4 Pharmacological Risk Assessment for Dental Implants

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Abstract

The process of osseointegration around dental implants is similar to the biological events occurring during bone repair and fracture healing. Therefore, bone metabolic activity plays a crucial role on the success of osseointegration, and dysregulation of bone metabolism can have a negative impact on bone healing and implant osseointegration. Accordingly, it could be hypothesized that drugs interfering with healing and bone metabolism could affect osseointegration and implant survival. Looking into the relationship between pharmacology, osseointegration, and dental implant drugs can open the door for new pharmacological innovations to improve implant success and avoid unnecessary complications, and it is also of special interest because most implant patients are elder adults that are often polymedicated. In this commentary we discuss the discoveries made by us as well as by other researchers regarding the effect of several drugs on bone, osseointegration, and implant survival. Of particular interest is the growing evidence showing that commonly used drugs such as nonsteroidal anti-inflammatories, serotonin reuptake inhibitors, and proton pump inhibitors could lead to implant failure.

Osseointegrated dental implants are considered one of the most important innovations in oral rehabilitation [1, 2]. Despite this importance and many advances in techniques, materials, and implant design, the potential for clinical failure remains a significant concern for both dentists and patients [1]. Osseointegrated dental implant success is dependent on the successful osseointegration [3]. Osseointegration is the direct structural and functional connection between the living bone and the dental implant surface, with a physiological process that resembles bone fracture healing [3]. Therefore, bone metabolic activities play crucial roles on the success of osseointegration [3].

Bone is continuously remodeling throughout life [4]. Osteoblastic bone formation and osteoclastic bone resorption are closely coordinated by a variety of local and systemic pathways that maintain bone mass constant [4]. Some pharmacological agents can interfere with the pathways that regulate bone metabolism and subsequently affect bone turnover, osseointegration, and ultimately implant survival. In addition, a large proportion of the population suffering from diseases or conditions are under medical management, but

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relatively little is known about the effects of these medications on osseointegrated dental implants. Therefore, in this chapter we list the main groups of drugs known to affect bone metabolism and discuss their impact on bone metabolism, osseointegration, and implant success (Table 4.1).

4.1 Drugs Targeting the Central Nervous System

The central nervous system (CNS) is a main regulator of bone metabolism [5]. For this reason, neurological drugs can have an effect on bone accrual, bone healing, osseointegration, and implant survival. Underneath we discuss four types of neurological drug that have been found to affect bone and even osseointegrated implants, including selective serotonin reuptake inhibitors (SSRIs), acetylcholinesterase inhibitors (AChEIs), melatonin, antiepileptic drugs (AEDs), and opioids.

4.1.1 Selective Serotonin Reuptake Inhibitors (SSRIs)

There is evidence from cohort studies indicating that SSRIs could have negative effects on implant survival [6] and bone fracture [7]. SSRIs, such as Celexa, Paxil, Lexapro, Prozac, and Zoloft, are drugs designed to inhibit the reuptake of serotonin and boost its levels to treat depression [5, 8]. Because of their unique effectiveness in depression treatment, SSRIs have become the most widely used antidepressants all over the world [9].

Serotonin, also called 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter [10], which is popularly thought to be a contributor to feelings of well-being and happiness [11]. Biochemically derived from tryptophan, serotonin is primarily found not only in the nervous tissue but also in peripheral tissues such as the digestive tract, blood platelets, and bones of animals, including humans [11]. Accordingly, SSRIs can affect the function of the digestive, cardiovascular, and skeletal systems [9]. In the skeletal system, serotonin regulates bone cells by acting on 5-HT1B, 5-HT2B, 5-HT2C receptors and serotonin transporters (5-HTTs) in osteoblasts and osteoclasts [9]. SSRIs block 5-HTTs on bone cells, resulting in a direct negative effect on bone formation [12, 13] and metabolism [9] by increasing osteoclast differentiation [14] and inhibiting osteoblast proliferation [9]. As a result, SSRIs decrease bone mass and bone mineral density (BMD) [12–14], at an annual reduction rate of 0.60%–0.93% [12, 13], increasing the risk of osteoporosis [15] and bone fracture [5], especially osteoporotic fracture [15]. In the retrospective cohort study conducted by Tamimi research group on 490 patients treated with 916 dental implants, we found that SSRI could be significantly associated with an increased risk of dental implants failure [6].

4.1.2 Acetylcholinesterase Inhibitors (AChEIs)

Clinical evidence from case-control studies, retrospective cohort studies, and in vitro studies shows that the use of AChEIs, such as rivastigmine, donepezil, galantamine, etc., is associated with lower risk of fracture and enhanced fracture healing by affecting osteoblasts and osteoclasts [16, 17]. AChEIs, also called anticholinesterase, are drugs that inhibit the acetylcholinesterase, the enzyme responsible for breaking down acetylcholine, thereby increasing both the level and duration of action of the neurotransmitter acetylcholine [18]. AChEIs have been widely used for the treatment of Alzheimer's disease (AD), Lewy body dementia, Parkinson's disease, and other dementias [19, 20]. Recent research has revealed the presence of acetylcholine receptors (AChRs) subunits in bone tissues, highly expressed on osteoblasts, especially during the osteoblast differentiation stage, which may play a possible role in regulating alkaline phosphatase (ALP) activity [21, 22]. Accordingly, AChEIs can affect the proliferation and differentiation of osteoblasts [22, 23] and subsequently exert positive effects on bone mass and fracture healing [16, 17]. It is also shown that AChEIs would suppress bone

