	1.92	1.2	0.86	0.80	-2.11	3.38	

Table 8: Mixed effects model to evaluate difference between groups T4≤2 mm and T4>2 mm and marginal bone loss from T1, T2 and T3 at overall bone level:

Overall bone level	N	Mean bone loss at T4 (mm)	SD	Mean Bone Loss Progression (T1-T3)(mm)	SD	Min	Max	p-value
T4 ≤ 2mm	117	1.08	0.63	0.59	0.67	-1.96	2.87	< 0.001
T4 >2mm	93	2.83	1.02	1.12	0.71	-0.59	3.43	
Total	210	1.86	1.20	0.82	0.71	-1.96	3.43	

Table 9: Association of Risk Indicators with Marginal Bone Loss

	Mesial bone level		Distal bone level		Overall bone level	
	Adjusted	**Non-adjusted**	**Adjusted**	**Non-adjusted**	**Adjusted**	**Non-adjusted**
T4 ≤2mm vs T4 >2mm	**≤ 0.001**	**≤ 0.001**	**≤ 0.001**	**≤ 0.001**	**≤ 0.001**	**≤ 0.001**
Age	0.758	0.935	0.347	0.630	0.283	0.761
Gender	0.236	0.366	0.946	0.890	0.424	0.670
Periodontitis	0.164	0.092	0.078	**0.038**	0.146	**0.045**
Smoking status	ab-0.590 ac-0.478 bc-0.372	ab- 0.597 ac- 0.391 bc- 0.316	ab-0.878 ac-0.747 bc-0.741	ab -0.825 ac- 0.626 bc-0.893	ab- 0.499 ac- 0.931 bc- 0.540	ab- 0.755 ac- 0.482 bc- 0.467
Maxilla vs mandible	**0.009**	**0.01**	0.060	0.066	**0.019**	**0.017**
Ant/ post	0.296	0.731	0.151	0.388	0.115	0.624
Prosthesis retention	0.856	0.650	0.466	0.470	0.765	0.892
Native vs regenerated bone	0.716	0.824	0.381	0.529	0.412	0.689
Implant/bone graft	0.533	0.722	**0.009**	0.112	**0.031**	0.283
Implant diameter	de- 0.052 **df– 0.008** dg- 0.242 ef- 0.222 eg- 0.645 fg- 0.923	**de- 0.012** **df- 0.013** dg- 0.576 ef- 0.97 eg- 0.725 fg- 0.733	de- 0.326 df- 0.439 dg- 0.368 ef- 0.860 eg- 0.579 fg- 0.538	de- 0.242 df-0.817 dg-0.745 ef- 0.216 eg- 0.925 fg- 0.804	de-0.095 **df- 0.039** dg- 0.256 ef-0.459 eg- 0.583 fg- 0.729	**de 0.043** df- 0.129 dg- 0.627 ef - 0.504 eg- 0.817 fg - 0.959

Table 10: Mixed effects model to evaluate difference in the average distal bone level from T1, T2, and T3 in subjects with history of periodontitis

History of Periodontitis	**N**	**Mean**	**SD**	**min**	**max**	**p-value (non-adjusted)**	**p-value (adjusted)**
No	102	0.75	0.72	-2.11	3.16	0.038	0.078
Yes	108	0.97	0.86	-1.63	3.38		
Total	210	0.86	0.80	-2.11	3.38		

Table 11: Mixed effects model to evaluate difference in the average overall bone level from T1, T2, and T3 in subjects with history of periodontitis

History of Periodontitis	N	Mean	SD	min	max	p-value (non-adjusted)	p-value (adjusted)
No	102	0.72	0.69	-1.96	2.63	0.045	0.078
Yes	108	0.92	0.76	-1.20	3.44		
Total	210	0.82	0.73	-1.96	3.44		

Table 12: Mixed effects model to evaluate difference in the average mesial bone level from T1, T2, and T3 between the maxilla and mandible.

Location	N	Mean	SD	min	max	p-value (non-adjusted)	p-value (adjusted)
Maxilla	138	0.68	0.82	-2.17	3.49	0.01	0.009
Mandible	72	0.95	0.64	0	2.55		
Total	210	0.82	0.77	-2.17	3.49		

Table 13: Mixed effects model to evaluate difference in the average mesial bone level from T1, T2, and T3 between the implant diameters.

