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INTEGRATED STUDY MASTER'S THESIS

Success of Dental Implants in Patients Undergoing Osteoporosis Treatment

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LIST OF ABBREVIATIONS:

Alendronate - ALN
Bisphosphonates – BP
Bone Mass Density - BMD
Estrogen replacement therapy – ERT
Fibroblast growth factor - FGF
Hormone replacement therapy - HRT
Ibandronate - IBN
Insulin-like growth factor-1 - IGF-1
Marginal bone loss - MBL
Medication-related osteonecrosis of the jaw - MRONJ
Parathyroid hormone - PTH
Parathyroid hormone-related protein - PTHrP
Pamidronate - APD
Platelet-derived growth factor - PDGF
Platelet-rich fibrin - PRF
Platelet-rich plasma - PRP
Plasma-rich growth factors - PRGF
Receptor activator of nuclear factor kappa beta - RANKL
Risedronate - RSN
Selective estrogen receptor modulators - SERMs
Teriparatide - TPTD
Transforming growth factor - TGF
Vascular endothelial growth factor - VEGF
Zoledronic acid - ZA

ABSTRACT:

Background: Dental implants are one of the best ways to restore lost teeth. However, their successful osseointegration is crucial for long-term successful results. Patients who are suffering from osteoporosis and are receiving medications for this disease may face potential failure risks in terms of osseointegration and long-term success.

Objectives: This extended literature review aims to investigate the impact of osteoporosis medications, especially antiresorptive drugs, on the success rate of dental implants.

Methods: Electronic searches were performed from September 2023 to December 2023 for "oral implant" OR "dental implant" AND (antiresorptive drugs OR bisphosphonates OR denosumab OR osteoporosis treatment were performed using PubMed, Scopus, ResearchGate, Ovid, and ScienceDirect. Time restrictions were applied and included the years from 2010-2024. Manual searches were conducted to supplement the digital searches in the following scientific journals: Journal of Osseointegration and Journal of the Endocrine Society.

Results: A total of 17 studies were included, which met the eligibility criteria. The studies assessed dental implants' success/failure rate in patients suffering from osteoporosis who underwent treatment for this disease before and/or during implant placement. At present, the literature review did not find a difference in the success rate of dental implants in patients who are or have been undergoing medical treatment for osteoporosis compared to healthy patients. Hormonal therapies seem to influence peri-implant bone loss but do not significantly impact the overall implant success rate. The use of blood products can be recommended to support the healing phase and to lower the risk of possible complications. There is a lack of a widely accepted consensus regarding implant success criteria, which is needed to facilitate further research and to allow an accurate comparison of the results.

Conclusion: Within the limits of the study, the literature review did not find a difference in the success rate of dental implants in patients who are or have been undergoing medical treatment for osteoporosis compared to healthy patients. More extensive clinical trials, longer follow-up times, detailed success criteria, and surgical techniques are recommended to understand further and investigate the associated risks of osteoporosis medications on dental implantation.

Keywords: Osteoporosis; Bisphosphonates; Antiresorptive drugs; Dental Implants; Oseeointegration.

1. INTRODUCTION

1.1 PROBLEM STATEMENT

Over the last few years, dentistry, and especially the field of oral surgery, has been continually evolving while adapting to the population's constantly changing needs and demographics (1). Throughout this course, innovations have evolved, such as dental implants, which are redefining the boundaries of how tooth loss is treated (1). In terms of oral rehabilitation, a new standard of quality has been set with these prosthetic devices by resembling the shape and function of natural teeth while allowing patients to regain their smiles and improve their masticatory function and overall oral health (2). Due to their great success, dental implants have become a fundamental component of modern dentistry, allowing various treatment options, from single tooth loss to full mouth restorations of edentulous jaws (3).

Despite the overall success rate of dental implants, it is essential to mention that success can not be universally guaranteed and is highly dependent on various kinds of factors, including underlying medical conditions (4). One of these medical conditions is osteoporosis, which has obtained increasing attention in recent years due to its impact on altering the success rate of dental implants (5).

1.2 AIM

This extended literature review aims to investigate the impact of osteoporosis medications, especially antiresorptive drugs, on the success rate of dental implants.

1.3 OBJECTIVES

[1] To clarify the medications and their impact on bone healing and implant osseointegration.
[2] To evaluate the medication's impact on complication rates after dental implantation.
[3] To assess the impact of different blood products on the healing process.
[4] To compare long-term success results of dental implants between patients having osteoporosis and healthy patients.

2. MATERIALS AND METHODS

2.1 RESEARCH QUESTION

The PICO model (Table 1) (P = population, I = Intervention, C = comparison, O = outcome) has been used to form the focused question of this literature review, which is the following:

Does the success rate of dental implant treatment differ in terms of success, failure, and medication-related osteonecrosis of the jaw (MRONJ) in patients who are or have been undergoing medical treatment for osteoporosis compared to patients not receiving medical treatment for osteoporosis?

Table 1. The PICO model for the literature review.

Component	Description
Population (P)	Patients who are suffering from osteoporosis and have been treated with antiresorptive or antiangiogenic medications
Intervention (I)	Placement of dental implants during or after receiving antiresorptive or antiangiogenic medications
Comparison (C)	Comparison of success rates, failure rates, MRONJ with patients who do not suffer from osteoporosis and, therefore, do not receive any treatment for this disease
Outcome (O)	Implant sucess, Implant failure, MRONJ

2.2 SEARCH STRATEGIES

The literature review was conducted by searching the following databases: PubMed, Scopus, ResearchGate, Ovid, and ScienceDirect. The research was performed from September 2023 to December 2023. Time restrictions were applied and included the years from 2010-2024. The terms used for the conduction of the research were the following: ("oral implant" OR "dental implant" AND (antiresorptive drugs OR bisphosphonates OR denosumab OR osteoporosis treatment). A manual search for the following journals was performed: Journal of Osseointegration and Journal of the Endocrine Society.

2.3 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria: Human studies with a patient minimum age of 18+; administration of antiangiogenic or antiresorptive drugs for the treatment of osteoporosis either before and/or during the placement of the dental implant; a minimum of one placed dental implant per patient independent of the placement location; comparative prospective studies, retrospective case series, cross-sectional studies, randomized control studies, prospective case series, retrospective chart-review studies, prospective cohort studies, and randomized controlled trials; English or German language

Exclusion criteria: Failure to meet all inclusion criteria; administration of antiangiogenic or antiresorptive drugs for diseases other than osteoporosis; patients undergoing or previously receiving radiation therapy; Animal and *in vitro* studies; studies published in languages other than English and German.

2.4 STUDY SELECTION

a) Study selection:

One reviewer screened the titles and abstracts of all articles according to the inclusion and exclusion criteria. The full report was acquired for studies that seem to fulfill the inclusion criteria and for those studies with insufficient details in the title and abstract. One reviewer carried out the full-text assessment, which was monitored by associate professor dr. Ieva Gendvilienė.

b) Data extraction:

After screening and excluding non-relevant articles, 17 articles were left and included in this literature review dating from 2010 to 2019. All studies included osteoporotic patients who were undergoing or have been undergoing medical treatment for this disease before or during dental implant treatment. Detailed data of the included studies were evaluated and presented in Table 2. Table 2 describes each of the included studies in terms of author, study type, number of cases/controls, disease, medication, number of implants, outcome parameters, outcome, and follow-up. The included studies were comparative prospective studies, retrospective case series, cross-sectional studies, randomized control studies, prospective case series, retrospective chart-review studies, prospective cohort studies, and randomized controlled trials.