Table 4.1 Impact of drugs on bone and implants

Drug category	Drug name	Mechanism[a]	Effects on the bone							Effects on implants	
			BMD[b]	Bone formation[b]	Bone resorption[b]	Bone turnover[b]	Fracture risk[c]	Osteoporosis[c]	Bone/ fracture healing[c]	Osseointegration[b]	Implant survival[c]
Drugs targeting the central nervous system	SSRIs	↑OC ↑RANKL	↓	↓	↑		↑	↑			↓
	AChEIs	↑OB ↓OC ↑Calcification ↑ALP		↑	↓		↓		↑		
	Melatonin	↑OB ↓OC	↑	↑	↓				↑	↑	
	AEDs	↓OB ↑ PTH ↓Vitamin D	↓				↑				
	Opioids	↓Gonadotrophins	↓				↓				
Antihypertensive drugs	β-Blockers	↑OB ↓OC ↑β-receptor inhibition ↑Bone accrual	↑	↑	↓		↓	↓	↑	↑	↑
	Thiazide diuretics	↑OB ↑RUNX2 ↑Osteopontin ↑Serum calcium	↑	↑	↓	↓	↓				↑
	ACE inhibitors	↓OC ↑ PTH ↑Calcium	↑	↑	↓		↓				↑
	ARBs	↑OB ↓OC	↑	↑	↓		↓		↑		↑
	CCBs	↑OB ↓OC ↕Calcium homeostasis ↑Vitamin D			↓						
Antidiabetic drugs	Metformin	↑OB ↑AMP ↑BMP-2 ↑ALP		↑	↓		↓				
	GLP-1	↑OB ↓OC ↑Calcitonin	↑	↑	↓	↑					
	DPP-4 inhibitors	↑OB ↓OC ↑Calcitonin	↑	↑	↓		↓				
	Thiazolidinedione	↑Osteoclastogenesis ↓ALP ↓PTH			↑		↑	↑	↓		

(continued)

Table 4.1 (continued)

Drug category	Drug name	Mechanism[a]	Effects on the bone							Effects on implants	
			BMD[b]	Bone formation[b]	Bone resorption[b]	Bone turnover[b]	Fracture risk[c]	Osteoporosis[c]	Bone/ fracture healing[c]	Osseointegration[b]	Implant survival[c]
Gastrointestinal drugs	PPIs	↓OB ↓OC ↓BMP-2, BMP-4 ↓PHOSPHO1 ↓ALP ↓Calcium level ↓Apoptosis	↓	↓	↑	↓	↑		↓	↓	↓
Immunosuppressants	Calcineurin inhibitors	↓OB ↑OC ↕Calcineurin/NFAT	↓	↓	↑		↑	↑			
	Cyclosporine	Immunosuppressive	↓	↓	↑	↑	↑	↑	↓	↓	
Antineoplastics	Anti-VEGF	↓OC ↓Angiogenesis				↓		↓		↓	
	Radium-223	↓OB									
	Exemestane	↑ALP ↑PINP ↑Osteocalcin ↑CTX ↑NTX	↓			↑	↑	↑			
Chemotherapy		↓Bone cells		↓					↓		
Anti-inflammatories	NSAIDs	↓OB ↓OC	↓	↓			↑	↓	↓	↓	↓
	Glucocorticoids	↑OC ↓Vitamin D		↓	↑		↑	↑			
Hormone replacement therapy	Thyroid	↑OB ↑IGF-1 ↑Calcitonin ↑Growth factor		↑			↓	↓			
	GIP	↑OB ↑Calcium ↓Apoptosis		↑	↓		↓				
	Sex steroids	↓OC ↕RANKL/ RANK/OPG	↑	↑	↓	↓	↓				
Anti-osteoporosis	PTH	↕Calcium homeostasis	↑	↑	↓		↓	↓	↑		
	Calcitonin	↓OC	↑		↓		↓	↓			
	Bisphosphonate	↓OC			↓	↓	↓	↓			
	Sclerostin inhibitors	↓LRP5/6 ↓Wnt signaling	↑	↑				↓			

Hypercholesterolemia medications	Statins	↑OB ↓OC ↑BMP ↑COLLIA1 ↑Osteocalcin ↓RANKL	↑				↓	↓		↑	
Antihistamines		↓RANKL	↑		↓				↓		
HIV therapy	Antiretrovirals	↑OC	↓		↑		↑	↑			
Anticoagulants	Heparin	↓OB ↑OC	↓	↓	↑		↑	↑			
Alcohol		↓OC impair immune system	↓	↓				↑	↓	↓	↓

↑ = increase; ↓ = decrease; ↕ = two-way regulate

OB osteoblasts, *OC* osteoclasts, *BMD* bone mineral density, *SSRIs* selective serotonin reuptake inhibitors, *AChEIs* acetylcholinesterase inhibitors, *AEDs* antiepileptic drugs, *ACE inhibitors* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *CCBs* calcium channel blockers, *GLP-1* glucagon-like peptide-1, *DPP-4 inhibitors* dipeptidyl peptidase-4 inhibitors, *PPIs* proton pump inhibitors, *Anti-VEGF* anti-vascular endothelial growth factor, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PTH* parathyroid hormone, *GIP* gastric inhibitory polypeptide, *ERT* estrogen replacement therapy, *RANKL* the receptor activator of nuclear factor κB ligand, *ALP* alkaline phosphatase, *RUNX2* runt-related transcription factor 2, *AMP* thymidine kinase, *BMP-2* bone morphogenetic protein-2, *PHOSPHO1* phosphoethanolamine/phosphocholine phosphatase, *NFAT* nuclear factor of activated T cells, *PINP* procollagen type 1 amino-terminal propeptide, *CTX* C-telopeptide, *NTX* N-telopeptide, *IGF-1* insulin-like growth factors, *RANK* the receptor activator of nuclear factor κB, *OPG* osteoprotegerin, *LRP* low-density lipoprotein receptor-related protein, *COLLIA1* candidate genes 136–41 collagen

[a]Mechanism is based on in vitro studies

[b]From clinical evidence

[c]From in vivo evidence

resorption rate by promoting osteoclasts apoptosis [23]. In summary, AChEIs may accelerate calcification at the fracture site, favor bone mass, minimize healing complication, and have a beneficial effect on bone turnover that could translate into reduction of bone fracture risk [16, 17]. However, future studies are needed to assess if AChEIs have effects on osseointegration and dental implants.