Implant Diameter	N	Mean	SD	min	max	p-value (non-adjusted)	p-value (adjusted)
Narrow	46	1.05	0.97	-1.80	3.49		
Regular	81	0.68[a]	0.73	-1.13	2.55	0.012	0.052
Wide	79	0.70[b]	0.67	-2.17	2.10	0.013	0.008
Extra wide	4	0.84	0.43	0.40	1.42		
Total	210	0.77	0.77	-2.17	3.49		

** a= Narrow vs Regular b = Narrow vs wide

Table 14: Mixed effects model to evaluate difference in the average distal bone level from T1, T2, and T3 between implant/bone graft group

Implant + Graft	N	Mean	SD	min	max	p-value (non-adjusted)	p-value (adjusted)
No	141	0.79	0.76	-2.11	3.16	0.112	0.009
Yes	69	1.00	0.88	-1.04	3.38		
Total	210	0.86	0.80	-2.11	3.38		

Table 15: Mixed effects model to evaluate difference in the average bone level from T1, T2, and T3 between the maxilla and mandible

Location	N	Mean	SD	min	max	p-value (non-adjusted)	p-value (adjusted)
Maxilla	138	0.73	0.77	-1.96	3.44	0.02	0.02
Mandible	72	0.99	0.63	0	2.63		
Total	210	0.82	0.73	-1.96	3.44		

Table 16: Mixed effects model to evaluate difference in the average bone level from T1, T2, and T3 between implant diameters

Implant Diameter	N	Mean	SD	min	max	p-value (non adjusted)	p-value (adjusted)
Narrow	46	1.03	0.94	-1.96	3.44	0.043	0.039
Regular	81	0.70[a]	0.68	-1.08	2.87		
Wide	79	0.82[b]	0.64	-1.20	2.63		
Extra wide	4	0.82	0.34	0.60	1.34		
Total	210	0.82	0.73	-1.96	3.44		

** a = Narrow Vs regular – b= Narrow Vs Wide

Table 17: Mixed effects model to evaluate difference in the average bone level from T1, T2, and T3 between implant/bone graft group.

Implant + Graft	N	Mean	SD	min	max	p-value (non adjusted)	p-value (adjusted)
No	141	0.78	0.66	-1.96	2.63	0.28	0.03
Yes	69	0.91	0.86	-1.20	3.44		
Total	210	0.82	0.73	-1.96	3.44		

