Obesity and dental implant treatment: a review

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ABSTRACT

Aim Success of dental implants depends mainly on osseointegration between bone and titanium surface. Since osseointegration relies on balanced bone turnover, it can be assumed that any conditions that interfere with homeostasis of bone modelling/remodeling might be detrimental to survival of dental implants. Obesity has become a serious public health problem, and has been shown to be closely linked to a wide array of pathophysiologic consequences, including insulin resistance or pre-diabetes. Obese-insulin resistance or pre-diabetic condition is characterized by hyperinsulinemia with euglycemia. The impacts of type 2 diabetes mellitus (T2DM) on the success of dental implants and the factors to improve osseointegration in diabetic condition have been thoroughly investigated. Much evidence demonstrated that T2DM impaired the bone healing around dental implants, possibly due to hyperglycemic condition. However, the effect of obese-insulin resistant condition or pre-diabetes on survival of dental implants has not been investigated. This review aims to summarize the current findings of effect of obesity toward bone health and osseointegration of dental implants.
Conclusion The studies favor the relatively negative impact of diabetes on osseointegration, but more scientific studies are necessary.

The relevance between success of dental implant and various systemic conditions has been investigated in many studies during the past decade (1-3). Obesity is a risk factor for insulin resistance and non-insulin dependent diabetes (NIDD) or type 2 diabetes (T2DM) (4, 5). Insulin resistance is a condition where cells fail to respond properly to insulin actions in glucose homeostasis leading to impaired glucose tolerance (IGT) (6). Obese-insulin resistance or pre-diabetic condition is characterized by hyperinsulinemia with normal blood sugar or euglycemia (7, 8). The excessive adipose tissue in obesity results in increased non-esterified fatty acids (NEFA), glycerol, abnormal production of leptin and adiponectin and elevated pro-inflammatory cytokines (9). All of these alterations were found to be partly responsible in the development of insulin resistance, although the underlying biological mechanism of how obesity leads to insulin resistance is still not fully understood (5, 9, 10). The coexistence of insulin resistance, hyperglycemia and decreased insulin production by pancreas results in T2DM (11).

Bone is a metabolically dynamic tissue which undergoes continuous bone formation and resorption throughout life. Bone turnover is a coupling process by the counteraction between osteoblasts (bone formation) and osteoclasts (bone resorption) (12); therefore, any conditions that interfere with normal homeostasis of bone might have detrimental effects on the survival of dental implants (13-15).

Beside the well-known negative association between obesity, insulin resistance, metabolic syndrome and type 2 diabetes (16), the mechanism for the effects of obesity on bone health and quality is not well understood (17). While there was controversy regarding to the impact of obesity on bone in clinical studies (17, 18), *in vivo* and *in vitro* experiments showed that high-fat diet-induced obesity demonstrated reduced bone quantity and quality (19, 20). The impairment of insulin function in obesity was found by many preclinical studies to adversely affect many organs including bone (21-23). Although how obesity leads to bone loss remains largely unknown, more than one mechanism might account for the deleterious effects of obesity on bone health.

Little was known regarding the relationship between obesity and dental implants and its underlying mechanism toward osseointegration. This review aims to summarize current findings regarding to how obesity affects bone health and its possible adverse effect on osseointegration of dental implants.

OBESITY

Obesity is defined as having abnormal or excessive fat that may impair health. Obesity has recently become a major concern for the public health. In 2014, over 600 million people worldwide were obese and this number has more than doubled since 1980 (24). Obesity is no longer considered only as a cosmetic problem (25). Determined by having Body Mass Index (BMI) of more than 30 kg/m^2, Obesity was found to be associated with many chronic diseases such as T2DM (9), hypertension (26), dyslipidemia (27), coronary heart diseases (28, 29), musculoskeletal diseases such as osteoporosis (30, 31) and osteoarthritis (32, 33), and some kinds of cancer (34). Waist circumference (WC) is also used as a good indicator for excessively unhealthy fat accumulation. WC was found to be strongly linked to many obesity-associated risks and was proposed as a more appropriate risk threshold than BMI to predict the cardio-metabolic risk of obesity (35, 36). It is recommended that men and women should have no more than 40 inches and 35 inches of WC respectively to lower their obesity related health risks (37). One of the consequences and metabolic characteristics of obesity is insulin resistance (8). Obese-insulin resistance together with hyperinsulinemia and euglycemia was generally referred to pre-diabetic and it was the principal cause for metabolic syndrome and T2DM (8, 16).

