# Updating on dental implant osseointegration and survival rate in osteoporotic bone

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**ABSTRACT**
**Background**: Systemic diseases may impact osseointegration of dental implants. Osteoporosis has become one of the concerning diseases since its prevalence reached 18.3% in the world and 10.3% in Indonesia. It is characterized by the decrease in bone thickness, alteration of trabecular structures, and increase in ratio of carbonate and phosphate, making the bone more fragile and prone to fracture. Consequently, the issue of bone quantity and quality will have a great impact on dental implant survival rate. **Objectives**: To know the effect of osteoporosis on survival rate and osseointegration of dental implants. **Conclusion**: Dentists should be more cautious if patients receiving dental implant treatment have a bone mineral density score of -2.5 < T-Score < -1 and an estrogen deficiency, because both are directly related to osteoporosis. Consumption of bisphosphonates should also be asked because it could cause osteonecrosis of the jaw. Most studies show no significant differences between survival rate of implants placed on osteoporotic patients and healthy patients after a short time period, 0-1 year. However, most studies show significant differences after a long time period, 5-7 years, so evaluation of implants is recommended.
**Keywords**: survival rate, osseointegration, dental implants, osteoporosis

## INTRODUCTION

Over time, dental implant treatment replacing single tooth loss to edentulous jaw has become popular. One of the keys to success of dental implants is osseointegration. Patients often come with specific medical conditions or the consumption of certain drugs that can affect the osseointegration of dental implants. Several diseases such as diabetes mellitus, cardiovascular disease, hypothyroidism, rheumatoid arthritis and osteoporosis may affect the osseointegration of dental implants.[1] There are 86 studies in total being assessed for the prevalence of osteoporosis worldwide. From 86 studies with a total of 103,334,579 samples ranging in age from 15-105 years, the prevalence of osteoporosis in the world was 18.3%.[2] In Indonesia, osteoporosis needs to be concerned because it has a prevalence of 10.3%, which means that 2 out of 5 Indonesians are at risk for osteoporosis.[3] Osteoporosis is characterized by a decrease in bone thickness, changes in trabecular bone structure and increase in the ratio of carbonate to phosphate so that the bone becomes susceptible to fracture.[4]

Based on the World Health Organization, the diagnosis of osteoporosis is established based on the value of bone mineral density (BMD) -2,5 < T-score < -1.0.[5] Osteoporosis is classified into primary and secondary osteoporosis, type I primary osteoporosis is closely related to low levels of estrotrogen in postmenopausal women. The decrease in estrogen levels in women occurs about 2-3 years before entering the menopause phase and will continue for 3-4 years after entering the menopausal phase.[6] Estrogen is essential for bone metabolism; deficiency of the hormone causes inhibition of osteoclast cell apoptosis, resulting in bone loss until fracture.[7]

Tooth loss can lead to reduced quality of life for a person because it causes problems in mastication and aesthetics. One of the treatments to replace missing teeth is dental implants. A dental implant is a form of metal screw that is implanted in the jawbone to support a crown, partial or full denture or prosthesis.[8] The choice of dental implant treatment has now drastically increased due to osseointegration ability of implants to bone, so the success rate is high and the risk of complications is low.[9] Calculation of the success or survival rate of the implant is based on 4 clinical categories which contain conditions of success, satisfactory survival, compromised survival, and failure. An implant is said to have failed if it had to or had been removed.[10]

Success of dental implant treatment is highly dependent on osseointegration. Failure of bone osseointegration with dental implants occurs when bone decreases in mass and density.[11] The estrotrogen deficiency causes type-1 primary osteoporosis (post-menopausal osteoporosis) resulting in a decrease in bone mass by 2-5% per year and a decrease in trabecular bone density by 50% and cortical bone by 35%.[12] Therefore, osteoporosis is considered to be one of the risk factors for dental implant treatment.[11] This study aims to further ana-

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lyze osteoporosis as a risk factor for dental implant treatment and its effect on survival rate.