Table 2 – Characteristics of included studies

Author	Study type	Number of case/ control	Disease	Medication	No of Implants	Outcome parameters	Outcome	Mean success rate	Follow up
Tomas Siebert et al. (2015)	Comparative prospective study	12,12	Osteoporosis	ZA, IV 5 mg/year	Group A: 30 Group B: 30	a) implant survival b) MRONJ c) Mean bone loss	a) 100% b) none c) similar in both groups; according to protocol	100 %	1 year
Mozzati et al. (2015)	Retroperspective case series	235,0	Osteoporosis	ALN (141) IBN (68) RSN (45)	1267	a) implant failure b) success rate	a) 16/1267 b) 98,7%	98,7 %	2 years
Mohanad Al-Sabbagh et al. (2015)	Cross sectional study	39, 376	Osteoporosis	BPs	39	a) Implant success b) implant failure	a) 89,7% (35) b) 10,3% (4)	89,7 %	NR
Pandey A et al. (2019)	Randomized control study	30,0	Osteoporosis	ALN 10mg/day (15) TPTD 20mg/day (15)	26 in ALN 32 in TPTD	a) failure cases b) MRONJ	a) group 1 - 1 (3,84%); group 2 - 1 (3,12%) b) none	96,04 %	7 years
Yajima N et al. (2017)	Randomized control study	25,0	Osteoporosis	Bisphosphonates (11) SERM (8) PTH (6)	BP: 25 non BP: 28	a) failure cases b) MRONJ	a) Group BP: 3; 88% success Group non BP: 0 b) none	88 %	3.2 years
Tallarico M et al. (2016)	Prospective case series	32,0	Osteoporosis	ALN 70mg/week	98	a) failures cases b) marginal bone loss	a) 1 implant loss; 99% success rate b) 1.35 ± 0.21 mm after 3 years	99 %	3 years
Suvarna S et al. (2016)	Retroperspective case series	112,0	Osteoporosis	ALN (40) RSN (10) IBN (8)	140	a) Implant success b) implant failure	a) 130 (92,86%) b) 10 (7,14%)	92,86 %	3 years
Zahid TM et al. (2011)	Retroperspective study	26,0	Osteoporosis	BPs	51	a) Implant success b) implant failure	a) 48 (94,11%) b) 3 (5,88%)	94,11	26 months
Bell CL et al. (2011)	Retroperspective study	655 total patients	Osteoporosis	BPs	898 24/898 in BP patients	a) Implant success b) implant failure	a) 100% b) 0%	100 %	19.75 months
Martin DC et al. (2010)	Cross sectional study	589,0	Osteoporosis	ALN (95%) RSN IBN	NR	a) implant loss b) MRONJ	a) 16 patients out of 589 had 26 failing implants; success rate b) none	97,24 %	NR, Early and late failure less 1 year later 1 year
Famili P et al. (2011)	Retroperspective study case series	211 in total; 22 osteoporsis	Osteoporosis	Oral BPS ALN IBN	347 in total; 75 in oral BP group	a) implant loss b) MRONJ c) overall success rate	a) 1 failed in bp patient b) none c) 98,7%	98,7 %	NR
Sreenivas Koka et al. (2010)	Retroperspective study case series	82 BP, 55 non BP	Osteoporosis	BPs	166 in non-BP 121 in BP	a) MRONJ b) survival rate	a) none b) NON BP: 163/166 = 98,19% BP: 120/121 = 99,17%	99,17 %	NR
Memon S et al. (2012)	retrospective chart-review study	100 BP, 100 non BP	Osteoporosis	Oral BPs	153 in oral BP 132 non-BP	a) success rates	a) BP: 93,5%; non-BP: 95,5%	93,5 %	4-6 months
Nelson B Watts et al. (2019)	Randomized controlled trial	4550 in total; 212 patients osteoporosis	Osteoporosis	Denosumab 60mg/6 months	212 patients recieved implants	a) MRONJ b) failure case	a) 1 out of 212 b) none	100 %	NR
Koszuta P et al. (2015)	Prospective cohort study	20 HRT, 50	Osteoporosis	HRT with low doses of estrogen	NR	a) implant success rate b) peri-implant bone loss	a) 75% HRT, 92,9% in control group. b) 25% in HRT, 15% in control group	75 %	6 months
Demarosi F et al. (2010)	Prospective study	21,0	Osteoporosis	BPS ALN 18x Clodronate 2x RSN 1X All oral	38	a) implant sucess b) implant failure c) MRONJ	a) 36/38 (94,73%) b) 2/38 (5,27%) c) None	94,73 %	12.1 months
Dubey P et al. (2020)	Prospective clinical study	26,0	Osteoporosis	ALN 22x RSN 3x Calcitonin 1x	40	a) implant failure b) implant success	a) 6 (15%) b) 34 (85%)	85 %	42.1 months.

2.5 CONTENT AND SCOPE

The thesis consists of an abstract, keywords, a problem statement, literature search methods, an explanation of the mechanisms of action of osteoporosis medications, the process of osseointegration, and post-surgical complications with a discussion of the success of dental implants in patients undergoing osteoporosis treatment.

2.6 STATISTICS

To determine overall mean values for the implant success in osteoporotic patients undergoing medicational treatment, the following calculations were performed with Microsoft® Excel 2024:
The mean success rates of the included studies were added and divided by the total number of included studies.
The same method was applied to get values for a more specific outcome parameter, such as a mean failure rate.
To determine the percentage distribution of failed implants according to their location the number of implants in a specific location was multiplied with 100 and divided by the total number of failed implants.
For the determination of a mean age the ages of the individuals were added and divided by the total number of people, which were taken into account.

3. LITERATURE REVIEW

3.1 OVERVIEW OF OSTEOPOROSIS, PREVALENCE, ITS CAUSES AND TYPES

Osteoporosis, also called a silent disease, is a skeletal condition characterized by a decrease in the mass and volume of normally mineralized bone (6,7). As the name indicates, the bone is becoming more porous, directly impacting its mechanical strength, making it more fragile and more susceptible to fractures. Due to an increase in the age of the population and, therefore, an increased life expectancy, osteoporosis has become a global epidemic (8). The disease is also referred to as a silent disease, meaning its course is asymptomatic until fractures occur, which, by implication, can lead to secondary health problems and even death (8). Regarding recent statistics from the International Osteoporosis Foundation, it has been estimated that currently, more than 200 million people are affected and suffering from osteoporosis worldwide, including both sexes and all races (8). According to recent estimations, one in five men and one in three women over 50 years will

experience osteoporosis fractures in their lifetime. Although this disease affects all genders, ages, and ethnicities, it is more prevalent in Caucasians, older people, and women (8).

The bone tissue undergoes a continuous remodeling process to maintain a healthy skeleton, which is essential for executing important skeletal functions (9). This process consists of two phases, known as the bone resorption phase, in which bone is broken down, and the remodeling phase, in which new bone is formed (9). Bone loss occurs as soon as the rate of bone resorption is more extensive than the rate of bone formation (8). The bone mass grows from youth to adulthood and peaks at puberty when bone loss starts (8). The peak bone mass varies and is primarily determined by several factors, including genetic factors, endocrine status, overall health, gender, and physical activity (8). The process of bone remodeling has a crucial function in repairing microfractures and preventing them from becoming macrofractures, subsequently leading to a weakened bone (8). Several factors (e.g., age, hormones, nutrition, lifestyle, medical conditions) can cause an increased imbalance in the rate between bone resorption and bone formation, leading to an architecturally weakened structure with a remarkably reduced bone mass (8). These different factors, which affect bone metabolism, make up the classification for osteoporosis based on two groups: primary and secondary osteoporosis (8).

Primary osteoporosis can be divided into two subgroups, which are involutional osteoporosis type I and involutional osteoporosis type II (8). Involutional osteoporosis type I is often referred to as postmenopausal osteoporosis, occurring in women after menopause, and mainly affects the resorption rates of trabecular bone caused by a deficiency of estrogen (8). Involutional osteoporosis type II instead occurs in men and women and is often referred to as senile osteoporosis, meaning that the lost bone mass is due to the ageing of trabecular and cortical bones (8).

Secondary osteoporosis is caused by several different factors, such as lifestyle changes, medications, and different diseases (8). Lifestyle changes include, e.g., vitamin D insufficiency, high salt intake, smoking, alcohol abuse, and low intake of calcium, whereas genetic diseases such as cystic fibrosis, osteogenesis imperfecta, hemochromatosis, and Marfan syndrome are also secondary causes for osteoporosis (8). Other secondary causes for osteoporosis include endocrine disorders, such as central obesity, diabetes mellitus type 1 and type 2, hyperparathyroidism, as well as other factors such as AIDS/HIV, Amyloidosis, congestive heart failure, or idiopathic scoliosis (8).

Although there are currently many known risk factors associated with causing osteoporosis, it is still a silent disease, which in many cases remains undetected (8). The pertinent clinical sequelae of osteoporosis are fractures and the complications resulting from them (8). That is why fractures in adults older than 50 years at any skeletal site, such as in the vertebrae, distal forearm, or proximal femur, need further assessment and diagnosis (8). Osteoporosis is preventable by a recurrent assessment of the bone mineral density and early treatment if needed (8). By implication, increased

awareness among doctors and the general population can slow this epidemic, and the big financial burden on the health insurance systems can be lowered (8).

3.2 COMMON MEDICATIONS AND THEIR GROUPS

The treatment of osteoporosis is broadly diversified, including a broad spectrum of treatments, ranging from lifestyle changes to medications (8). The medications for treating osteoporosis can be classified into two main groups: antiresorptive and anabolic agents (9).

Antiresorptive agents are designed to decrease bone resorption while slowing down the cells that break the bone (8). On the contrary, anabolic agents promote the cells that form the bone (osteoblasts), therefore inducing bone formation (10). Antiresorptive agents compromise estrogen; bisphosphonates (BPs) such as risedronate, alendronate (ALN), zoledronic acid, and ibandronate (IBN); selective estrogen receptor modulators (SERMs) such as raloxifene; human monoclonal antibody against receptor activator of nuclear factor kappa beta (RANKL), such as denosumab; and strontium ranelate (8). In terms of anabolic therapy, there are currently only two approved agents, which are teriparatide (TPTD) and abaloparatide (10).