4.1.3 Melatonin

In vivo [24, 25] and in vitro [26] studies reveal that melatonin has positive effects on bone and implant osseointegration and promotes bone fracture healing [27]. Melatonin, also known as the sleep hormone, is a tryptophan-derived indolamine secreted by the pineal gland that plays an important role in the biologic regulation of circadian rhythms, sleep, aging, tumor growth, reproduction [28], and bone physiology [29]. Studies indicate that bone marrow cells are capable of synthesizing melatonin, leading to high concentrations of melatonin in bone marrow [30].

Melatonin binds specifically to its membrane-bound G protein-coupled receptors (MT1 and MT2), found in many cells including osteoblasts and osteoclasts [31]. Melatonin can promote osteoblastic proliferation and differentiation, increase production of osteoblastic protein osteoprotegerin, and inhibit osteoclastic activities, leading to bone strengthening [26, 29, 32]. Moreover, melatonin administration releases growth hormone, a very important hormone for normal longitudinal bone growth in both rats and humans [33, 34].

Melatonin can also have therapeutic activity in bone by affecting calcium uptake [29]. Suppression of melatonin secretion in newborn rats lowers serum calcium concentration, while melatonin treatment prevents serum calcium decrease [29]. Researchers speculated that melatonin might interact with calcium-calmodulin signaling [35], because it can reduce systolic blood pressure in humans by increasing serum calcium level [36–38].

Therefore, it is suggested that melatonin supplement could improve the health of bones, acting as an antiaging and anti-osteoporosis therapy for bone deterioration. Besides, melatonin could also be a potential agent to stimulate the peri-implant bone response and osseointegration during implant placement, which may need more research to confirm.

4.1.4 Antiepileptic Drugs (AEDs)

There is evidence from epidemiological studies, in vivo studies, and also in vitro studies suggesting that AEDs can increase bone fracture and reduce BMD and bone mass by affecting bone mineralization and calcium metabolism [39]. AEDs, including phenobarbital, carbamazepine, valproate, oxcarbazepine, gabapentin, etc., are usually required as long-term treatment for people with epilepsy, which is a common chronic neurological disorder, with episodes that can vary from brief and nearly undetectable to long periods of vigorous shaking [40, 41].

The association between AEDs use and increased risk of fracture has been widely recognized [39, 42, 43]. It is reported that patients chronically taking AEDs suffer from clinical bone disorders, including altered calcium metabolism and radiographic rickets [44–46]. The reason of AEDs-associated bone diseases and complications remains controversial. The possible mechanisms contributing to AEDs-induced bone problems include vitamin D inactivation, altered calcium metabolism, increased parathyroid, vitamin K deficiency, decreased calcitonin, and/or osteoblast inhibition, etc. [39]. More specifically, AEDs are more proven to induce cytochrome p450 enzymes (CYP450), such as phenytoin and phenobarbital, leading to changes in calcium metabolism due to increased vitamin D degradation and vitamin D deficiency [47].

Given their overwhelming negative effect on bone, it could be speculated that AEDs could also have a negative effect on bone healing and osseointegration. However, future studies will be needed to assess the gap in knowledge in regard to the impact of AEDs on bone healing, osseointegration, and dental implants.

4.1.5 Opioids

Opioids, acting on opioid receptors medically to relieve pain, have been shown to be associated with a decreased BMD [48], possibly related to a suppression of the gonadotrophins (luteinizing hormone and follicle-stimulating hormone) and thus sex steroid deficiency in vivo and clinically [49]. Increased risk of fractures has been observed with the use of opioids, although significant differences may exist between different types [50]. One mechanism behind the increased risk of fractures is falls, which may be related to dizziness and altered postural balance related to the CNS effects of opioids [51]. However, changes in bone structure and thus bone biomechanical competence are also a possibility [52].

4.2 Antihypertensive Drugs

Antihypertensive medications, such as β-blockers, thiazide diuretics, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs), are the most commonly prescribed drugs for people suffering from hypertension, a chronic medical condition in which the blood pressure in the arteries is elevated [53]. Antihypertension medications are observed to be associated with oral tori and an increased survival rate of osseointegrated implants due to their bone-stimulating properties [54–56].

4.2.1 β-Blockers

Evidence from epidemiological studies, in vivo studies, and in vitro studies suggests that β-blockers reduce the risk of bone fracture and also increase BMD, BM, bone healing, osseointegration, and dental implant survival rate, by stimulating bone formation and inhibiting bone resorption [54, 57–61]. β-Blockers are among the most widely used treatments for hypertension. They exert their effect on blood pressure by inhibiting the sympathetic β-adrenergic receptors [62]. Besides their cardiovascular effects, it appears that stimulation of these β-receptors may also have catabolic actions on bone cells [63], leading to increased bone resorption by stimulation of osteoclastic differentiation, proliferation, and activity [64, 65]. On the other hand, the activation of β2-adrenergic receptors, the only β-adrenergic receptors known to be expressed by osteoblasts, results in the downregulation of bone formation [63, 66, 67].

The potential mechanism by which β-blockers affect bone may be similar to the leptin-sympathetic nervous system pathway [64]. In animal models, leptin deficiency results in a low sympathetic tone, and genetic or pharmacological ablation of adrenergic signaling leads to leptin resistance and high bone mass [64]. β-Blockers, as anti-sympathetic agents, increase bone mass via the same pathway, which acts locally through β2-adrenergic receptors on bone osteoblasts [57, 64]. It is proven that bone resorption can be inversely decreased by β-blockers [68]. Furthermore, there is evidence that propranolol, a commonly used β-blockers, increases cross-linking of type 1 collagen in tissues, enhancing the tensile strength [69]. Taken together, in vivo and in vitro results suggest that β-blocker use has a beneficial effect on bone health. This is also confirmed by clinical studies showing that β-blockers seem to be associated with lower risk of bone fracture and exert beneficial effects on bone structure, metabolism, fracture healing, osseointegration, and implant survival [54, 57–59, 61, 64, 70].