## LITERATURE STUDIES

### Osteoporosis

Osteoporosis is a multifactorial disease that interferes with the bones, including maxilla and mandible, characterized by the decreased bone strength and increased risk of bone fracture. Osteoporosis risk factors are genetic, intrinsic, exogenous and lifestyle that influence each other.[13] Osteoporosis' particular features are a decrease in bone density and bone quality. The disease causes the decrease in bone thickness, mineral level of the bone, changes in trabecular structure, and an increase in ratio of carbonate to phosphate so that the bone becomes susceptible to fracture. This greatly affects the treatment in prosthodontics which requires good bone quality.[4]

### Classification of osteoporosis

Based on the cause of the disease, osteoporosis is classified into primary and secondary. Primary osteoporosis is divided into two types. Type 1, called postmenopausal osteoporosis, is associated with low levels of estrogen. The decrease in estrogen levels in women does not occur during the menopausal phase, but about 2-3 years before entering the menopausal phase and will continue to be persistent until 3-4 years after the menopause. Type-2 is osteoporosis associated with old age, calcium and vitamin D levels in the bones. Individuals over 70 years of age have twice the risk of osteoporosis than people with type-1 osteoporosis. The cause of secondary osteoporosis are diseases such as Ehler-Danlos syndrome, hyperthyroidism, hypothyroidism, Cushing's syndrome, result of a surgery, or taking drugs that accelerate bone loss.[6]

### Pathophysiology of osteoporosis

Homeostasis of human bone is maintained by the presence of three main cells that play a role in bone remodeling, namely osteocytes, osteoblasts and osteoclasts. The process of bone remodeling can repair bone damage, maintain bone structure and homeostasis of calcium and phosphate, which are important minerals in bone. To maintain its strength, bone needs to hold resorption and new bone formation continuously.[14] In osteoporosis, the process does not run normally. The number of osteoprotegerin (OPG) receptors decreased so that they could not bind to the *receptor activator of nuclear of kappa*-B *ligand* (RANKL) optimally, as a result there was no inhibition of osteoclast differentiation and decreased osteoclast apoptotic activity. Increased osteoclast activity causes an imbalance in the function of osteoblasts-osteoclasts, resulting in a decrease in bone mass leading to bone loss.[6]

### Bone mineral density

The BMD is a value obtained from the amount of inorganic minerals in bone. The BMD value is influenced by several factors, namely age, gender, disease, genetics, and lifestyle.[15] Determination of the diagnosis of osteoporosis is by looking at the BMD value. The normal BMD-value of adult human is T-Score > -1. Whereas osteoporosis patients have an average BMD value of -2,5 < T-Score < -1.0.[5] BMD is one of the important risk factors for bone fractures in osteoporosis patients. The lower the T-Score value that determines the BMD value, the greater the risk of a person's bone fractures.[16]

### Estrogen deficiency

Estrogen deficiency is associated with primary osteoporosis type-1 or postmenopausal osteoporosis. Estrogen has an important role in the maturation, mineralization and maintaining the bone mass.[17] Estrogen deficiency accelerates bone loss by stimulating the formation of inflammatory cytokines that act as osteoclast regulators, such as IL-1, IL-2, IL-6 and prostaglandin-E (PGE).[6] When estrogen levels in the blood fall below normal, what happens is an increase in osteoclast formation causing excessive bone resorption. Low estrogen also inhibits osteoclast cell apoptosis and when all of them occur together, it will cause bone loss and eventually fracture.[7] The importance of estrogen to bone was proven in a study conducted by Hendrijanti et al[12] that decrease in estrogen levels in osteoporosis patients causes a decrease in the bone mass by 2-5% per year and a decrease in trabecular bone density by 50% and in cortical bone mass by 35%. Estrogen deficiency with aging can interfere with bone formation processes involving oxidative stress mechanisms.[17]