APPENDIX B

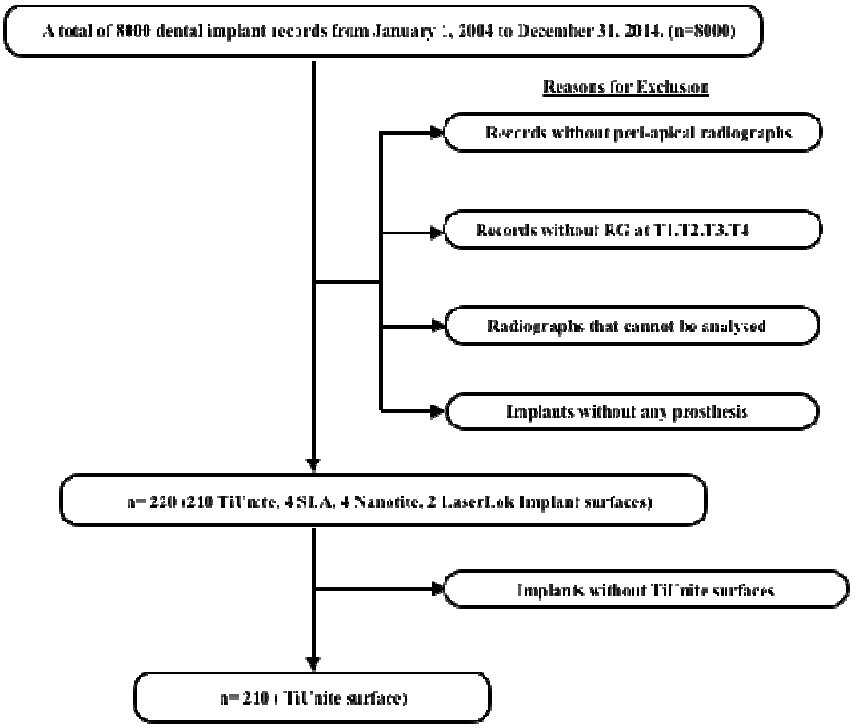

Figure 1: Flow chart depicting the screening process
T1 – implant insertion, T2 – abutment connection, T3 – prosthesis insertion and T4 – 2 years post loading.

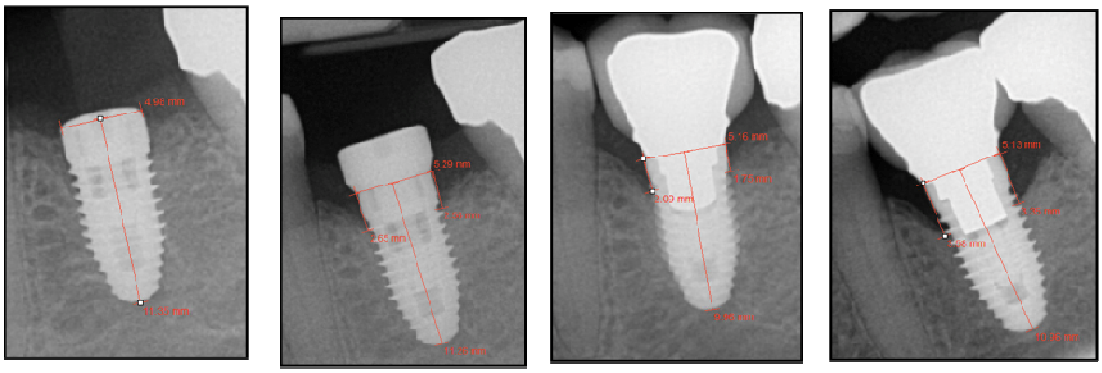

Figure 2: Measurements recorded for dental implants on peri-apical radiographs.
Linear measurements were recorded from implant shoulder to first alveolar bone crest to implant contact at mesial and distal surfaces.