4.2.2 Thiazide Diuretics

Observational studies and in vitro studies showed that thiazide diuretics reduce the risk of bone fracture [71], increase BMD [72], and reduce bone loss [73]. Thiazide diuretics control high blood pressure by inhibiting the thiazide-sensitive sodium chloride cotransporter (NCC) in the distal tubules of the kidney reducing renal calcium excretion and subsequently enhance calcium uptake [74]. Thiazide diuretics can also affect bone through the following potential mechanism:

1. Decreased urinary calcium excretion leading to increased serum calcium levels that could in turn lead to reduced parathyroid hormone (PTH) levels, which result in reduced bone turnover and increased BMD [75].
2. Thiazide diuretics may have a direct positive homeostatic effect on bone by blocking the NCC expressed on osteoblasts and osteoblast-like cells [76, 77].
3. Thiazide diuretics also exert effects on bone by stimulating osteoblast differentiation through osteoblast differentiation markers, runt-related transcription factor 2 (RUNX2) and osteopontin [78].

The abovementioned mechanisms could be the reason why in a recent cohort study [54] an association was found between usage of antihypertensive medication, including thiazide diuretics, and lower risk of dental implant failure, although in vivo studies in more depth are required to confirm the effect of the drugs on implant osseointegration.

4.2.3 Angiotensin-Converting Enzyme (ACE) Inhibitors

Cohort studies, case-control studies, randomized clinical trials, as well as in vivo and in vitro studies indicate that ACE inhibitors are associated with higher BMD and lower risk of bone fracture, by acting on the renin-angiotensin-aldosterone system (RAAS) locally in bone [79–82]. ACE inhibitors are among the primary prescriptions for hypertension [83]. They inhibit the production of ACE, an enzyme responsible for the conversion of angiotensin I converting to angiotensin II in RAAS [83]. RAAS operates systemically and locally in several tissues including bone [84]. Osteoblasts and osteoclasts express angiotensin II type 1 receptors, suggesting the existence of local RAAS [85]. Moreover, angiotensin II induces the expression of receptor activator of NF-kappaB ligand (RANKL) in osteoblasts, leading to the activation of osteoclasts resulting in bone resorption and detrimental effects on bone [86, 87]. In addition, angiotensin II can also affect bone by interfering with the calcium metabolism; angiotensin II decreases plasma ionic calcium levels resulting in a concomitant increase in PTH levels [88]. Therefore, by hindering the angiotensin II production, ACE inhibitors seem to have positive effects on bone metabolism both directly and indirectly. However, future in vivo studies are needed to assess the effect of ACE inhibitors on osseointegration and dental implants.

4.2.4 Angiotensin II Receptor Blockers (ARBs)

Just as ACE inhibitors, there are epidemiological, in vivo, and in vitro studies indicating that angiotensin II receptor blockers (ARBs) exert protective effects on relative fracture risk over time, by acting on the RAAS locally in bone [79–82, 89]. ARBs, also known as angiotensin II receptor antagonists, sartans, or AT_1-receptor antagonists, are a group of pharmaceuticals used to treat hypertension when patients are intolerant to ACE inhibitor therapy [90]. ARBs target the RAAS (see in ACE inhibitors) and inhibit angiotensin II production in bone by blocking angiotensin II AT_1 receptors, leading to protective effects bone metabolism [83].

Animal studies confirmed that ARBs, including telmisartan, olmesartan, and losartan, could reduce bone loss [91] and attenuate the ovariectomy-induced decrease in BMD by inhibiting the activity of tartrate-resistant acid phosphatase, an enzyme responsible for bone resorption [86]. Moreover, telmisartan promotes fracture healing and protects from bone loss by actively blocking thiazolidinedione-induced anti-osteoblastic activity via maintaining peroxisome proliferator-activated receptor-γ (PPAR-γ) serine 112 phosphorylation [92, 93]. Overall, ARBs seem to increase bone strength, mass, and trabecular connections [94, 95], which can lead to interesting investigations about their effects on osseointegration and dental implant survival in the future.

4.2.5 Calcium Channel Blockers (CCBs)

In vivo and in vitro studies demonstrated that CCBs seem to inhibit bone resorption by suppressing osteoclast function and stimulating the growth and differentiation of osteoblasts [96–98]. CCBs are a group of medications that inhibit the voltage-activated inward influx of calcium from the extracellular medium, exerting potent cardiovascular effects that are very useful for the treatment of hypertension [99]. Through similar ways, CCBs also influence bone homeostatics [85]. During bone resorption, osteoclasts can sense changes in ambient calcium concentration, which triggers a sharp cytosolic calcium increase through both calcium release and calcium influx [85]. The change in cytosolic calcium is transduced into inhibition of bone resorption, regulating growth and differentiation of osteoblasts and stimulating the function of these cells [96]. Although epidemiological studies show increased vitamin D levels in patients taking CCBs [100], there is no literature indicating if CCB use is associated with bone fractures, bone healing, osseointegration, and/or dental implants, which needs future studies to assess.

4.3 Antidiabetic Drugs

Worldwide, more than 171 million people have diabetes, and its prevalence is expected to double by 2030 [101]. And many antidiabetic drugs are now used to control hyperglycemia. These drugs might have positive or negative effects on bone metabolism and subsequently implants. According to available studies, metformin, glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) seem to exert positive effects on bone, but thiazolidinedione can have negative effects on bone.