Obesity affects bone health

Obesity was traditionally considered as beneficial to bone due to its mechanical strength of the increasing body mass (38-40). However, whether body mass or excessive fat accumulation from obesity has positive effects on bone formation, and thus protect against osteoporosis, is still controversial according to clinical studies. Some observations in obese individuals found the positive association between high body mass index (BMI) in obesity and bone mineral density (BMD), especially in load bearing areas such as lumbar spine and femur head (41, 42), while other observations revealed the opposite when body fat was taken into consideration besides BMI (43, 44). There were also reports (45, 46) of higher fracture rates among obese population; therefore, obesity's favorable result on bone becomes questionable. At cellular level, there are several possible mechanisms through which obesity can deleteriously affect bone formation. Firstly, adipocytes and osteoblasts are derived from common multi-potential mesenchymal stem cells, so increased adipocytes differentiation and fat accumulation in obesity may result in decreased osteoblasts differentiation and bone formation (20, 47, 48).

Secondly, obesity is associated with systemic low grade chronic inflammation by increasing number of macrophages in adipose tissue and the abnormal cytokines production from adipocytes such as tumor necrosis factor-∝ (TNF-∝), interleukin-6 (IL-6), C-reactive protein (CRP), interleukin 1 (IL-1), leptin and adiponectin (49-53). TNF-∝, IL1, IL6 are important regulators for the process of osteoclast differentiation and associated with bone resorption by stimulating osteoclast activity through modifying receptor activator of (NF)- B RANK/RANK ligand/ osteoprotegerin (OPG) pathway (54). Moreover, it was shown that advancing bone loss at menopause was also accompanied by increased production of these pro-inflammatory cytokines (55). Interestingly, these cytokines or adipokines were also found to induce bone resorption in patients with periodontitis (56).

Thirdly, insulin resistance in obesity might play a role in affecting bone formation and bone resorption by reducing osteoblast signalings (21). Insulin is an important hormone associated with obesity and diabetes; therefore, its possible roles in various organs including bone were extensively investigated (19). Insulin was first discovered in 1922 by Banting and Best, since then, its actions toward various tissues have been extensively studied (57). In normal condition, insulin helps transport blood glucose into cells of different tissues by binding to insulin receptors of cell membrane (58). However, in case of insulin resistance, cells or tissues are resisted to the action of insulin by being less sensitive to insulin receptors leading to abnormal homeostasis of glucose (7, 59). To compensate this event, Langerhans islets beta-cells of pancreas try to produce more insulin in order to reduce hyperglycemia resulting in a condition called compensatory hyperinsulinaemia. If the insulin sensitivity of tissue is not improved through time, the pancreas will at some point stop functioning due to overwork and stop producing insulin and this leads to T2DM (60). Studies found that insulin was associated with the development of bone by stimulating bone biomarkers such as osteocalcin, alkaline phosphatase and collagen (61, 62). In preclinical studies, rats fed by high fat diet not only develop peripheral insulin resistance, but also osteoblast insulin resistance, which leads to reduced osteoblast signalings and, as a result, decrease bone formation, increase bone resorption, produce jaw bone porosity and decrease jaw bone quality by developing osteoporosis (19, 63).

Effect of obesity on bone in clinical studies

Body Mass Index (BMI) is commonly used in clinical studies as an indicator for obesity suggested by WHO (24). BMI can be calculated by the body mass divided by the square of body height. A person is considered obese when he or she has BMI of 30kg/m^2 or more.