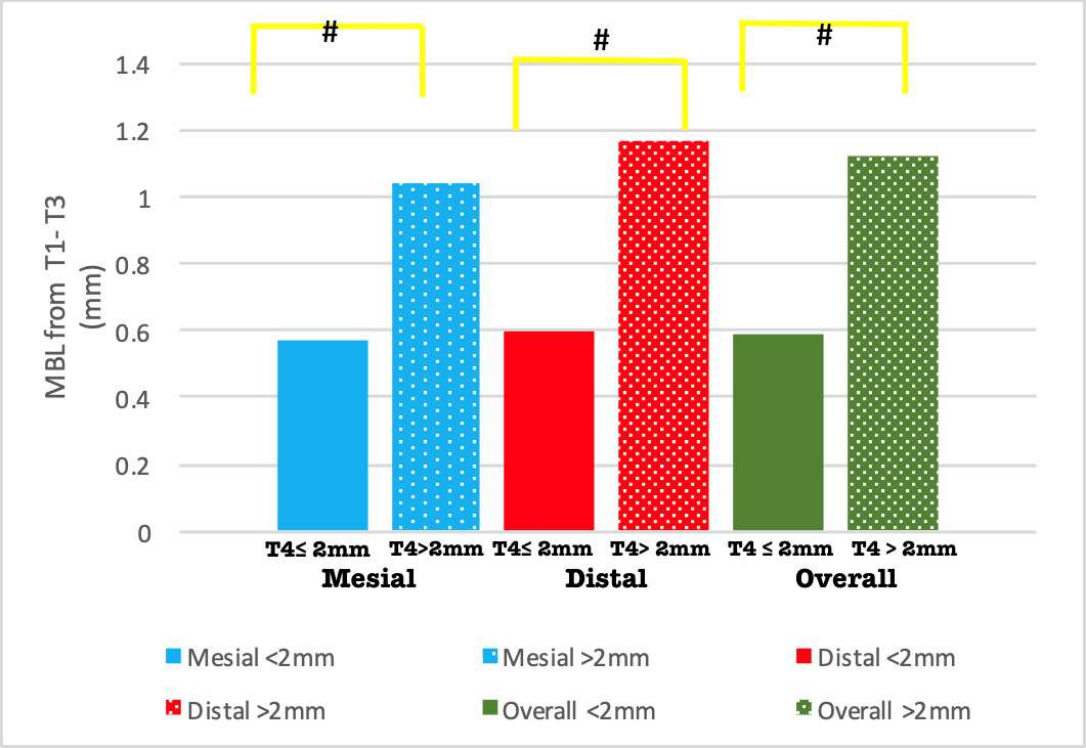

Figure 3: Relationship between bone level at T4 for ≤2mm and >2mm and MBL from T1- T3 for mesial, distal and overall MBL.
- p value <0.001

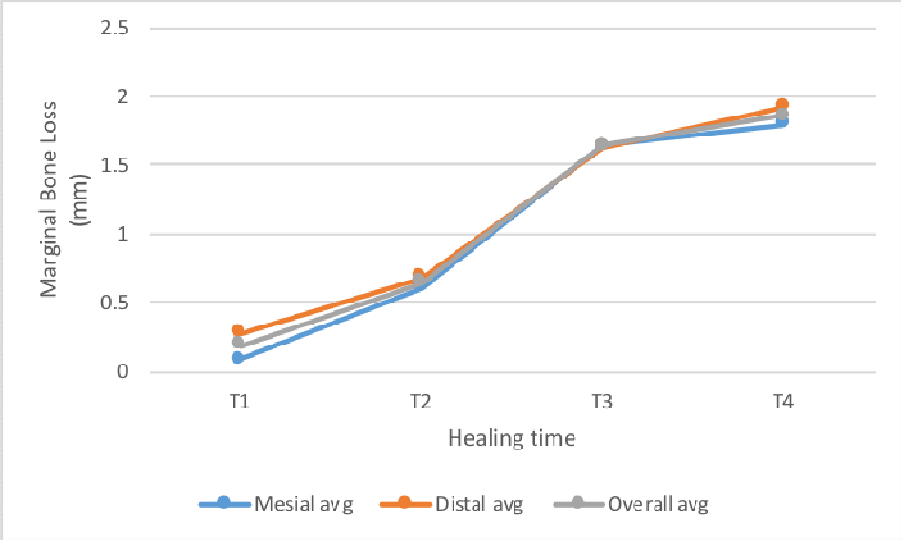

Figure 4: Pattern of marginal bone loss from T1 to T4 in relationship with the healing times: T1, T2, T3, T4

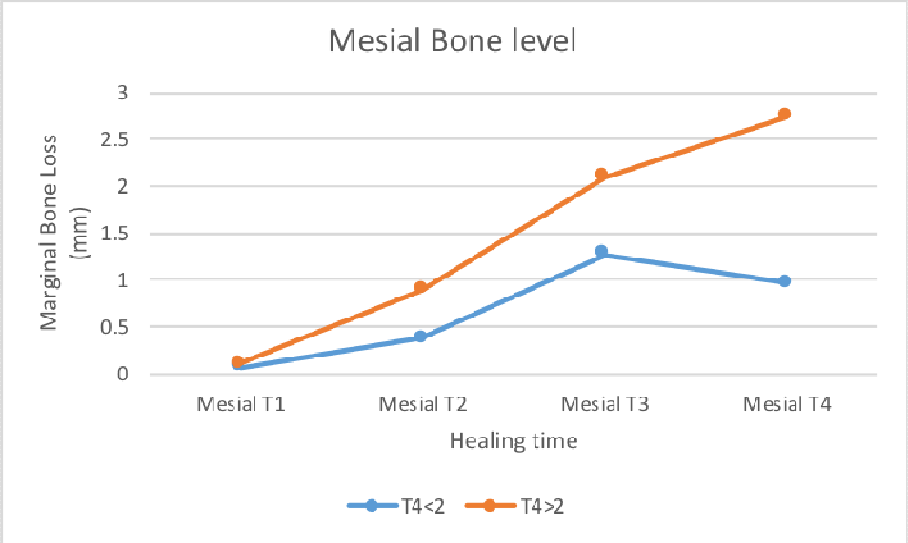

Figure 5: Pattern of marginal bone loss from T1 to T4 in relationship with the healing times: T1, T2, T3, T4 (based on T4 groups for mesial bone level).