### Aging

Older people are at greater risk of osteoporosis. Entering the fourth decade of life, humans will begin to experience a progressive decline in BMD values. The risk of bone fracture will increase starting from the ninth decade of life and beyond.[18] When osteoporosis patients will undergo implant treatment, age is important to determine the prognosis of successful installation. The elderly pati-

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ents tend to have systemic health problems, have poor bone conditions and their healing abilities are not as good as when they were young.[11]

**Osteoporosis manifestation in the oral cavity**

Osteoporosis can manifest in bones throughout the body, including the maxilla and mandible. The manifestations include decreased cementum vascularity, alveolar ridge, jaw bone mass and density and bone metabolic capacity as well as changes in the stomatognathic system due to the patient's low BMD, increased maxillary and mandibular porosity, periodontal tissue changes, and increased the trabecular bone spacing. In addition, the temporomandibular joint also undergoes changes, in particular, reabsorption in the condyle area. Radiographic examination is important to see the manifestations of osteoporosis in the oral cavity, the commonly used is panoramic radiography.[19]

**Bisphosphonate therapy in the osteoporotic patients**

Osteoporosis patients often receive bisphosphonate over therapy. Intravenous administration of bisphosphonate causes the patient to develop osteonecrosis of the jaw. The bisphosphonates will accumulate at the site of bone remodeling centers that interfere with the bone replacement process, cause surgical trauma to the alveoveolar bone, increase postoperative drug accumulation, and increase the risk of peri-implantitis because the bisphosphonates reduce peri-implant bone resistance to oral bacteria.[11] Osteonecrosis of the jaw because of bisphosphonates is referred to as Bisphosphonate (BP)-related osteonecrosis of the jaw (BRONJ). Zoledronic acid in the bisphosphonates makes patients feel pain. BRONJ manifests as necrotic bone in the maxilla or mandible. Its conditions can be exacerbated by infection with the *actinomyces.* For that, oral hygiene osteonecrosis patients must be maintained to reduce pathogenic bacteria.[20]

Implant treatment in prosthodontics among patients with osteonecrosis need special attention. Meanwhile, the survival rate of implant placement in osteonecrosis patients within a period of 1-4 years is still 100%. Siebert, et al showed from 120 implants placed in the mandibular interforaminal area in the group of osteoporosis patients who received bisphosphonate therapy every year and non-osteoporosis patients who did not receive bisphosphonate therapy results in no significant difference, no implant mobility was found and there was no difference in the mean marginal bone loss and crestal bone loss in both groups of study subjects.[20]

**Dental implants**

Tooth loss is a problem that humans always have to face. During the era when food was minimally processed, tooth loss would make the mastication and chewing processes less effective, endangering the human survival. However, in this modern era, survival is no longer a problem, due to advancements in food processing. Now, aesthetic factors and the ability to enjoy various food textures are the important reasons to replace lost teeth.[21]

One of the ways of replacing the lost teeth is through dental implants. Dental implant is a metal screw placed in the jaw bone through surgical procedures, and acts as a replacement for lost root. Dental implants can support single tooth replacement as crowns, fixed partial or full dentures or maxillofacial prosthetics.[8] A dental implant has 3 main components which are 1) implant body, inserted into the bone, 2) abutment, on top of implant body, 3) superstructure or denture. High success rate and low risk of complications have made dental implants frequently chosen to repair aesthetics and mastication processes of a patient.[22,9]

**Indications and contraindications of the dental implants**

Indications for dental implants are 1) replacing a single tooth, 2) distal extension base, 3) completely edentulous state, 4) long edentulous spans, 5) when a fixed partial denture is compromised due to weak support, long edentulous spans, cantilever, and unfavorable number and location of abutments, 6) when full denture is compromised by poor muscle coordination, low mucosal tolerance, compromised supporting tissues, parafunctional habits that affect denture stability, unrealistic prosthodontic expectations, hyperactive gag reflex, and patient's requirement for fixed dentures and psychological inability to wear removable dentures.[22]