4.3.1 Metformin

Metformin inhibits bone loss in vivo, and it has osteogenic potency in vitro. It is also noted that the use of metformin may be associated with reduced bone fractures [102]. Metformin is an antidiabetic agent widely used for the treatment of type 2 diabetes as adjunct to insulin therapy in selected patients of type 1 diabetes since the late 1950s [103]. Metformin acts primarily by suppressing glucose production by the liver [103], but several recent studies have reported the positive effects of this agent on bone metabolism by activating thymidine kinase (AMP) signaling pathway, upregulating endothelial nitric oxide synthase, and expressing bone morphogenetic protein-2 (BMP-2) [104, 105], thereby exerting a direct inhibition on bone loss in vivo [103]. In vitro metformin promotes the osteogenic action of osteoblasts, including cell proliferation, type 1 collagen production, ALP activity, mineral deposition, and osteoblast-like cells differentiation [104]. Based on these findings, metformin may exert a positive effect on bone. Therefore, it is necessary to investigate whether metformin has positive effects on bone healing, osseointegration, and dental implant survival.

4.3.2 Glucagon-Like Peptide-1 (GLP-1)

In vivo and in vitro studies demonstrated that GLP-1 seems to have anabolic effects on bone as a bone turnover modulator that increases BMD by inducing osteoblast differentiation and inhibiting osteoclastic activity [106–108]. GLP-1, also known as incretin, is a neuropeptide derived from the transcription product of the proglucagon gene, exerting insulin-like effects upon glucose transport and/or metabolism [109, 110]. GLP-1 also affects bone by directly stimulating the secretion of calcitonin, a potent inhibitor of osteoclastic bone resorption [111, 112]. It is believed that GLP-1 mainly targets calcitonin to modulate bone turnover because genetic loss of GLP-1 receptor signaling increases osteoclastic bone resorption activity, without affecting bone formation, leading to a significant reduction in trabecular separation and an increase in bone strength [108]. In summary, GLP-1 might be useful as a pharmacological

agent for improving bone formation and bone structure; however, there is no literature on its effects on bone fracture, bone healing, osseointegration, and dental implant survival which needs to be addressed in future studies.

4.3.3 Dipeptidyl Peptidase-4 Inhibitors (DPP-4 Inhibitors)

In vitro studies suggest that drugs capable of increasing incretin levels, such as DPP-4 inhibitors, could exert beneficial effects on the bone, and epidemiological studies indicate that DPP-4 inhibitors are associated with decreased bone fractures [113]. Inhibitors of dipeptidyl peptidase-4, also known as gliptins, are a class of oral hypoglycemics that block DPP-4, and they are used to treat diabetes mellitus type 2 [114]. Treatments with DPP-4 inhibitors for type 2 diabetes patients could have a protective effect on bone and have been associated with a reduced risk of bone fractures. These drugs affect bone metabolism by increasing the circulating levels of GLP-1 and gastric intestinal polypeptide, both involved in the regulation of bone metabolism [107, 108, 113, 115–118]. Despite their positive effects on bone metabolism, the effects of DPP-4 inhibitors on osseointegration and dental implant survival have not been investigated and require future researches.

4.3.4 Thiazolidinedione

Thiazolidinedione, glucose-lowering agent, has been reported to reduce BMD, increase bone loss, delay bone healing, and increase the incidence of fractures [119–123]. Thiazolidinedione, also known as glitazones, are a class of medications used in the treatment of diabetes mellitus type 2 with a beneficial effect on insulin sensitivity [124]. Thiazolidinedione exerts their antidiabetic effects by activating PPAR-γ nuclear receptor, which controls glucose and fatty acid metabolism, and is also a key regulator of bone cell development and activity in the skeleton [125]. In bone, PPAR-γ controls differentiation of cells of mesenchymal and hematopoietic lineages, and its activation by thiazolidinedione leads to unbalanced bone remodeling [125].

In vivo, thiazolidinedione induces bone loss by affecting the bone remodeling process, suppressing new bone formation by osteoblasts, and increasing bone resorption by osteoclasts, which leads to significantly decreased BMD, bone volume, and changed bone microarchitecture [126, 127]. The observed bone loss was associated with changes in the structure and function of the bone marrow, including a decreased number of osteoblasts, decreased osteoblastic function, an increased number of adipocytes, promoted osteoclast differentiation, and increased osteoclastogenesis [123, 128–130]. It is also reported that thiazolidinedione has a negative effect on markers of bone formation such as ALP and PTH [131–133]. Overall, thiazolidinedione seems to exert an adverse effect on bone health, so further studies are necessary to assess the effects of thiazolidinedione on osseointegration and dental implants.

4.4 Gastrointestinal Drugs

Given the skeletal requirements of calcium, amino acids, and energy for bone turnover and renewal, it is not surprising that the gastrointestinal tract is of major importance for skeletal integrity [134]. So far proton pump inhibitors (PPIs) have been found to affect bone [135–137], but given the importance of gastrointestinal function in bone, it could be speculated that more gastrointestinal drugs would be found to affect bone in the future.

4.4.1 Proton Pump Inhibitors (PPIs)

In vivo, in vitro, and clinical studies indicate that PPI usage is associated with decreased bone healing, bone accrual, bone turnover, and osseointegration, as well as increased risk of bone fracture and dental implant failure, by affecting

osteoblasts, osteoclasts, and calcium balance [135–137]. PPIs are a group of drugs that are rapidly becoming the third most prescribed pharmaceutical products worldwide [138]. This type of medication, including omeprazole, lansoprazole, pantoprazole, dexlansoprazole, esomeprazole, rabeprazole, etc., is very effective in both prevention and treatment of gastrointestinal acid-related conditions, such as peptic ulcer, gastroesophageal reflux disease (GERD or GORD), dyspepsia, *Helicobacter pylori* infections, eosinophilic esophagitis, gastrinomas, and stress gastritis [138]. In the past 20 years, a marked increase of PPI exposure has been observed [139], and besides occasional use of this medication, millions of individuals are also using PPIs as a continuous or long-term therapy [140]. This is of particular relevance because a relationship between PPI administration and bone metabolism has been acknowledged by the US Food and Drug Administration [141].