A number of studies have found that higher BMI and weight gain can positively alter bone mechanical properties such as bone mineral content (BMC) and bone mineral density (BMD) (39, 41, 42, 45, 46, 64, 65). Dual energy x-ray absorptiometry (DXA) scan is regularly used as a non-invasive tool to examine bone mineral density in clinical studies (66). For example, a study (42) was conducted to examine the relationship between

body weight change and bone mineral density (BMD) in one-year follow up. The weight gain group showed an increase of BMD of lumbar spine comparing to weight loss group. In addition, Oldroyd and colleagues (41) found that increasing BMI up to 35kg/m² was associated with increasing bone mineral density of both lumbar spine and femoral neck. Similar finding by Felson and colleagues (39) also confirmed that the effect of weight and weight change appeared to have positive effects on BMD especially in load bearing sites such as femur and spine, but not significant in other areas. Bone has the ability to adapt to the force produced by muscles by undergoing local mechanical elastic deformation as described by the Mechanostat theory. Under slightly overload strain, bone is capable to adapt itself to the new threshold and increase its mass and strength (67). Furthermore, increased ovarian hormone in obesity

might also play a role in increasing bone mass (68). This might be the explanation for the positive effect of obesity toward bone density in these findings due to increased body weight. Therefore, all of these findings suggested that higher BMI is associated with higher BMD especially in load bearing areas such as spine and femur. Nevertheless, other studies demonstrated contradictory results (43, 69-74). It is well known that obesity is associated with increased visceral fat and insulin resistance and it is one of the risk factors for metabolic syndrome (MetS). Thus, the beneficial effect of higher BMI on bone mineral density in some studies must be interpreted cautiously, as the relatively high adiposity in obese population group and its association to MetS must be taken into consideration (16). A study (71), for example, demonstrated that excess body weight in form of body fat did not appear to be advantageous to bone

Model	Method	Major Findings	Interpretation	Ref.
• Male (n=1263) • Age: >50years	• Cross-sectional analysis • Dual energy X ray absorptiometry for BMD analysis • spine L1-L4, Femoral neck BMD	• higher BMI. Higher BMD, association up to BMI=35kg/m² • BMI>35kg/m², no association between BMI & BMD	• BMD is positively associated with higher BMI but not beyond 35kg/m²	(41)
• 4288 total subjects • obese Female (n=1056) • obese Male (n=229) • mean age 66years	• cross sectional analysis • DXA for analysis BMD of hip and spine	• Prevalence of osteoporosis is less in obese compared to overweight & normal categories • BMI↑, risk of osteoporosis ↓	• higher BMI increases BMD	(45)
• Female(n=615) • Male (n=230) • mean age=75yr ± 4.4 • Mean BMI was 28.1±4.7 kg/m2	• cross-sectional analysis • Measure body weight and height, and BMI • use Lunar Prodigy Double beam densitometer to measure BMD of femoral neck	• higher BMI has protective effect on BMD among elderly • the risk of osteoporosis of BMI>30kg/m² is 33% compared to normal BMI	• High BMI is protective against osteoporosis	(64)
• Obese female(n=24) • Obese male (n=12) • Control (n= 36) • Age: 25-56yrs	• DXA to measure aBMD of hip & spine • HR-pQCT to measure bone geometry, volumetric BMD & micro architecture of radius & tibia • FEA to test Fracture Load (FL)	• DXA: in Obese BMD& BMC of hip↑, BMD of spine↑ but not BMC compared to control • HR-pQCT: obese's architectural compostion ↑ (BV/BT, Tb.N, Tb.th, Tb.sp) in tibia not radius. • FEA: Fracture load per kg body weight were inferior to control	• obesity enhanced trabecular microarchitecture in both radius & tibia, higher cortex area & thickness in tibia but not in radius • bone strength adaption may be inadequate for mechanical demand in site-specific fracture risk in obesity	(65)
• women (n=693) • men (n=439) • mean age= 76yrs	• cohort study, check weight repeatedly over 40yrs • use DPA xray to evaluate BMD of femur and radius • spine measurement	• weight and weight change positively affect BMD in women in all sites, but only weight bearing bone in men	• weight and weight change positively affect BMD but much less in men, possibly due to adipose tissue production of estrogen after menopause in women	(39)
• Male BMI≤25kg/m2 (n=26298) • Male 25≤BMI<30kg/m2 (n=70851) • Male BMI≥30kg/m2 (n=42270) • age: ≥65years	• retrospective cohort study of incident fracture in men • find relation between BMI & fracture	• significant reduction of spine & rip fracture in obese & overweight • fewer wrist/forearm & pelvic fracture for obese • however, multiple rib fracture were frequent in overweight & obese	• obesity was associated with a reduced risk of clinical fractures when compared to normal or underweight in elderly men	(46)