Contraindications for dental implants are divided into two categories, absolute and relative. Absolute contraindications are 1) high dose irradiated patients, 2) hematologic systemic disorders, 3) psychiatric problems, such as psychosis and dismorphophobia, 4) surgical contraindications due to systemic conditions. Relative contraindications are 1) low dose irradiated patients, 2) diabetes, 3) smoking, alcohol consumption and drug abuse, 4) children up to 18 years old (until jaw bone

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growth has stopped), 5) pregnancy.[22]

### Survival rate of dental implants

On the 5th October of 2007, a Pisa, Italy Consensus Conference sponsored by *International Congress of Oral Implantologists* (ICOI), modified James-Misch Health Scale and agreed on four clinical categories. They consist of success, *satisfactory survival*, *compromised survival*, and failure. Success category describes implant in optimal condition, survival category describes a functioning implant but not in ideal condition, and failure category describes implants that must be or have been removed.[10]

**Table 1** Health scale for dental implants.[10]

| Implant Quality Scale Group | Clinical Conditions |
|---|---|
| I. Success (optimum health) | a) No pain or tenderness upon function<br>b) 0 mobility<br>c) <2 mm radiographic bone loss from initial surgery<br>d) No exudates history |
| II. Satisfactory survival | a) No pain on function<br>b) 0 mobility<br>c) 2–4 mm radiographic bone loss<br>d) No exudates history |
| III. Compromised survival | a) May have sensitivity on function<br>b) No mobility<br>c) Radiographic bone loss >4 mm (less than 1/2 of implant body)<br>d) Probing depth >7 mm<br>e) May have exudates history |
| IV. Failure (clinical or absolute failure) | Any of following:<br>a) Pain on function<br>b) Mobility<br>c) Radiographic bone loss >1/2 length of implant<br>d) Uncontrolled exudate<br>e) No longer in mouth |

## DISCUSSION

### Effect of osteoporosis on the dental implant survival rate

Human bone metabolism goes through a balance between bone formation and bone resorption that occurs throughout life. If at any time this process is disturbed until an imbalance occurs, for example, systemic skeletal disorders such as osteoporosis, later the bones will become more brittle, lose strength (decreased bone mass) and are at risk of fracture. The balance of this process is also very closely related to the estrogen hormone. In general, a deficit of estrogen can disrupt the balance of bone metabolism, increasing osteoclastogenesis so that the formation process decreases and is dominated by the bone resorption process, making bone mass and quality decreases and is at risk for fracture, this condition is often the cause of patients with primary type-1 osteoporosis or what is often called osteoporosis postmenopausal.[23]

Although studies have shown association of osteoporosis with small implant failure, bone quality still plays a major role as a benchmark for good implant treatment outcomes. So, in systemic conditions where there is a decrease in bone quality and quantity, such as osteoporosis, need to be considered before implant treatment in patients. To help dentists diagnose osteoporosis as a risk factor for implant treatment, the WHO has determined the criteria for the diagnosis of osteoporosis patients based on the value of BMD which is -2.5 < T-Score < -1.0. In addition, female patients who have entered the menopause phase should also be suspected of having osteoporosis due to estrogen deficiency. If a patient undergoing the implant treatment has osteoporosis, the survival rate of the dental implants needs to be reviewed before treatment.[7,23,24]