PPIs suppress gastric acidity by inhibiting the functions of the proton pump (H+/K+ ATPase) [142, 143]. The proton pump can also be found in bones, and its inhibition in osteoclasts can decrease their activities, leading to reduced cortical thickness, bone weight, and bone biomechanical properties [144, 145]. In addition to their effects on osteoclastic behavior, PPIs might also interfere with osteoblastic cells, by inhibiting phosphoethanolamine/phosphocholine phosphatase (PHOSPHO1) and ALP in bone [146–148]. Other mechanisms suggest indirectly negative effects of PPIs on bone metabolism by affecting calcium homeostasis [141, 149]. Specifically, PPIs impair calcium absorption in the gastrointestinal track by increasing the pH in the small intestine and thus reducing calcium availability for incorporation in bone, thereby decreasing its mineral density [141, 149]. Clinically, observational studies have shown an association between the use of PPIs and high risk of bone loss and bone fractures [150]. Our recent in vivo and epidemiological studies also confirmed the negative effect of PPIs on bone healing and implants [136, 137]. Indeed, usage of PPIs reduces osseointegration, delays bone healing, and is associated with increased dental implant failure [136, 137].

4.5 Immunosuppressants

Bone remodeling is strongly influenced by the immune system [151, 152]. Accordingly, dysregulation of the immune system by some drugs might be associated with bone loss and fracture [152]. It is worth mentioning that RANKL, a crucial signal for osteoclast function, is expressed by several immune cells (e.g., CD8, CD4, TH1, TH2) [153, 154]. Moreover, T cells can suppress osteoclastogenesis through expression of interferon-γ (INF-γ), IL-4, or T lymphocyte protein 4, which in turn suggests a protective effects of T cells on bone [155].

4.5.1 Calcineurin Inhibitors

In vivo and in vitro studies indicate that calcineurin inhibitors have adverse effects on bone, leading to increased bone loss and decreased BMD [156]. Calcineurin is a calcium- and calmodulin-dependent serine/threonine protein phosphatase [157]. And inhibitors of calcineurin are immunosuppressant agents used to prevent organ transplant rejection and to treat autoimmune diseases and some non-autoimmune inflammatory diseases [158]. Patients treated with the calcineurin inhibitors develop osteopenia and have an increased incidence of fractures [159–162]. It is suggested that calcineurin inhibitors suppress bone formation and stimulate bone resorption by hindering osteoblast differentiation and promoting osteoclast activity [163]. And it is possible that calcineurin inhibitors affect bone metabolism through the regulation of calcineurin/nuclear factor of activated T cell (NFAT) signaling pathway, which is necessary for osteoclastogenesis [163]. However, no data is yet available on the effects of calcineurin inhibitors on bone healing, osseointegration, as well as dental implants, and this might need more investigation in the future.

4.5.2 Cyclosporine

Cyclosporine A (CsA) is an immunosuppressant drug widely used in organ transplantation to prevent rejection [164]. It reduces the activity of the immune system by interfering with the activity and growth of T cells [165]. In vivo and in vitro studies indicate that CsA might have anti-anabolic effects in bone remodeling by suppressing the critical role of T lymphocytes, leading to increased bone turnover and bone loss and increased risk of osteopenia, bone fracture, and osteoporosis [166–168]. It is suggested the reason why CsA affects bone metabolism may be related to its immunosuppressive mechanisms mediated by cytokines, but the specific mechanism is still unclear [169].

Moreover, in vivo studies also demonstrated that the use of CsA might delay bone healing and hinder osseointegration around dental implants [170–172]. Given the negative effects of CsA on bone metabolism, it might be reconsidered that patients with CsA therapy undergo implant placement. However, clinical studies are needed to confirm the effects of CsA on dental implants survival.

4.6 Antineoplastic Drugs

Osseointegration and bone healing require cell proliferation, differentiation, and angiogenesis. Antineoplastic drugs act mainly by inhibiting cell proliferation and angiogenesis. Therefore, it is expected that this type of medication would have negative effects on bone healing, osseointegration, and implants. Underneath we discuss some antineoplastic drugs known to have negative effects on bone.

4.6.1 Anti-vascular Endothelial Growth Factor (Anti-VEGF)

In vivo and in vitro studies suggest adverse effects of anti-vascular endothelial growth factor (anti-VEGF) on bone turnover, bone healing, and osseointegration by hindering angiogenesis and osteoclasts [173, 174]. Vascular endothelial growth factor (VEGF), originally known as vascular permeability factor (VPF), is a signal protein produced by cells that stimulates vasculogenesis and angiogenesis [175]. VEGF is considered a key regulator in blood vessel growth associated with angiogenesis that is crucial for bone repair and also can stimulate bone turnover through osteoclast chemotaxis and activity [176]. Therefore, VEGFs inhibition by some medications can have a negative impact on bone health [173]. These include inhibition of bone growth, decrease of bone turnover, and impairments in wound healing, because of the inhibition of newly formed blood vessels [177], which lead to delayed bone healing and less osseointegration for Ti implants [173]. However, epidemiological studies are needed to confirm this.