Abbreviation
BMI: Bone Mass Index
DXA : Dual enery X-ray Absorbtiometry
BMD: Bone Meneral Density
BMC: Bone mineral content
FEA: Finite element analysis
DPA: Dualphoton absorptiometry
HR-pQCT: High resolution Peripheral Quantitative Computed Tomography

TABLE 1 Evidence of positive effect of obesity on bone from clinical studies.

health when compared between high fat and normal fat subjects in late adolescence. As for osteoporosis and fracture protection, even higher BMD found in obese patients showed lower fracture load resistance at the finite element analysis (FEA) (65). In addition, in a study on a group of adult Korean women, it was found that the subjects with abdominal obesity or hypertriglyceridemia had significant lower BMD than their lean counterparts (69). Another observation demonstrated that obese individuals had significant lower lumbar BMD than expected at age comparable to osteoporosis (70). Furthermore, when cardio-metabolic risk factors such

as insulin resistance, low high-density lipoprotein (HDL), were taken into consideration, higher BMI was found to adversely influence bone mass (44). Therefore, all of these findings suggest that BMI alone should not be the only parameter to assess the quality of bone mass in obesity. One must take into consideration of the metabolic changes in obese subjects, such as insulin sensitivity, fasting glucose plasma and lipid profile since these parameters were found to be negatively involved in metabolic alteration of bone in many animal studies (19, 75, 76). The summary of effect of obesity on bone in clinical studies can be found in table 1 and 2.

Model	Method	Major Findings	Interpretation	Ref.
• Obese men (n=35) • Mean age: 33.8±6.4 yrs • Mean BMI: 36.5±5.8kg/m^2	• Measure radius microarchitecture and mechanical properties by HR-pQCT • Micro-FEA, body composition by CT • Bone marrow fat by proton magnetic resonance spectroscopy	• Men with high VAT had impaired bone mechanical properties compared to men with low VAT • Bone marrow fat (-) associated with cortical parameters	• VAT and bone marrow fat are (-) predictors and high muscle mass is (+) predictor to bone microarchitecture and mechanical properties in obese men.	(73)
• Women (n=291) • Men (n=107) • Meag age : 44.1±14.2 yrs • Mean BMI 35.8±5.9 kg/m^2	• Measure BMD , body fat, lean mass, by DXA	• BMD of overweight is neutral or protective of osteoporosis, while obese subjects had low bone mass comparable to osteoporosis	• Obese individuals have significant low BMD than expected for age	(70)
• Women with MetS (n=511) • Age: 18+	• Measure WC, BMI, BP, fasting glucose, lipid profile (LDL-C), CRP • Insulin resistance assessment(HOMA-IR) • Check BMD using DXA	• Women with abdominal obesity/hypertriglyceridemia had significant lower vertebral BMD • Mean BMD was lower in women with MetS	• Abdominal obesity and MetS might be a risk factor for osteoporosis and related fractures.	(69)
• Female(n=1767) • Male(n=698) • age: 50-75 years	• Cross-sectional study	• weight adjusted total Fat Mass (or %FM) negatively associated with BMD in both women & men	• weigh adjusted FM(%FM) negatively associated with BMD	(43)
• overweight adolescents • age : 14-18yrs	• DXA to measure BMD of lumbar spine, left total hip & whole body • Calculate fat mass & %fat mass • To compare bone mass of overweight with/without CMR	• Healthy group has greater bone mass compared to 1CMR and ≥2CMR group	• Being overweight with metabolic abnormalities such as Insulin resistance, low HDL & visceral adiposity may adversely influence bone mass	(44)
• grouped by cardiometabolic risk factors (CMR) • Healthy (n=55) • 1 CMR (n=46) • ≥2CMR(n=42) • Female with Normal Fat (NF) body (n=33) • Female with High fat (HF) body (n=15) • Age: 18-22 yrs	• CMR difined by pediatric definition of metabolic syndrome • Use DXA to measure Fat Free soft tissue mass(FFST) & % body fat • Use pQCT to measure BMD & BMC	• High fat group had lower total cross-sectional area(CSA), Cortical CSA, strength-strain index of all cortical site of tibia & radiu	• Adiposity in obesity adversely influence cortical bone strength	(72)
• Female (n=1467) • Male (n=1164) • Mean age : 47.7±14.2 yrs	• Use DXA to study association between BMD/BMC & fat distribution • Adjustment of BMI, fasting Insulin & adiponectin	• Negative association between fat distribution and BMD after adjustment of BMI	• After adjustment of BMI, fat deposition is possibly deleterious for bone	(74)