The most widely used drug for the treatment of osteoporosis are BPs (8). Risedronate (RSN) is used in both men and women for the treatment and prevention of glucocorticoid-induced osteoporosis and postmenopausal osteoporosis. At the same time, a drug holiday is recommended after seven years of therapy (8). It has successfully reduced vertebral, non-vertebral, and hip fractures (8). Another BP used in the prevention and treatment of osteoporosis is IBN, which has shown efficiency in reducing spinal fractures in postmenopausal women but has no proven effect in reducing the risk of hip and non-vertebral fractures (8). Zoledronic acid (ZA) is administered intravenously once a year and is effective in preventing and treating postmenopausal osteoporosis as well as osteoporosis in men and glucocorticoid-induced osteoporosis (8). Its effect reduces the risk of vertebral, non-vertebral, and hip fractures (8).

Other antiresorptive therapies include estrogen replacement therapy (ERT), which is used only as a prevention for osteoporosis in postmenopausal women who are at high risk and can not receive non-estrogen medications (8). Raloxifene is a SERM and is indicated in women with postmenopausal osteoporosis (8). It has a proven effect in reducing vertebral fractures, while its effect in lowering non-vertebral fractures and hip fractures has not been demonstrated (8). Denosumab, which is a human monoclonal antibody against RANKL, is the choice of treatment for postmenopausal women at high risk of fractures, patients with a history of osteoporotic fractures, and the choice of treatment in patients who do not tolerate or failed other therapies (8). It reduces the risk of fractures in the vertebral, non-vertebral, and hip sites (8).

An anabolic agent that is used in the treatment of postmenopausal osteoporosis, as well as in patients who have failed other treatment options, is TPTD (8). Additionally, TPTD is used in treating idiopathic and hypogonadal osteoporosis in men to increase bone mass (8). The second anabolic agent that is approved for clinical use is abalaoparatide, which is indicated in patients with severe osteoporosis, intolerability to other medications, and in glucocorticoid-induced osteoporosis (10) Both anabolic agents have been proven to increase bone mineral density in the femoral, hip, and spine regions and, thus, effectively reduce the risk of fractures in the vertebral, non-vertebral, and hip sites (10,11).

It can be concluded that all therapies are thoroughly effective, but it is important to mention that BPs are usually the first choice for osteoporosis treatments, closely followed by denosumab (12).

3.2.1 BISPHOSPHONATES, DENOSUMAB, AND ANABOLIC AGENTS MECHANISM OF ACTION

The structure of BPs is similar to the structure of native pyrophosphate, and it can be divided into two groups, which are nitrogen-containing (N-BPs) and non-nitrogen-containing BPs (non-N-BPs) (13). N-BPs and non-N-BPs primarily differentiate in their chemical structure and their mechanism of action (14).

ALN, RSN, IBN, pamidronate (ADP) and ZA are N-BPs, while non-N-BPs include etidronate, clodronate, and tiludronate (13). All BPs attach to the hydroxyapatite binding sites on the bone, especially in areas with active resorption, thereby inhibiting bone resorption (13). As soon as osteoclasts resorb the bone, the BPS embedded in the bone are released and impair the osteoclast's ability to resorb bone (13).

The main mechanism of action of N-BPs is by inhibiting farnesyl pyrophosphate synthase, which is a key regulatory enzyme in the mevalonic acid pathway and also has a crucial role in promoting the attachment of osteoclasts to the bone (13,15). By inhibiting this regulatory enzyme, the osteoclasts detach from the bone surface, consequently inhibiting bone resorption (13). Non-N-BPs become incorporated into molecules of the newly formed adenosine triphosphate (ATP) due to their structural similarity to inorganic pyrophosphate (15). These non-functional and nonhydrolyzable analogues of ATP are thought to be cytotoxic to osteoclasts since they inhibit several ATP-dependant processes, thereby initiating osteoclast apoptosis, which consequently leads to a decreased bone breakdown (13,15). Another effective osteoporosis medication is denosumab, a fully human monoclonal antibody against RANKL (16). RANKL can stimulate osteoclast formation and activity and, therefore, is a crucial mediator in terms of bone resorption (17).

Denosumab is capable of binding to the cytokine RANKL with high affinity and specificity and, therefore, inhibits its action; as a result, RANKL can not interact with its receptor RANK on osteoclasts, consequently leading to inhibited osteoclast action and maturation (17). Corresponding to that sequence of events, bone resorption is slowed down (6).

Although both BPs and denosumab target osteoclasts and are very effective in treating osteoporosis, their disposition throughout the body is a crucial difference (16).

BPs have a strong affinity to the bone and, therefore, become enmeshed in the bone mineral, where they stay until they are released during bone resorption (16). On the other hand, denosumab is present in the extracellular milieu and is not associated with bone tissue, meaning that it is located between bone cells and does not bind or interact with the components of the bone tissue itself (16).

The mechanism of action of anabolic agents lies within promoting the cells that form the bone (osteoblasts), therefore inducing bone formation (9). The parathyroid gland secretes the parathyroid hormone (PTH), which is a crucial mediator in calcium homeostasis that increases serum calcium concentrations (10). The increase of serum calcium concentrations is achieved by promoting calcium release from the bone, reuptake of renal tubular calcium, and intestinal calcium absorption (11). PTH and parathyroid hormone-related protein (PTHrP) bind to the identical receptor, namely the PTH 1 receptor (11). TPTD is a synthetic analogue of PTH, whereas abaloparatide is a synthetic analogue of PTHrP (11). Occasional administration of these anabolic agents leads to a constant manifestation of PTH and PTHrP, leading to augmented bone production (11).

3.3 ANTIRESORPTIVE AND ANABOLIC DRUGS IMPACT ON BONE FRACTURE HEALING

Since BPs inhibit osteoclast-mediated bone resorption, which is a crucial component of fracture repair, there have been rising concerns about their effect on bone healing (18). A meta-analysis of randomized control trials by Deting Xue et al. in 2014 examined the effect of BPS on bone healing (19). Eight qualifying randomized control trials with 2,508 patients were included (19). The findings of the meta-analysis showed that no significant differences could be observed in indirect bone healing either in the short time (within three months) or within the long term (more than 12 months) postoperatively between the BP-receiving group and the control group (19).

Another meta-analysis, conducted by Yongquan Gao et al., researched the effect of BPs on fracture healing time and changes in bone mass density (BMD) (20). A thorough examination was conducted on 16 studies, including 5,022 patients (20). The meta-analysis concluded that BPs demonstrated no significant impact on the required time for fracture healing, whereas they could significantly increase BMD (20).

Another study, which was conducted by Stephen L Kates and Cheryl L. Ackert-Bicknell, examined how BPs affect fracture healing (21). Larger fracture calli and delayed remodeling from woven bone into lamellar bone have been observed for BP treatment in animal models (21). Although a larger fracture callus is observed in the animal models, the fracture callus formation itself is not delayed (21). On the other hand, the *de novo* use of BPs for humans after a fracture has been studied and has shown no effect on fracture healing (21). On the contrary, it has been observed that fracture healing in patients undergoing long-term treatment with BPs is slightly delayed (19). Still, there are no differences in terms of fracture union (21). Several authors reported that the long-term use of BPs is linked to a possible development of atypical femoral fractures, which, by implication, show a delay in healing in 26% of these fractures (21).

Stephen L Kates and Cheryl L. Ackert-Bicknell concluded that the use of BPs in acute fracture management is considered safer compared to the long-term use of BPs (21). This conclusion is based on the unknown effect of the long-term use of BPs before typical fractures and the proven evidence suggesting a negative influence on healing in the case of atypical fractures (21).

According to an evidence-based review conducted in 2020 by Young Ho Shin et al., denosumab seems to have properties similar to BPs in bone healing (22). Animals treated with denosumab have been shown to have an increased callus volume, as well as delayed remodeling (22). Regarding denosumab-treated patients, the clinical data is rather little (22). The importance of evaluating fracture reduction in osteoporosis patients treated with denosumab becomes clear when looking at the extent of the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every six months) study (22). This international study, conducted in 2009, results from a three-year randomized and placebo-controlled research effort (22). The study included 7,808 postmenopausal women, who were randomly given either subcutaneous injections of 60 mg denosumab or a placebo every six months. During the study's conduction, 851 non-vertebral fractures in 667 patients were observed (22). The study showed that in patients receiving denosumab, either six weeks before or after the fracture, no signs of delayed healing or nonunion of the fracture site could be observed (22). Regarding the complication rates associated with fractures, no significant differences could be observed between the denosumab-receiving and placebo-receiving groups (22). The primary SERM used in the treatment of osteoporosis is Raloxifene (22). An animal study that involved ovariectomized rats concluded that Raloxifene moderately inhibited callus remodeling but did not have any negative influence on the effect on the rate at which fracture repair progressed (22). Moreover, the study concluded that Raloxifene causes calluses with larger chondrocyte areas, greater mineralization, and decreased time for fracture healing (22). These results could be observed in metaphyseal and diaphyseal bones (22). Unfortunately, to date, there is no clinical study evaluating the impact of SERMs on fracture healing in humans (22).