4.6.2 Radium-223

The principal use of radium-223 (Ra-223, ^{223}Ra) is to treat metastatic cancers in bone as a radiopharmaceutical, with the advantages of its chemical similarity to calcium and the short range of the alpha radiation it emits [178]. ^{223}Ra, an isotope of radium with an 11.4-day half-life, is a targeted α-particle emitter that selectively targets bone metastases with high energy [179]. As a calcium mimetic, ^{223}Ra has a natural bone-seeking capability and preferentially binds to newly formed bone matrix, targeting osteoblastic metastatic lesions [180]. The high-energy, short-range α-particle radiation predominantly induces irreparable double-stranded DNA breaks resulting in potent cytotoxic activity localized to target areas while minimizing damage to bone marrow and adjacent healthy tissue [180, 181]. Despite its effect on bone, no data is yet available on the effects of ^{223}Ra on bone fracture, bone healing, osseointegration, and/or dental implants, which might need more investigations in future studies.

4.6.3 Exemestane

In vitro and clinical studies suggest that exemestane treatment reduces BMD, increases osteoporosis, accelerates bone turnover, and increases bone fracture risk [182–184]. Exemestane is an aromatase inhibitor, and it is used in the treatment

of early and advanced breast cancer, acting by substantially reducing estrogen synthesis [185]. Exemestane has an anabolic effect on bone metabolism, increasing both markers of bone formation (i.e., bone alkaline phosphatase (BAP), procollagen type 1 amino-terminal propeptide (PINP), and osteocalcin) and bone resorption (i.e., C-telopeptide (CTX) and N-telopeptide (NTX)) [182]. The fact that not only bone resorption but also bone formation is increased in patients treated with exemestane is interesting, and it may be because the enhanced bone degradation could lead to enhanced synthesis per se [186]. Nevertheless, future studies are needed to look into the effects of exemestane on osseointegration and dental implants.

4.7 Chemotherapeutic Agents

Chemotherapy is a treatment using chemotherapeutic agents (cytostatic or cytotoxic agents) to treat cancer by preventing the proliferation of cancer cells [187]. The problem of using chemotherapeutic agents is their lack of selectivity, which might lead to actions on normal cells that have an accelerated cell cycle, including bone cells [187]. In vivo studies indicate that the use of chemotherapeutic agents is associated with delayed bone healing and less osseointegration [187]. On the other hand, studies report no detrimental effects of chemotherapeutic agents on osseointegration and dental survival [188]. So it seems that there is no available evidence to prove that patients undergo chemotherapy cannot take dental implant placement. However, given the negative effects of postoperative chemotherapy on bone formation, we should be aware of the risk to place implants on patients who are using chemotherapeutic agents.

4.8 Anti-inflammatories

Anti-inflammatories are a group of drugs that used to treat or reduce inflammation or swelling [189]. Underneath we discuss the anti-inflammatories known to affect bone and/or dental implants.

4.8.1 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

In vivo, in vitro, and clinical studies indicate that nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit bone healing, decrease BMD, inhibit newly formed bone, and increase the risk of bone fracture, playing a detrimental role in bone metabolism [190, 191]. NSAIDs, such as ibuprofen, indomethacin, aspirin, ketorolac, and naproxen, are widely used to relieve pain and inflammation, particularly for symptoms associated with osteoarthritis and other chronic musculoskeletal conditions [192]. NSAIDs reduce pain and inflammation by inhibiting the synthesis of prostaglandin [193]. However, NSAIDs present negative side effects on bone since prostaglandin plays an important role in bone metabolism [194].

One particular situation in which NSAIDs can have a negative impact on bone is in procedure involving bone healing [195]. Bone injuries result in the local production and release of prostaglandins [195]. This release of prostaglandins triggers inflammation and increases the activity of osteoblasts and osteoclasts, all of which are ultimately required for proper bone healing [193]. NSAIDs inhibit this production of prostaglandins and thereby interfering directly with the proper process of bone healing [195–198].

Our epidemiological study [137] also discovers that NSAIDs exert adverse effects on osseointegrated dental implants (HR = 2.47; 95% CI = 1.09–5.58), and this might be exacerbated by the fact that patients who need NSAIDs therapy are often given co-therapy of gastro-protectants (i.e., PPIs), as prevention for gastroesophageal side effects [199], which also has negative effects on bone. However, in vivo studies also confirm that loss of osseointegration and delayed peri-implant bone healing are observed after NSAID administration [200, 201]. Therefore, it may be advisable to avoid NSAID prescription before or after bone surgeries and/or implant placement [202].

4.8.2 Glucocorticoids

Glucocorticoids, such as cortisone, are a class of corticosteroids that are highly effective in the

treatment of inflammatory and autoimmune conditions [203]. In vivo, in vitro, and clinical studies indicate that glucocorticoids affect bone by increasing bone resorption and decreasing bone formation, mediated by direct actions on bone cells, leading to increased osteoporosis and risk of bone fracture [204, 205]. Glucocorticoids act directly on differentiated osteoclasts to extend their life span and on osteoblasts to stimulate their apoptosis [206] and also reduce vitamin D plasma level [207]. Glucocorticoids cause bone loss in two phases: a rapid, early phase in which bone mass is lost due to excessive bone resorption and a slower, later phase in which bone is lost due to inadequate bone formation [206, 208].

Regarding the effects of glucocorticoids on osseointegration and dental implants in vivo, there are conflicting results. Some studies report that delayed implant healing and decreased osseointegration are associated with glucocorticoids treatment [209, 210]. But others suggest no association between glucocorticoids users and nonusers [211, 212]. However, given their negative effects on bone metabolism, clinical studies should be carried out to address the influence of glucocorticoids on bone healing, osseointegration, and dental implants.

4.9 Hormone Replacement Therapy

Hormones are chemicals made by glands that travel throughout the body and have effects on growth, maturation, energy, weight, and bone strength [213]. Sex hormones (estrogen made in the ovary of females and testosterone made by the testes in males) control ability to reproduce and also lead to increased bone strength especially in early teenage years [213]. Other hormones come from the thyroid gland, the parathyroid gland, the pituitary gland near the brain, and the brain itself. These hormones control levels of calcium in the blood, energy levels, and ability to grow [214]. They act the same in both genders. Underneath we discuss some of the main hormones and hormone replacement therapy.