Abbreviation
FM : Fat mass
VAT: Visceral adipose tissue
MetS: Metabolic syndrome
BP: Blood pressure
CPR: C-reactive protein
FFST: Fat free soft tissue
CSA: Cross sectional area
CMR: Cardiometabolic risk factors
HDL: High density lipoprotein

TABLE 2 Evidence of negative effect of obesity on bone from clinical studies.

Effects of obesity on bone in preclinical studies

Pre-clinical studies showed consistent results of the adverse impact of high fat diet (HFD) on bone. These studies showed that animals fed with HFD developed obesity and this high-fat-diet-induced obesity, as a result, altered bony structures including alveolar bone loss accompanied by metabolic changes such as insulin resistance and hyperlipidemia (19, 20, 22, 75, 77-80). For example, some studies (19, 20, 78) reported that mice fed with HFD developed obesity and insulin resistance and their trabecular bone mineral contents (BMC) and bone mineral density (BMD) were significantly decreased by reduced trabecular volume, number and density accompanied by increased trabecular separation when compared to the normal diet (ND) group. Interestingly, cortical bone was not affected in these study groups. The authors explained that duration of high fat feeding may account for this findings, since bone turnover rate of trabecular bone is normally faster than cortical bone due to its less mineral content by nature. Moreover, Hinton and colleagues (22) used torsional loadings to evaluate the breaking force followed by microcomputed tomography examination (μCT). The torque at fracture was significantly lower in the HFD group. Interestingly,

Model	Method	Major Findings	Interpretation	Ref.
• 4 weeks obese male rats group • obese rats with exercise group • control group • (n=5-8) per time point :13, 20, 40 weeks	• use pQCT to measure tibia for total volumetric content of cortical, trabecular & total bone • use torsional loading to test bone strength and evaluated by μCT	• total body BMD ↓ & BMC ↓ in obese group compared to control group • obese group with exercise did not show excessive weight gain, obesity, insulin resistance or diabetes & had BMD ↑ than obese group	• excessive adiposity & insulin resistance have negative impact on intrinsic & extrinsic bone strength • Exercise protects against obesity associated skeletal changes	(22)
• 1 month old male mice fed with HFD & ND • n=14 per group	• pQCT of femurs for BMC analysis • μCT scan to analyze new bone volume (BV), tissue volume (TV), and the BV/TV ratio. • Histomorphometric analysis of femurs	• BMC were significantly lower in the HF than ND • histomorphometric analysis showed structural parameters ↓ in HFD, ↓ trabecular thickness, and trabecular number with ↑ trabecular separation • μCT showed HF group had reduced bone structure	• high fat diet contributes to bone loss associated with osteopenia	(77)
• 27 male rats fed Fed with HFD, medium fed diet (MFD), low fed diet (LFD) for 4 weeks,	• measure Body Weights, Body Fat and Bone Composition • measure bone turnover markers (RatLaps, osteocalcin) • measure adipogenic and osteoblastogenic signaling molecules (PPAR-γ and βcatenin)	• HFD group trabecular BMC ↓ compared to MFD & LFD • No difference in total & cortical BMD • βcatenin ↓ in HFD < MFD<LFD • PPAR-γ ↑ in HFD	• HFD increases serum non-esterified fatty acid (NEFA) and impairs bone formation by stimulation bone marrow adipogenesis • Short term HFD affects trabecular but not cortical BMD	(20)
• 50 male Wistar rats • 2 groups: ND & HFD feed for 12 weeks	• μCT of mandible • measure plasma glucose, cholesterol, insulin, osteocalcin • assess bone apposition rate by tetracycline injection	• HFD developed peripheral insulin resistance compared to ND • Osteocalcin ↓ & Mineral apposition ↓ in HFD • alveolar bone porosity ↑ at the molar area of HFD rats both 2D & 3D μCT images	• HFD induced obesity & insulin resistance. • HFD reduce bone formation and increase jaw bone porosity	(19)
• 6 weeks old mice • n= 11 control ND	• Use μCT to measure bone micro structures • Measure osteoblastic expression of key markers (Alkaline phosphatase & Calcium nodule formation) by cultured Bone marrow stromal/ osteoblastic cells (BMSC).	• In HFD, trabecular volume ↓, trabecular separation ↑, trabecular number ↓, density ↓ compared to ND group.	• obesity induced by HFD decreases cancellous bone mass but has no effect on cortical bone mass in the tibia.	(78)
• n=10 HFD group fed for 14 weeks.				
Abbreviation HFD: High fat diet ND: normal diet MFD: Medium Fat diet LFD: Low fat diet PPAR-γ : Peroxisome proliferator-activated receptor gamma μCT: Micro Computed tomography BV: Bone volume TV: Tissue volume				