In terms of anabolic agents the use of PTH has shown beneficial effects on bone fracture healing in animal studies (23). However, a strong beneficial effect on fracture healing in human studies could not be confirmed (23). Until today only one animal study assessed the influence of PTH on fracture healing in maxillofacial bones, concluding that PTH might have a beneficial impact on fracture healing (24). Another clinical study concluded that the administration of PTH results in a faster fracture healing in hip fracture cases seen radiologically (25). However, this had no positive or negative effect on the occurrence rates of delayed or non union rates of fractures (25).

3.4 ANTIRESORPTIVE DRUGS AND MRONJ: COMPLICATIONS IN BONE HEALING

Although antiresorptive drugs, in general, seem to be quite safe, there are still severe complications associated with them, which are not fully understood yet (26). MRONJ is defined as a rare but serious reaction to drugs leading to progressive bone destruction in the maxillofacial region (26). The disease is characterized by exposed bone, which does not heal and especially appears in patients with past or ongoing use of antiresorptive or antiangiogenic agents without them being exposed to radiation in the region of the head and neck (26).

The clinical expression of MRONJ is classified according to a four-stage grading system (27). Stage 0 patients have non-specific symptoms, clinical and imaging findings involving pain or non-healing bone in the extraction socket (27). In stage 0 patients, there is no specific exposed bone (27). Stage 1 is characterized by fistulas that probe to bone or by exposed and necrotic bone, while the evidence of infection is absent (27). The patients are asymptomatic (28). Stage 2 patients show exposed and necrotic bone or a fistula, which is probable to the bone (28). An infection is present, which is characterized by pain and erythema (28). Purulent drainage can be present or absent, and the pain is usually located around the region where the bone has been exposed (28). Stage 3 patients are showing severe clinical expressions, such as extra-oral fistula, pathologic fracture, or osteolysis, which extends from the mandibula's inferior border to the maxillary sinus floor (27). The exposed necrotic bone extends past the region of the alveolar bone, e.g., *ramus mandibulae*, *sinus maxillaris*, and zygoma in the maxilla (28).

The detailed pathophysiology of MRONJ remains unknown, although MRONJ is closely associated with antiresorptive drugs (28). The time of MRONJ occurrence greatly varies between BPs and denosumab and is highly dependent on the dosage, way of administration, as well as duration of the treatment (26). BPs administered orally tend to develop MRONJ within 33 months, whereas BPs administered intravenously can develop MRONJ within up to 48 months (26). However, denosumab instead has an early onset of the disease, typically occurring shortly after administration (26).

The prolonged use of BPs, as well as high dosages and intravenous administration, are all risk factors that are independently contributing to an increased risk of MRONJ (29). The prevalence numbers for the occurrence of MRONJ comparing intravenous vs oral BPs differ from country to country (28). According to a 4-year retro perspective study conducted in Sweden, the prevalence of MRONJ among patients treated with oral BPs is 0.043%, while the risk among patients treated with intravenous BPs is significantly higher at 1.03% (30). The same study conducted that high-dose usage of denosumab results in a 3.64% risk of developing MRONJ (30).

Further data was collected in a literature review conducted by M. Kawahara in 2021 (31). The incidence of MRONJ in patients taking oral BPs for osteoporosis ranges from 1.04 to 69 per 100,000 patient-years, while the incidence in patients receiving intravenous BPs ranges from 0 to 90 per 100,000 patient-years (31). In terms of patients receiving denosumab as a treatment for osteoporosis, the incidence ranges from 0 to 30,2 per 100.000 patient-years (31).

The overall risk of developing MRONJ after surgical intervention amidst osteoporosis patients taking BPs extends from 0.02% to 0.05%, according to the American Association of Oral and Maxillofacial Surgeons (AAOMS) (32). This result intersects with the placebo group, which showed a 0%-0.02% risk of developing MRONJ after surgical intervention (32).
However, for osteoporosis patients undergoing treatment with Denosumab, the prevalence of MRONJ is higher, ranging from 0.04% to 0.3% (32).

Although the risk of developing MRONJ is inevitable, the incidence of this disease in osteoporotic patients taking BPs is 0.02%- 0.05% and, therefore, not significantly different from that in healthy patients (29). However, the prevalence of MRONJ in patients receiving Denosumab is significantly higher, ranging from 0.04% -0.3 % (32).

3.5 PROCESS OF IMPLANT OSSEOINTEGRATION

Osseointegration of dental implants is of enormous importance and plays a major role in terms of implant stability as well as in long-term clinical success (33). Osseointegration is defined as ”*A direct connection between living bone and a load-carrying endosseous implant at the light microscopic level.”* (33). The American Academy Of Implant Dentistry defined osseointegration as *“Contact established without interposition of nonbone tissue between normal remodeled bone and an implant entailing a sustained transfer and distribution of load from the implant and within the bone tissue.”* (33).

Any lesion of the pre-existing bone matrix will activate direct bone healing, which occurs in defects, primary fracture healing, and during osseointegration (34). When the matrix is revealed to extracellular fluids, growth factors and non-collagenous proteins are released and initiate bone repair

(34). Due to chemotaxis, osteoprogenitor cells from the endocortical and periosteal bone and the bone marrow relocate into the lesion site (34). Proliferation of the osteoprogenitor occurs, which will then differentiate into osteoblasts and osteoblast precursors (34). Following this, bone deposition in the defected area, in the fragment ends, and on the implant surface is initiated (34). Once the activation process has finished, osseointegration undergoes a three-stage biologically determined program that includes integration by forming woven bone, adapting the bone mass to load, and adapting the bone structure to load (34).

Woven bone is the first bone tissue that forms and is considered a primitive type of bone tissue (34). It is characterized by a relatively low mineral density, profuse and irregularly shaped osteocytes, and a random orientation of its collagen fibrils (34). Woven bone expands by forming a scaffold of plates and rods and can rapidly spread in the adjacent tissue (34). The formation of primary spongiosa, which is capable of bridging gaps less than 1 mm in a few days, is the result of the formation of the primary scaffold linked with the development of the vascular net (34). It can be concluded that woven bone is an ideal filling material for open spaces and for creating bridges between the implant and the bony walls (34).

From the second month on, the properties of the newly formed bone are modified into lamellar bone or another less-known modification, the parallel-fibered bone (34). Lamellar bone is the most detailed type of bone tissue (34). Due to the arrangement of collagen fibrils into parallel layers with an interchanging course, the highest strength is achieved (34). Parallel-fibered bone can be considered a medium between lamellar and woven bone due to its collagen fibrils, which are orientated parallel to the surface with no preferred orientation (34). The orientation of the fibrils is a crucial difference and makes lamellar bone anisotropic, whereas parallel-fibered bone is isotropic (34). Another key difference is the linear apposition rate, which is 3-5 times larger in parallel-fibered bone than in lamellar bone (34). Unlike woven bone, parallel-fibered bone and lamellar bone can not form a scaffold and only grow by apposition on a preformed stable foundation, such as woven bone, existing or untouched bone, and the implant surface (34).

The adaption of bone structure to load includes bone remodeling and modeling, which represents the final step of osseointegration (35). Bone remodeling is a lifelong process that repeats itself repeatedly and is further subdivided into five underlying steps: activation, resorption, reversal, formation, and termination (34,35).

During the activation step, osteoclast precursor cells from the circulation are mobilized and activated (35). The lining cells detach from the underlying bone and form an elevated canopy over the resorption site, thereby exposing the bone surface (35). The resorption pit of the surrounding bone is isolated by mononuclear cells, which fuse and then form multinucleated preosteoclasts (32). The preosteoclasts bind to the bone matrix and create sealing zones around the bone-resorbing

compartments (35). This step is of great importance to ensure that bone remodeling only takes place when it is required (35).