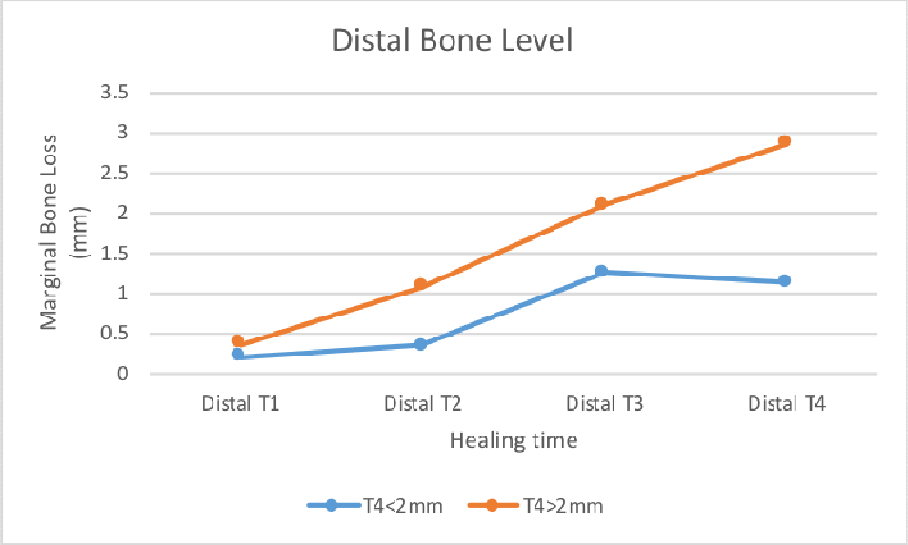

Figure 6: Pattern of marginal bone loss from T1 to T4 in relationship with the healing times: T1, T2, T3, T4(based on T4 groups for distal bone level).

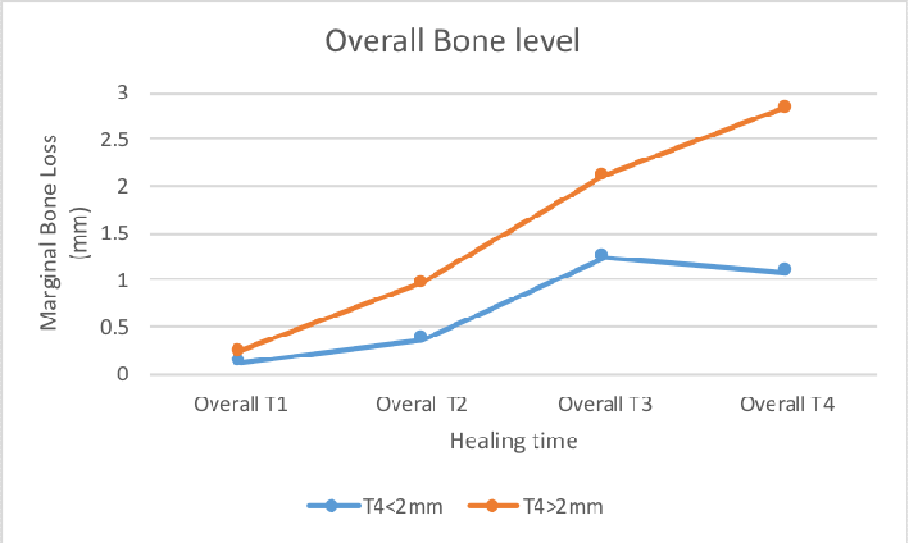

Figure 7: Pattern of marginal bone loss from T1 to T4 in relationship with the healing times: T1, T2, T3, T4(based on T4 groups for overall bone level).

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