TABLE 3 Evidence of effects of obesity on bone from *in vivo* and *in vitro* studies.

the exercise group prevented all of the negative effects observed in HFD group in the same study. Therefore, all of these findings suggested that high fat diet coexistent with insulin resistance affected bone microstructures in animal studies.

High fat diet not only leads to insulin resistance, but also reduced insulin signaling molecules on osteoblast such as insulin receptor (IR), insulin receptor substrate-1 (IRS-1), protein kinase B (PKB/Akt), which were demonstrated in animal model after 12 weeks of feeding (19). These molecules are important for osteoblast proliferation and differentiation. As a result, deletion of these osteoblastic specific insulin signaling molecules exhibited decreased osteoblast proliferation and differentiation as well as increased osteoblast apoptosis in genetically insulin receptor knock-out mice (81-83). Table 3 is the summary of these findings.

OBESITY AND DENTAL IMPLANTS

Up to date, there is no clinical studies observing the success or survival of dental implants in pre-diabetic condition or obese-insulin resistance. Little is known about effect of obesity to peri-implant health. Due to the possible adverse effects of obesity and its associated complications toward bone health in general (18), it is hypothized that obesity may negatively influence long-term success of osseointegration of dental implants. However, more scientific studies are required to elucidate this assumption.

This hypothesis was tested by an animal study which evaluated osseointegration in mice fed with high fat diet (HFD). Animals were divided into two groups: normal diet (ND) and high fat diet group. After feeding them for 12 weeks, titanium implants were placed in the femur of all animals in both groups. Result showed that implant loss was greater in the HFD group with hyperlipidemia compared to controls and bone implant contact (BIC) was significantly higher in ND group both at 4 (P<0.01) and 8 (P<0.05) weeks by means of micro-computed tomographic scanning (μCT). Interestingly, this study did not evaluate insulin sensitivity, therefore, it demonstrated that HFD with lipid profile alteration lead to decreased osseointegration and higher implant loss (84).

Another similar study was conducted to examine the effect of HFD on osseointegration. Biochemical analysis of Alanine Aminotransferase (ALT), serum glucose, triglyceride did not show any significant difference between the groups. In addition, insulin sensitivity was not tested either as in the previous study. Contrary to the previous finding, this study on rabbits did not find reduced BIC in the HFD group (85). This could possibly due to the smaller number of animals and timing of high fat diet which was fed after the implant placement rather than before. In this manner, the high fat diet may not reach sufficient time to cause metabolic change in the animals during implant healing period as explained by a study on the timing effect of high fat diet on bone, which required at least 12 to 14 weeks to show alteration of bone mechanical properties (22).