Regarding the resorption phase, it is important to mention that osteocytes regulate osteoclast activation and differentiation (35). The rearrangement of osteoclast results in a cascade of different actions (35). Following this event, it results in attachment to the bone surface, the creation of a sealing zone, and the creation of a disarranged border that enhances the secretory surface (35). Carbonic Anhydrase II is an enzyme that generates protons pumped by osteoclasts into the resorbing compartment to dissolve the bone mineral (35). In more detail, the proton pump H+-ATPase pumps H+ into lacunae, which is coupled to the transport of CL- via chloride channels and thereby maintains electroneutrality (35). Consequently, the proteases cathepsin K and matrix metalloproteinases degrade the collagen-rich bone matrix (35). The programmed cell death of osteoclast ends the resorption phase and assures that the resorption rate does not exceed (35).

The reversal phase is the third phase of bone remodeling, where bone resorption switches to bone formation (35). To date, this process is not fully understood but is thought to be composed of two major events (35). In the first step, the bone surface, which has been resorbed, is prepared for the accumulation of a new bone matrix, and further signalling, which is not fully understood yet, occurs that couples resorption to formation (35). This bone surface preparation is executed by osteoblastic lineage cells (35). These lineage cells remove unmineralized collagen matrix while embedding a non-mineralized matrix line to improve osteoblast adherence (35).

The penultimate stage of bone remodeling is formation, which can be subdivided into two parts (35). In the first step, type 1 collagen osteoid matrix is secreted by synthesized osteoblasts, while in the second step, osteoid mineralization is regulated by osteoblasts (35) The bone mineralization process is complex and poorly understood (35). In this process, hydroxyapatite crystals are deposited among collagen fibrils, and it is controlled by regulating systemic phosphate and calcium concentrations, local phosphate and calcium concentrations, and by non-collagenous proteins and pyrophosphate, which are local inhibitors of mineralization (35).

The termination of bone remodeling is initiated once the mineralization process is completed (35). During the termination phase, osteoblasts endure apoptosis and change into bone-lining cells or differentiate into osteocytes when they become encased in the bone matrix (35).

3.6 DENTAL IMPLANT SUCCESS CRITERIA

It is crucial to define the success parameters for dental implants further to evaluate their success accurately. To date, there is still a lack of unity in terms of the criteria defining the success of dental implants (36). Precise success criteria were brought forward by Albrektsson et al., declaring

an implant successful if there is no mobility and radiolucency around the implant and the absence of infection and pain after the implant treatment (37). Other factors that are of great importance to achieving a successful outcome in terms of dental implantation include the following (36):

1. The implants'materials biocompatibility
2. The implants'macroscopic and microscopic surface
3. The surgical technique itself
4. Osseointegration of dental implant
5. During the healing phase, immobility of the implant in relation to the bone

There is still a discourse on whether marginal bone loss (MBL) should be considered a success criterion or not (36). In some classifications, including Albrektsson et al., it is stated that a MBL of 0.2 mm occurring in the first year around dental implants still considers the implants to be a success (36). Another study conducted by Galindo-Moreno P et al. aimed to analyze if MBL can be established as a criterion to determine the prognosis of an implant (38). It has been concluded that 0.5 mm of radiographic MBL within six months is the limit for determining whether the dental implant succeeds. Radiographic MBL of more than 0.5 mm within the first six months usually displays no radiographic success in the 12-month follow-up (38). Three studies, included in Table 2, have analyzed the MBL, which will be considered a criterion in this literature review to determine success or failure rates (39,44,53).

3.7 DETAILED DATA OF INCLUDED STUDIES

As a matter of course, all treatments bring forward survival and failure rates (36). The mean success rate of dental implants in patients undergoing medicational treatment for osteoporosis is 94.25%, according to the data from Table 2, consequently leading to a failure rate of 5.75% (Table 2). The medicational treatment for osteoporosis involves BPs, denosumab, SERMs, and PTH (Table 2). A single case of Osteonecrosis was reported in the studies (39-56).

Detailed data about follow-up periods could be obtained from 13 different studies (39,40,42-45,50,51,53-55). Four studies did not provide specific follow-up periods (41,48,49,52). Therefore, the articles were grouped according to their follow-up periods in the short term, from 4 months up to 3 years, and medium-term, from 3 to 7 years. The short-term follow-up group involved eight studies, whereas the long-term group involved five studies (39,40,42-45,50,51,53-55). The success rate in the short-term follow-up group was 94.01%, whereas in the medium-term group, it is 92.27% (39,40,42-47,51,53-55).

In the short-term follow-up group, three studies have been identified that gave detailed information on the failure cases (40,46,50). The reported failures in this group were the inability of the dental implant to osseointegrate and extensive mobility of the implant, which consequently led to its removal of it (40,46,50).

In the medium-term follow-up group, detailed information on failure cases could be obtained from two studies (43,55). Failures in this group included the inability of the dental implant to osseointegrate and implants that at first osseointegrated and later lost their integration (43,55).

These studies were analyzed and summarized in Table 3 in terms of author, age/gender, medical status besides osteoporosis, medication, duration of medication use, implant side, and the follow-up group they belong to (Table 3).

Table 3 - Detailed data of failed implants

Author	Age/Gender	Medical status (besides osteoporosis)	Medication	Duration of medication use	Implant side	
Yajima N, et al. (2017)	**68/F**	NR	Bisphosphonates	12m	46	Medium
Yajima N, et al. (2017)	**67/F**	NR	Bisphosphonates	48m	35	Medium
Yajima N, et al. (2017)	**75/F**	NR	Bisphosphonates	60m	46	Medium
Zahid TM, et al. (2011)	**72/F**	NR	Alendronate; 70mg/ week	NR	46	Short
Zahid TM, et al. (2011)	**75/F**	NR	Alendronate	6m	25	Short
Zahid TM, et al. (2011)	**75/F**	NR	Ibandronate; 150mg/month	NR	33	Short
Sreenivas Koka, et al. (2010)	**82/F**	NR	Fosamax (alendronate) 70mg/w	72m	NR	Up to three years short
Dubey P, et al. (2020)	**56/M**	NR	Alendronate	48m	13, 44, 46	Medium
Dubey P, et al. (2020)	**52/M**	NR	Alendronate	5m	36	Medium
Dubey P, et al. (2020)	**61/M**	NR	Alendronate	12m	11	Medium
Dubey P, et al. (2020)	**65/M**	NR	Alendronate	18m	26	Medium
Dubey P, et al. (2020)	**67/M**	NR	Risedronate	24m	22	Medium
Dubey P, et al. (2020)	**51/M**	NR	Alendronate	12m	11	Medium
Mozzati et al. (2015)	**56/F**	Smoker	Alendronate	12m	23	Short
Mozzati et al. (2015)	**59/F**	Smoker	Risendronate	2m	25,27 with sinus lift	Short
Mozzati et al. (2015)	**62/F**	Corticosteroids/ Smoker	Risendronate	37m	17 with sinus lift	Short
Mozzati et al. (2015)	**67/F**	NR	Risendronate	33m	25	Short
Mozzati et al. (2015)	**51/F**	Smoker	Risendronate	21m	17	Short
Mozzati et al. (2015)	**62/F**	NR	Ibandronate	27m	13	Short
Mozzati et al. (2015)	**67/F**	NR	Alendronate	37m	36	Short
Mozzati et al. (2015)	**74/F**	Diabetes/Smoker	Ibandronate	69m	33	Short
Mozzati et al. (2015)	**54/F**	Smoker	Alendronate	21m	16 with sinus lift	Short
Mozzati et al. (2015)	**67/F**	Smoker	Alendronate	66m	23	Short
Mozzati et al. (2015)	**58/F**	NR	Ibandronate	44m	27 with sinus lift	Short
Mozzati et al. (2015)	**61/F**	Diabetes	Ibandronate	69m	34	Short
Mozzati et al. (2015)	**71/F**	Corticosteroids/ Diabetes	Alendronate	45m	33	Short
Mozzati et al. (2015)	**77/F**	Corticosteroids/ Smoker	Alendronate	82m	27 with sinus lift	Short
Mozzati et al. (2015)	**57/F**	Smoker	Risedronate	37m	27 with sinus lift	Short

In total, detailed data regarding failed dental implants could be obtained from 5 included studies for 31 cases in 28 patients (40,46,50,55). In a single case, the location of the implant was not provided

(47). Out of the 28 patients, 22 were females with a mean age of 66.23 years, and 6 were males with a mean age of 58.7 years (40,43,46,50,55).

In the short-term follow-up group, 10 dental implants failed in the upper posterior region, 3 in the upper anterior region, 3 in the lower posterior region, and 3 in the lower anterior region, consequently leading to a failure distribution of 52.63%, 15.79%, 15.79%, and 15.79% (40,46,50).

In the medium-term follow-up group, 1 dental implant failed in the upper posterior region, 4 in the upper anterior region, 6 in the lower posterior region, and none in the lower anterior region, consequently leading to a failure distribution of 9.09%, 36.36%, 54.55%, and 0% (43,55).