Several scientific articles provide information on the *survival rate* of implant treatment in osteoporosis patients both in the short and long term. Merheb, et al[25] proved that of 160 dental implants placed in osteoporosis patients and after being followed up for 3 months, none failed, so the *survival rate* of the osteoporosis group was 100% not significantly different from the control group (healthy patients). Likewise, Temmerman, et al[23] conducted a study of installing 148 dental implants in osteoporosis patients and only 12 failed after being followed up for one year so that the *survival rate* was 98.4% at the implant level and 97.9% at the subject level. However, research by Holahan, et al[26] who installed 168 implants, after being followed up for a period of 5-10 years, only 26 implants failed, so the average *survival rate* was only 82.6%, much lower than the control group. Niedermaier, et al[27] installed 34 implants in osteoporosis patients and after 7 years of observation, only 2 of 34 dental implants failed, resulting in a *survival rate* of 94.1% lower than the control group. Temmerman, et al[28] also showed the results of a comparison of *survival rates* that differed significantly between dental implants in the control group and the osteoporosis group. Of the 63 dental implants installed, after being followed up 5 years later there were 5 dental implants that failed so that the *survival rate* was 91.5% at the implant level and 89.2% at the subject level. Finally, Alsaadi, et al[29] also investigated the installation of 120 dental implants in osteoporosis patients and the results of a 5-year follow-up showed that 1 implant failed, not much different from the installation of dental implants in non-osteoporosis patients. In this study, the *survival rate* of implants in osteoporosis patients was 96.3%.

Most studies show no significant differences

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**Table 2** Short term studies (0-1 year)

| Author | Short-Term Placement (0-1 year) | | | |
|---|---|---|---|---|
| | Total number of dental implants | Number of failed implants | Survival rate | Survival rate differences between osteoporosis and control group |
| Merheb J et al[25] | 160 (3 months) | 0 (3 months) | 100% (3 months) | Not significant |
| Temmerman A et al[23] | 148 (1 year) | 12 (1 year) | 98.4% on implant level and 97.9% on subject level (1 year) | Not significant |

**Table 3** Long term studies (5-7 years)

| Author | Long-Term Placement (5-7 years) | | | |
|---|---|---|---|---|
| | Total number of dental implants | Number of failed implants | Survival rate | Survival rate differences between osteoporosis and control group |
| Holahan CM et al[26] | 168 (5-10 years) | 26 (5 to 10 years) | 82.6% remains constant (5-10 years) | Significant |
| Niedermaier R et al[27] | 34 (up to 7 years) | 2 (up to 7 years) | 94.1% (up to 7 years) | Significant |
| Temmerman A et al[28] | 63 (5 years) | 5 (5 years) | 91.5% on implant level and 89.2% on subject level | Significant |
| Alsaadi W et al[29] | 120 (5 years) | 1 (5 years) | 96.3% (5 years) | Not significant |

between survival rate of implants placed on osteoporotic patients and healthy patients after a short time period (0-1 year). However, most studies show significant differences after a long time period (5-7 years) so evaluation of implants is recommended.

**Differences in results between human and animal**

Differences of results between experiments regarding implant osseointegration on osteoporotic humans and animals can be observed. On dental implants placed for at least 3 years in humans, there are no significant differences in the marginal bone loss (MBL), plaque index (PI), and probing depth between osteoporotic and non-osteoporotic groups.[29] Then, there is also no significant correlation between mandibular cortical index (MCI) of osteoporosis and MBL on the dental implants placed for at least 2 years in humans.[30] On the other hand, the implants on rats show the peri-implant bone volume, trabecular architecture, bone-to-implant contact (BIC), and biomechanical parameters decrease progressively and significantly within 12 weeks post-ovariectomy.[31] On implants placed for 28 days in rats undergone ovariectomy, results indicate significant decrease of bone volume/total volume (BV/TV) and BIC. Maximum torque, stiffness, and energy of torque are also lower on ovariectomy rats compared to normal rats.[32] Based on the experimental results above, it can be observed that osteoporosis has a greater negative effect on animals compared to humans.