Although there are numerous pre-clinical studies about the effect of high fat diet on bone, its effect on osseointegration by means of using histomorphometry is lacking; therefore, more studies are warranted to evaluate the osteoblastic behavior around titanium surface in obese insulin resistant condition. Clinically, a retrospective study comparing peri-implant clinical and radiographic inflammatory parameters among obese and non-obese men showed peri-implant bleeding on probing score (BOP) (P<0.05) and peri-implant probing depth (PD) were significantly higher among obese compared to non-obese subjects. In addition, whole salivary IL-1β (P<0.001) and IL6 (P<0.001) were also higher among obese patients. Therefore, it was suggested that obese patients receiving dental implants were at

Model	Method	Major Findings	Interpretation	Ref.
• 0.5 to 1 year old Newzealand rabbit • place 4 SLA implants on each animal • ND (n=2) • HD (n=2) • total implant 16	• 4 implants placed on tibia of each rabbits • then fed with ND & HD for 12 weeks, before sacrifice for histologic & histomorphometric evaluation	• no statistically significant different Bone implant contacts of the 2 groups (p>.05)	• Bone implant contact (BIC) is not different between the 2 groups	(85)
• 4 weeks old mices divided to 2 Groups • HFD(n≥6), • ND(n≥6) fed for 12 weeks	• 1x2mm smooth implants placed in femur bicortically. • at 4 & 8 weeks, animals were killed & blood taken • use μCT scanfor BIC evaluation • implant push-in test.	• Implant failure ↑ in HFD group • Push-in test ↓ in HFD • BIC is less in HFD group	• Hyperlipidemia/HFD leads to ↑implant failure, ↓osseointegration & poor mechanical strength	(84)
Abbreviation BIC: Bone implant contact SLA: Sandblasted and Acid etched μCT: Micro computed tomography				

TABLE 4 Evidence of effects of obesity on bone around implants from *in vivo* studies.

higher risk of developing peri-implant inflammation (86). It is interesting to note that systematic reviews and meta-analyses have confirmed that obesity is able to cause inflammation around natural teeth and increase the severity of periodontitis as well as alveolar bone loss (87-89). Moreover, since the etiology and pathogenesis of periodontitis and peri-implantitis were found to be very similar (90), it is hypothesized that obesity might alter peri-implant health in a similar manner it does to periodontal tissue. Nevertheless, these few studies are insufficient to draw definite conclusion about correlation between obesity and osseointegration of dental implants. The summary of effect of obesity on dental implant is in table 4.

CONCLUSION

Osseointegration is a predictable treatment modality. Osseointegration of dental implant is an ongoing process of coupling mechanism of osteoblastic and osteoclastic activities similar to other bone tissue areas. Therefore, any systemic risk factors that interfere with normal bone metabolism will adversely affect the quality of bone around implants and consequently affect long term success of implant.

Obesity is a major risk factor for insulin resistance and type 2 diabetes and one of the cluster signs for metabolic syndrome. Many studies found that type 2 diabetes leads to reduced osseointegration and increased implant failure; however, no large clinical study was conducted regarding to direct effect of obese insulin resistance or pre-diabetes on osseointegration. This is possibly due to absence of alarming symptoms of obesity during the early state of insulin resistant condition until patients develop T2DM. This could explain why there are more studies regarding the effects of T2DM on osseointegration of dental implants at both clinical and pre-clinical stages.

Despite the controversy of relationship between obesity and bone in clinical studies, the deleterious effects of obesity are clearly visible in pre-clinical studies by elevated free fatty acid, insulin resistance and hyperlipidemia. All these alterations led to reduced osteoblasts and increased osteoclasts manifested by diminished bone mineral content and density, thus, development of osteoporosis of bone including alveolar bone.

From individual studies regarding the possible inverse effects of obesity, there might be more than one mechanism responsible for bone loss in this disorder, whether it is the insulin resistance, hyperlipidemia, high fat content or the combination of these, need to be further studied.

Evidence is still lacking to explain how osseointegration responses to obese-insulin resistance or pre-diabetic condition both in terms of clinical performance and histology; although, the few existing studies favor the relatively negative impact of this systemic disorder. Therefore, more scientific studies are urgently required.

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