When combining these two groups to assess the overall distribution, the results are the following: 3 implants failed in the upper jaw incisor region, 4 in the upper canine region, 3 in the upper premolar region, 8 in the upper molar region, 3 in the lower canine region, 3 in the lower premolar region, and 6 in the lower molar region (40,43,46,50,55). The resulting percentage distributions of failed implants according to their location are summarized in Figure 1.

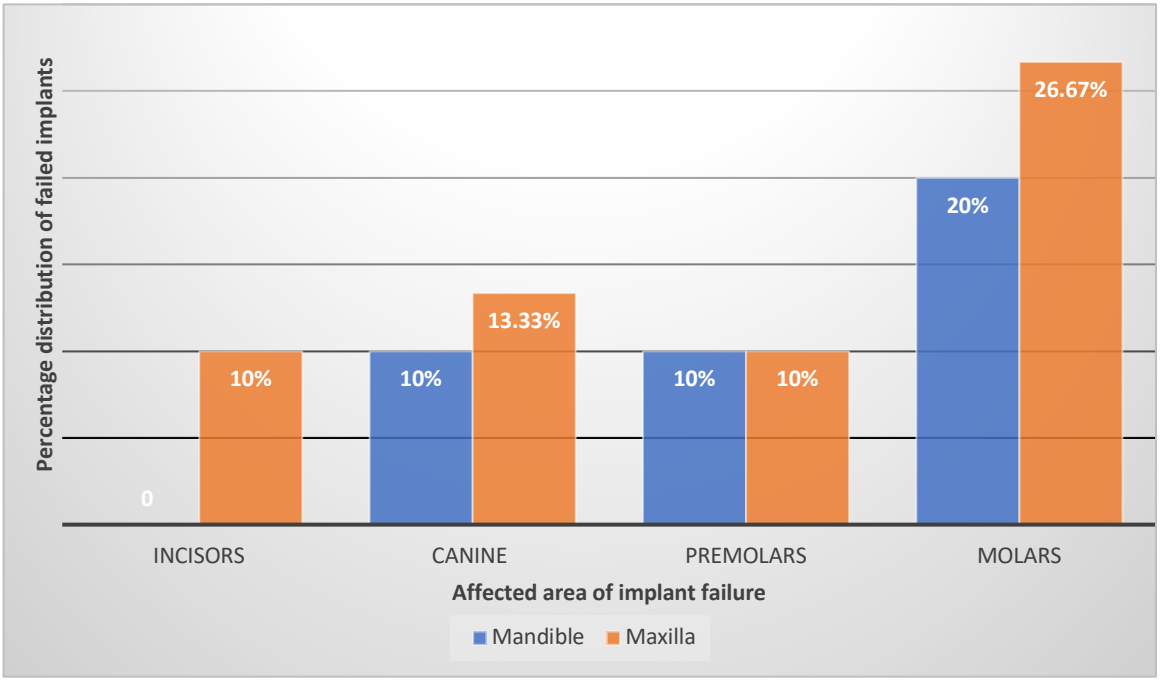

Fig. 1 - Distribution of failed implants according to their location

A sinus lift was performed on six out of the eleven failed implants in the upper posterior region (37). All six patients were reported smokers (37). The overall mean duration of osteoporosis medications use, including BPs and denosumab, was 35.3 months (40,43,46,50,55).

The studies stated two parameters to evaluate the outcome of the placed implants: implant success and implant failure (39-55). Out of all placed implants the implant success rate was 94.2%, whereas the implant survival rate was 96.8% (39-55).

However, most of the studies did not further specify the factors that consider an implant to have succeeded or survived (39-55). Moreover, the studies that stated detailed survival and success criteria displayed no uniformity in these (39-41,46,47,50,54).

Detailed data about bone loss around the implants could be obtained from four different studies (44,46,52,53). However, due to the lack of a mutual measuring system, the data could not be summarized in a mean value, which is why the results of all three studies must be looked at individually. Two studies reported a mean MBL of 1.35 mm ± 0.21 after three years and 0.66 mm ± 0.70 mm in patients receiving oral BPs (44,51). In patients undergoing HRT, the average bone loss was significantly higher, measuring 25%, whereas in the control group, the average bone loss measured 15% (53). Another study measured alveolar bone loss according to implant thread exposure (46). Fifty-one implants were placed in BP-receiving patients, of which 13 exhibited thread exposure ranging from one to eight threads (46). Only two out of the 13 implants showed thread exposure up to 8 threads, while all other thread-exposed implants showed 1 to 3 threads (46).

3.8 IMPACT OF BLOOD PRODUCTS AND IMPLANT PROPERTIES ON DENTAL IMPLANT SUCESS

To date, continuous research is ongoing in the field of medical care to further enhance healthcare practices. In terms of dental implants, research is conducted to facilitate better wound healing, as well as to improve the osseointegration of the implant (56,63). To achieve these goals, there have been new approaches, such as the involvement of blood products and modifications to the implant, such as to the shape, material, and surface coating (56,63).

3.8.1 PLASMA-RICH GROWTH FACTORS (PRGF), PLATELET-RICH FIBRIN (PRF), AND PLATELET-RICH PLASMA (PRP) IN IMPLANT DENTISTRY

PRGF has gained increasing attention in recent years in dentistry as a promising therapeutic modality (56). Anitua E. first described the use of PRGF in dentistry in 1999, stating advantages in terms of bone regeneration acceleration and acceleration of soft tissue healing (57). The main advantage of PRGF is the concurrent release of numerous growth factors, including transforming growth factor (TGF) -β, platelet-derived growth factor (PDGF), endothelial growth factor, insulin-like growth

factor-1 (IGF-1), vascular endothelial growth factor (VEGF), hepatocyte growth factor, and basic fibroblast growth factor (FGF) (56). VEFG is a potent mitogen factor that acts on endothelial cells, whereas PDGF, which is also a potent mitogen factor, stimulates osteoblast proliferation and thereby impacts bone resorption, which is mediated by osteoclasts (56). Another advantage of PRGF is the acceleration of bone regeneration around implants, especially when grafts have been used (40). Due to their gluelike quality, PRGF allows better fixation of the graft particles, preventing their distribution (40).

PRF is composed of a fibrin matrix rich in autologous leukocyte platelets (58). The fibrin matrix comprises a tetra molecular structure that compromises cytokines, platelets, and stem cells (58). This structure functions as a biodegradable scaffold and, therefore, favours microvascularization and is capable of leading epithelial cell migration to the surface (58). Furthermore, PRF can convey cells, which are involved in the regeneration of tissues, while continuing to release growth factors throughout the duration of 1 to 4 weeks, invigorating the setting for wound healing (58). Its complex structure, consisting of a robust fibrin matrix with advantageous mechanical properties, leads to a slow remodeling analogous to that of a blood clot (58). PRF exhibits excellent soft tissue and bone regeneration properties without causing inflammatory reactions and can be used alone or jointly with bone grafts (58).

PRP is characterized by a high concentration of autologous platelets within a small quantity of autologous plasma (59). The platelet concentration of PRP, at a minimum of 1.000.000/1L in a 5 mL volume of plasma, is multiple times higher than the average platelet count in human blood, which ranges from 150.000/1L to 350.000/1L (59). Following the initiation of the coagulation process in the wound site, the platelets enclosed in the autologous plasma release their alpha granules (60). The alpha granules incorporate many different growth factors, such as PDGF, VEGF, TGF, IFG-1, EGF, and FGF, which, by implication, encourage proliferation, chemotaxis, and cell differentiation (59,60). Not only does PRP have a procoagulant effect, but it is also a primary supply of growth factors, which supports fibroblast proliferation and tissue vascularization and, therefore, instigates and maintains wound healing (59).

It is essential to acknowledge that PRGF, PRF, and PRP not only share many advantages but also have some key differences in their properties and extraction methods, leading to varying advantages and disadvantages (60). In terms of extraction out of all three blood products, PRF is the only one that does not require the use of anticoagulants in the tube while it is being centrifuged (60). Furthermore, the extraction protocol varies, while the extraction protocol for PRF is considered easier than the extraction protocol of PRP and PRGF, resulting in reduced alterations due to an operator

error (60). After centrifuging, PRF presents the highest amount of platelets, the greatest amount of VEGF, PDGF, and TGF, around 65% of leukocytes, and a remarkable share of fibrin, fibronectin, and vitronectin compared to the other blood products (57). Another key difference lies within the speed of fibrin formation (60). PRGF and PRP interrelate with the additives calcium chloride and thrombin to initiate the process of fibrin polymerization, which directly affects the speed and mode of gelification (60). On the contrary, in PRF, thrombin is present in physiologic concentrations, leading to a slow and physiologic creation of the fibrin matrix, which is essential for the three-dimensional arrangement of the fibrin morphology (60). It can be concluded that growth factors play a significant role in wound, soft tissue, and bone regeneration (60). PRGF, PRF, and PRP all have shown promising results and thereby offer an excellent foundation for wound healing and tissue regeneration (60).