One of the factors that influence this phenomenon is the location of implants on animals which is usually the femoral or tibial bone. This creates an environment for implants that is different from the oral cavity, because actual dental implants are always exposed to chemical agents, bacteria, and mastication forces.[33] It is also shown in rats that femoral and tibial bone experience greatest bone loss post-ovariectomy, 75.0% and 70.4% respectively in week 36. In contrast, the jaw and cranial bones only experience 1-3% bone loss in week 36 post-ovariectomy. Trabecular structures of femoral and tibial bones also experience significant destruction, whereas jaw bones are relatively stable post-ovariectomy.[34]

**Bioactive agents and stem cells to improve osseointegration**

Technology and innovation in dental implants have progressed really far, making it as the main choices for replacement of lost teeth. However, the risk of implant failures still exists, especially in patients with systemic diseases such as osteoporosis, which causes a decrease in bone mass and interferes with osseointegration. Modifications of implant surfaces have been developed to modulate

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host tissue response to implant and improve osseointegration. Some methods that are currently studied are loading of bioactive agents and stem cells on implant surfaces to improve osseointegration, especially in osteoporotic patients.[35,36]

Loading of bioactive agents such as the anti-osteoporosis medications like bisphosphonates, RANKL antibody, parathyroid hormone (PTH) and selective estrogen receptor modulators (SERM) have been proven to increase implant osseointegration. Bioactive molecules like platelet-derived growth factor, insulin-like growth factor, fibroblast growth factor, vascular endothelial growth factor (VEGF), and bone morphogenetic protein (BMP) have also been used to improve osteogenic differentiation and mineralization of bone marrow stem cells. Inorganic elements such as calcium (Ca), strontium (Sr), magnesium (Mg), zinc (Zn), and silicone (Si) can also stimulate osteogenesis.[36] Strontium (Sr) is often used in treatment of osteoporosis due to its similarity to calcium (Ca) and its ability to simultaneously stimulate osteoblast and inhibit osteoclast. Implant surfaces loaded with Sr through hydrothermal reaction have a positive effect on promoting early osseointegration in osteoporotic rabbits.[37] Moreover, biomimetic coating of Ca-P or calcium-phosphate have been used frequently due to its excellent biocompatibility from mimicking natural bone mineralization process.[38]

Many researchers have also studied stem cells to improve the osseointegration. Stem cells have potential to undergo osteogenic differentiation and proliferate to promote the bone regeneration. Like the human umbilical cord mesenchymal stem cells (hUCMSCs) are proven to have high osteogenic effect and improve bone regeneration in osteoporotic animal model.[39] Human amniotic mesenchymal cells (hAMSCs) can also improve bone regeneration and osseointegration of implants in rabbits.[40] The bone marrow mesenchymal stem cells (BMSCs) coatings cultured in extracellular matrix on implant surface can also improve osseointegration in rats.[41] Studies on animals show that stem cells have a great potential to be used in dental implants. However, more clinical tests are needed to determine the safety, efficacy, and feasibility of stem cell application in humans.

It concluded that most studies show no significant differences between survival rate of implants placed on osteoporotic patients and healthy patients after a short time period (0-1 year). However, most studies show significant differences after a long time period (5-7 years) so evaluation of implants is recommended. Measurements of BMD level and estrogen are recommended before implant treatments because both are directly related to osteoporosis. Patients with BMD score of -2.5 < T-score < -1 must be observed cautiously because their bone mass and density have decreased which could in turn, decrease implant survival rate. Decrease of estrogen levels in women could also indicate postmenopausal osteoporosis, so they could potentially experience 2-5% bone loss every year, and decrease in trabecular and cortical density, 50% and 35% respectively. Consumptions of anti-osteoporosis drugs like bisphosphonates should also be asked because it could cause osteonecrosis of the jaw. Finally, studies on animals show that bioactive agents and stem cells have the potential to improve osseointegration but further clinical tests are needed to determine their safety, efficacy, and feasibility in humans.

Further studies regarding implant survival rate on osteoporotic patients should be conducted to help dentists when considering dental implant treatment for osteoporotic patients. Moreover, further studies are required regarding the reason why there is mostly a significant decrease of survival rate in osteoporotic patients after a long period of time but not after a short period of time. Further clinical tests of bioactive agents and stem cells are required before their application in humans.

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