3.8.2 IMPACT OF BLOOD PRODUCTS ON THE IMPLANT SUCCESS

BPs, especially zoledronic acid, exhibit an anti-tumor effect by reducing VEGF and PDGF levels (56).

The idea behind using PRGF in patients receiving BPs is the assumption that the presence of growth factors can be a supplementary stimulation for tissue healing and contrasts the inhibition that is caused by BPs, thereby enhancing soft tissue and bone healing (40). Marco Mozzati et al. investigated the failure risk estimates in women who have osteoporosis undergoing BP therapy after the placement of dental implants associated with applying plasma rich in growth factor (40). The study population included 235 middle-aged women receiving oral BPs for the treatment of osteoporosis with a mean age of 60,7 ± 7.3 (40). The minimum follow-up period was 24 months, but it was dated up to 120 months (40). The implant survival criteria were stated as the following: Immobility at clinical examination, functional service when connected to a fixed prosthesis, absence of pain and infection, and absence of peri-implant radiolucencies in radiographic images (40). A total of 1267 implants were placed in 235 patients (40). All patients underwent professional oral hygiene one week before implantation and received antibiotic prophylaxis with 1g of amoxicillin every 12 hours from the day before surgery until five days post-surgery (40). The use of PRGF accompanied all implantation cases according to the protocol proposed by Anitua et al. (40). All implants were placed in liquid PRGF to bioactivate the implant surface (40). In the cases where sinus augmentation was performed, Bio-Oss was combined with PRGF during the immediate positioning of the implant (40). No cases of MRONJ were observed during the follow-up period, and a total of 16 implants failed in 16 different patients, leading to an overall success rate of 93,2% on a patient basis and 98,7% on an implant basis (40). All removed implants did not show any signs of infection and were removed due to mobility 1-3 months post-insertion (40). After successful bone healing, all failed implants were replaced and considered

as successful (40). Seven out of the sixteen failed implants were placed in combination with a sinus lift (40). Mozzati et al. considered the sinus lift to have the greatest impact on the implant success rate in patients receiving PRGF (40). Nevertheless, scientific evidence behind this observation was not declared (40).

Another study conducted by Steller D. et al. in 2019 investigated the impacts of PRF and PRP on the primary osteoblast adhesion onto titanium implants in a BP *in vitro* model (62). The osteoblast adhesion onto the implant side is an essential step to achieve osseointegration (62). To investigate the effect of PRF and PRP, the implants were colonized for 24 hours with ZA and osteoblasts, and it was concluded that ZA decreases the adherence of osteoblasts onto the implant surface (62). PRF and PRP were shown to revert this influence and increase primary adherence to zoledronic acid-treated osteoblasts on the implant surface (62). Consequently, PRF and PRP benefit initial bone apposition, leading to better primary healing in BP-treated patients (62).

3.8.3 IMPLANT SURFACE PROPERTIES – HYDROPHILIC VS HYDROPHOBIC DENTAL IMPLANTS

The modification of the surface of dental implants is a major subject of interest (63). Wettability is one of the surface properties that has gained a lot of interest due to its impact on biologic interactions in the implant-to-bone and implant-to-soft tissue interaction (63). Different studies concluded that hydrophilic surfaces enhance the contact between bone and implant and, therefore, positively impact osseointegration (64). Siqueira R et al. investigated the impact of hydrophilic titanium surfaces on bone formation and gene expression during osseointegration in an experiment with osteoporotic mice (65). It was shown that hydrophobic and hydrophilic implant surfaces could regulate bone response regarding osteoblast differentiation (65). Furthermore, a hydrophilic surface was shown to improve the process of osseointegration and increase bone volume and bone-to-implant contact in patients with manifested osteoporosis (65).

A study conducted by Lotz EM et al. also researched the effect of implant surfaces on osseointegration in osteoporotic rats (66). It was concluded that both hydrophilic and hydrophobic surfaces could osseointegrate successfully, but the degree of osseointegration was higher in the hydrophilic surface (66). Hydrophilic implant surfaces can deploy their control over the modified bone turnover in osteoporotic patients and can, therefore, facilitate osseointegration (66).

Sánchez-Puetate JC et al. investigated bone formation on hydrophilic and hydrophobic implant surfaces in an experiment involving BP-receiving murine (67). Both implant surfaces successfully osseointegrated in the BP-receiving rats (67). Compared to the hydrophobic surface, the hydrophilic

surface displayed better biomechanical performance, greater bone-to-implant contact, and superior bone volume (67).

It can be concluded that hydrophilic implant surfaces exhibit several advantages over hydrophobic surfaces in terms of altered bone turnover, such as in osteoporosis and as well in individuals receiving BPs (66,67). Those advantages include increased bone volume, higher bone-to-implant contact, and better biomechanical performance (66,67).

4. DISCUSSION

The medicational treatment for osteoporosis involves two groups of medications: antiresorptive and anabolic agents (9). Antiresorptive agents act by decreasing bone resorption, whereas anabolic agents act by inducing bone formation (9). Anabolic agents are usually the second choice of medications, primarily used in patients who did not tolerate the treatment with antiresorptive drugs (1). The vast majority of the included studies focused exclusively on the impact of antiresorptive drugs on implant success in osteoporotic patients. Due to anabolic agents being the second line of treatment and the use of antiresorptive drugs usually showing good results, there is a lack of data analyzing the impact of anabolic agents in terms of implant success in osteoporotic patients.

Moreover, the majority of available studies in this field either investigated the effect of BPs on the occurrence of MRONJ or the dental implant outcome in patients receiving BPs. However, most of the available literature addressing the dental implant outcome in BP patients was based on high-dosage intravenous BPs, which are usually administered for other medical conditions than osteoporosis. All these factors individually contributed to the lack of available data, which made it inevitable to include different study designs and studies ranging from 2010-2024.

The overall effects of antiresorptive drugs, as well as SERMS, on bone healing are generally considered to be safe (19-22). However, the available data only covers the *de novo* use of bisphosphonates and does not address the effects of these drugs on bone healing in the long term (19-21). Therefore, the effect of the long-term use of BPs on bone healing still remains unclear (22).

To date (2024) the impact of other therapies, such as SERMs, on bone healing has only been assessed in animal studies, and data involving humans is still lacking (22). However, animal studies concluded that this therapy does not impact the progression rate of bone healing but rather even decreases the time for fracture healing (22). In terms of anabolic agents, such as PTH the overall effect on bone fracture healing remains unclear (24). Animal studies suggested enhanced fracture healing, which could not be confirmed in human studies (24).

It needs to be addressed that all human studies, involving antiresorptive drugs and anabolic drugs, analyzed the impact on bone/fracture healing in body regions distant from the head and face region (17-19). Therefore, possible alterations in terms of bone healing can not be excluded for the oral and face regions. Further research involving longer follow-up times, general human studies, and studies especially addressing the head and neck region are needed.

In terms of MRONJ, only one single case was reported, which proposes that the placement of dental implants in patients undergoing medical treatment for osteoporosis is associated with a relatively low risk of developing this complication (32,52). This result is in accordance with the American Association of Oral and Maxillofacial Surgeons, which reported an overall low risk for MRONJ in patients taking oral BPs for osteoporosis (32). Denosumab has shown greater prevalance numbers regarding the risk of developing MRONJ after surgical interventions (32).

Nevertheless, MRONJ is a serious complication, and it is inevitable and of great importance to educate the patient regarding its potential risks (32). Further research is needed to fully understand the pathophysiology of this complication, as well as to further understand the impact of the individual risk factors associated with this complication.

Besides the occurrence of one single case of MRONJ, no other complications associated with dental implant placement in osteoporotic patients were mentioned in the included literature (39-55). This leads to the assumption that the placement of dental implants in this specific patient group is associated with relatively few complications. However, the interpretation of this result must be approached with caution, as the absence of complications mentioned in the studies does not necessarily imply that there have not been any complications.

This issue becomes clear when addressing the study conducted by Zahid TM et al. (46). The author assessed the influence of BPs on the alveolar bone loss around implants and concluded an overall implant success rate in BP treated patients with osteoporosis of 94,11%. However, upon evaluating the study in detail out of 51 placed implants 13 implants exhibited thread exposure ranging from one to eight threads (46). Nevertheless, these 13 implants were not considered to have failed, as they were still in place and fulfilling their function (46). However, this occurrence will significantly limit the aesthetics and complicate the hygiene.

This issue coincides with the lack of a consensus regarding implant success/survival and failure criteria, which makes it very complicated to compare the result accurately. It is of great importance that authors report difficulties, such as delayed healing and other complications such as thread exposure and take it into account for the implant success value.

Further studies are needed to clarify the occurrence of other complications besides MRONJ, especially addressing the healing and osseointegration process as well as long-term complications.

The present study did not find a difference in the success rate of dental implants in patients who are or have been undergoing medical treatment for osteoporosis compared to healthy patients. The placement of dental implants in these patients showed an overall success/survival rate of 94.25%, which in turn does not imply an influential association between osteoporosis medications and implant failure.

Due to the lack of a widely accepted consensus regarding the success criteria, all the data can only be put into relation and comparison within a limited scope. The authors articulated different success/survival and failure criteria, and some failed to provide specific criteria at all, making it challenging for the reviewer to put them into context accurately. In terms of implant survival, the overall survival rate was 9.8%, which is slightly higher than the implant success rate, which was 94.2% (39-55). This result must be viewed with caution since, in many cases, the specific criteria leading to success or survival are not clear and might overlap or differ between the groups.

The success rates in the short-term follow-up group and medium-term follow-up group did not significantly differ. However, the results are only partially comparable since the exact failure time of the implants was not provided, as well as the overall location distribution of all placed implants. Therefore, it remains unclear whether the implants failed during the first months or after several years. It can be concluded that both the short-term follow-up group and the long-term follow-up group exhibited overall great implant success rates and that there is no significant increase in implant loss within seven years after implant placement.

The extended literature review found an interesting pattern in the distribution of the failed implants according to their location. Out of all detailed failed implant cases, the majority of failures could be observed in the maxillary molar area, with a distribution of 26,67%, and in the mandible molar area, with a distribution of 20% (Fig. 1). Two studies reported a conspicuous number of failure cases in the maxillary posterior region, which is in line with the present study results of the failure cases in Figure 1 (40,45). One study reported that 70% of the failed implants were placed in the maxillary posterior region, whereas the other study stated that 56.25% of failed implants were placed in the maxillary posterior region (40,45). Both studies did not declare scientific evidence behind this occurrence, but the majority of the patients in which the implants failed were reported smokers, which inevitably brings forward an additional risk for implant failure (40,45).

There are several different factors, such as bone morphology, disease, and patient factors which could have led to this distribution. According to Misch the dominant bone type in the upper jaw posterior region is D4, which has a core of low density trabecular bone surrounded by a thin layer of cortical bone (68,69). The reduced density of bone in this region is a risk factor for the implant success. Moreover all patients included in this study were suffering from osteoporosis, which could

have even further decreased the quality of the bone in this region. In 66 % percent of the failure cases in the upper molar region, a sinus lift was performed, which brings forward an additional risk factor for implant success (Table 3). The maxillary posterior region is characterized by a low density bone type, which could have been further reduced due to the patients' disease and commonly involves the need for more extensive implant surgery, such as the performance of a sinus lift (68,69).

Moreover, a noticeable amount of implants failed in the lower jaw molar region with a distribution of 20% (Fig.1). This occurrence was not described in any of the included studies (37,40,43,47,52). According to Misch, the dominant bone type in this area is D2 bone, which is characterized by a core of dense trabecular bone surrounded by a thick layer of compact bone (68,69). Although in this area, the bone type is more favorable, and there is no need for extensive surgery, such as a sinus lift, lots of implant failures are concentrated in this region (Fig.1). Further studies are needed to clarify the reasons for the specific failure concentration, especially in the upper and lower jaw posterior regions of this particular patient group.

In terms of hormonal therapies such as SERMS and PTH replacement therapies, the available data suggested an overall similar implant success rate compared to healthy patients but did find a significant correlation between hormone therapy and peri-implant bone loss (50). These findings do not exhibit a statistical influence on the success rate but could lead to a more splendid risk of osseointegration failure (50). Generally speaking, the patient should be informed about this risk of partial bone loss during the process of osseointegration, but hormonal therapies do not exhibit a statistically increased risk for implant failure and are, therefore, not a contraindication for implant placement (50).

In terms of BP therapy, most of the studies did not state any discrepancies in terms of MBL except for one, which observed a greater risk of peri-implant bone loss in patients receiving BPs (43). They conclude that this might be due to osteoblasts and osteoclasts apoptosis as a result of the BPs, which by implication leads to a higher amount of acellular and avascular bone, which could be less resistant to the bacteria in the oral cavity (43). However, one study reported bone loss levels that did exceed the norm values; these findings were not confirmed in two other studies, which reported bone loss levels around implants within the norm value (41,48). The currently available data addressing the correlation between hormone therapies/BPs and peri-implant bone loss in osteoporotic patients is limited and partially contradictory. Therefore, additional studies with larger sample sizes are required to make a more accurate statement.

The use of blood products, such as PRGF, PRP, and PRF, has shown overall great results in enhancing soft tissue and bone healing and leading to better primary healing in BP-treated patients (37,53,59). The use of PRGF in implant placement was described in one study, which showed a 93.2% success rate on a patient basis and 98.7% on an implant basis (37). However, the high success rate is not an individual occurrence but correlates with the overall high success rate, which was also achieved without the use of PRGF (46). Nevertheless, blood products have overall great properties in terms of further supporting all healing stages and can thereby be recommended as an adjunctive measure to improve the overall healing course as well as the overall outcome (57). Despite that, the literature involving this specific patient group is limited, and further research is needed to comprehensively evaluate the impact of blood products on implant osseointegration and wound healing for these patients.

Regarding altered bone turnover, hydrophilic implants exhibit several advantages compared to hydrophobic implants, including increased bone volume, higher bone-to-implant contact, and better biomechanical performance (63,64). Due to the superior properties of hydrophilic implants, they can be considered as the primary choice of implants for patients receiving treatment for osteoporosis. However, the study results are limited to animal studies and further research is needed to understand and evaluate the effect of hydrophilic implants in osteoporotic patients undergoing antiresorptive therapy.

The recommendation of a drug holiday for these patients remains a topic of controversy (29). The success rates of dental implants in patients who did undergo a drug holiday before and after the treatment did not significantly differ from the patients who did not undergo a drug holiday (41,51,46,47). Therefore, the present study suggests that a drug holiday for these patients is not explicitly necessary. This result is following the position paper of the American Association of Oral and Maxillofacial Surgeons, which evaluates a drug holiday during antiresorptive therapy for nonmalignant diseases as controversial (29).

5. CONCLUSION:

The medicational treatment of osteoporosis involves two groups of medicaments, which are antiresorptive (BPs and Denosumab) and anabolic drugs (TPTD, Abaloparatide). The overall effect of antiresorptive drugs on bone healing is generally considered to be safe. This result only includes the *de novo* use of BPs and assesses the body regions distant from the oral and face regions. Studies involving the oral and facial region are lacking, as well as studies involving the long-term use of BPs.

The use of anabolic agents, such as PTH, is succesful in increasing the bone mass, but its impact on bone fracture healing remains unclear. This result is based on body regions distant from the oral and face regions.

The only reported complication was a single case of MRONJ, which suggests an overall low risk of developing this complication. No other complications besides MRONJ were reported for this specific patient group. General prevalence numbers of MRONJ in osteoporosis patients taking oral BPs reach from 0.02%-0.05%. This result leads to the assumption that osteoporosis medications do not lead to severe or nonsevere complications other than MRONJ in patients who have received dental implants.

Within the limitations of the present study, no differences in the success rate and survival rate of dental implants in patients who are or have been undergoing medical treatment for osteoporosis compared to healthy patients have been found. With a mean survival rate success/survival rate of 94.25%, dental implantation is generally entirely successful in these patients. There is a possible correlation between hormone therapies/ BPs and peri-implant bone loss in osteoporotic patients that needs further research to draw more precise conclusions. The extended literature review found a pattern in the distribution of failed implants, primarily concentrating in the upper and lower jaw molar regions.

The recommendation of a drug holiday could not be confirmed and remains a topic of controversy.

Blood products such as PRGF, PRF, and PRP exhibit great properties in further supporting all healing stages and can, therefore, be recommended as adjunctive therapy to reduce postoperative complications and improve dental implant success.

A generally accepted consensus on dental implant success/survival and failure criteria is needed to properly put the results into context. This consensus is needed for future studies. Dental treatments are never uniform and must always be approached on a case-to-case basis. Carefully examining the patient's general health, medical history, medication use, and psychological factors should be carried out constantly to provide the most suitable treatment.

Every dental procedure should be as minimally invasive as possible, and additional trauma should always be avoided to prevent complications.

Although many authors spoke of long-term success, the results of the present extended literature review need to be considered as short-term outcomes since most of the included studies had a follow-up time of less than five years.

Therefore, more extensive clinical trials, longer follow-up times, detailed success criteria, and surgical techniques are recommended to understand further and investigate the associated risks of osteoporosis medications on dental implantation.

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