4.9.1 Thyroid Hormone

The thyroid is one of the largest endocrine glands in the body, controlling energy sources, protein synthesis, and the sensitivity to other hormones [215]. It participates in these processes by producing thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), synthesized from iodine and tyrosine [215]. In vivo, in vitro, and clinical studies show that T_3 is essential for the normal development of endochondral and intramembranous bone and plays an important role in the linear growth and maintenance of bone mass [216]. T_3 deficiency or excess results in severe skeletal abnormalities in childhood, and thyrotoxicosis is associated with osteoporosis and an increased risk of fracture in adults [217]. In the growth plate, T_3 inhibits chondrocyte proliferation and promotes hypertrophic differentiation, matrix synthesis, mineralization, and angiogenesis [218]. It also promotes osteoblastic proliferation, differentiation, and apoptosis, by its induction of IL-6, PGs, and RANKL, and also promotes osteoclast formation and activation [219]. Besides, thyroid hormones may act on bone cells indirectly by increasing secretion of growth hormone and insulin-like growth factor-1 (IGF-1) and also producing calcitonin that is crucial in calcium homeostasis [215, 219]. Future studies should address the influence of thyroid hormone on bone healing, osseointegration, and dental implants.

4.9.2 Gastric Inhibitory Polypeptide (GIP)

In vivo and in vitro studies indicate that gastric inhibitory polypeptide (GIP) exerts a protective effect on bone with decreased bone resorption and increased bone formation, by favoring osteoblast function, hindering apoptosis, and improving calcium intake [220, 221]. GIP is a gastrointestinal peptide hormone that is released from duodenal endocrine K cells after absorption of glucose or fat [222]. GIP is used for the treatment of type 2 diabetes, as well as obesity-related glucose intolerance and the alleviation of insulin resistance [223].

Besides gastric tissues, GIP receptor is also expressed in osteoblasts regulating bone turnover [224], and its activation with GIP protects osteoblasts from apoptosis and increases their function, leading to promoted osteoblastic bone formation [220, 224]. GIP also promotes the efficient storage of ingested calcium into bone, playing a positive physiological role in calcium homeostasis in vivo [220]. Therefore, the elevation of blood GIP levels elicited by meals plays a crucial role on preventing osteoporosis pathogenesis and development [220]. Given its positive effects on bone metabolism, further research is required to elucidate the role of GIP on fracture risk, bone healing, osseointegration, and dental implants.

4.9.3 Sex Steroids

In vivo, in vitro, and clinical studies indicate that sex steroids, the steroid hormones that interact with vertebrate androgen or estrogen receptors, play a major role in the regulation of bone turnover [225]. This is why gonadectomy in either sex is associated with increased bone remodeling, increased bone resorption, decreased BMD, and a relative deficit in bone formation, resulting in accelerated bone loss and increased risk of bone fracture [226].

The effects of cellular and molecular mediators of sex steroid on the bone-forming osteoblasts and bone-resorbing osteoclasts can be explained by the fact that both estrogen and androgens inhibit bone resorption via the RANKL/RANK/osteoprotegerin system, as well as by reducing the production of pro-resorptive cytokines, along with their direct effects on osteoclast activity and life span [225].

Also studies show that serum osteoprotegerin (OPG) and RANKL concentrations might be influenced by menopause [227]. Therefore, it is indicated that estrogen replacement therapy exerts beneficial effects in preventing and treating osteoporosis in postmenopausal women, increasing BMD, and decreasing the risk of fracture [228–230]. As abovementioned, estrogen depletion is an important risk factor for the development of osteoporosis [231], so it is important to consider the estrogen replacement therapy as a possible underlying factor for bone-related diseases [228]. Regarding to dental field, estrogen deficiency results in significant loss of interproximal bone density, and the use of estrogen replacement therapy led to increased density in the crestal and subcrestal regions of the alveolar bone [232].

However, currently there is no literature available on the effects of sex steroid or estrogen replacement therapy on bone healing, osseointegration, and dental implant survival, especially for aged women, and future research is needed on this.

4.10 Anti-osteoporosis Drugs

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture [233]. Bone strength primarily reflects the integration of bone density and bone quality [234]. Many pharmacological agents are approved for the treatment of osteoporosis [233]. We find that grouping them into anticatabolic and anabolic classes based on the mechanisms of their actions on bone remodeling [233] that we discuss underneath.

4.10.1 Sex Steroids (See section 4.9.3)

4.10.1.1 Parathyroid Hormone (PTH)

PTH, an 84-amino acid peptide secreted by the parathyroid glands, is essential for the maintenance of calcium homeostasis, and its actions can regulate bone remodeling [235]. PTH regulates calcium homeostasis because the signal for its production and secretion is a reduced extracellular ionized calcium concentration, while the signal for its reduction is an increase in extracellular ionized calcium concentration [236]. In vivo, in vitro, and clinical studies prove that PTH has direct effects on osteoblasts and osteocytes and indirect actions on osteoclasts, exerting either anabolic or catabolic effects depending on the duration and periodicity of PTH exposure [236]. The intermittent adminis-

tration of PTH has anabolic effects on the skeleton, while the catabolic actions can be seen upon continuous exposure to PTH [237]. With continuous PTH infusion, PTH receptor signaling in osteoblasts and osteocytes can increase the RANKL/OPG ratio, thereby stimulating bone resorption [238]. In contrast, PTH induces bone formation due to its ability to downregulate SOST/sclerostin expression in osteocytes, unleashing the anabolic Wnt signaling pathway, and also stimulate the expression of runx2, osteocalcin, ALP, and collagen type 1 alpha 1 (COL1A1), which are all typical signals of bone formation [238].

Preclinical and clinical studies indicate that PTH given intermittently has beneficial effects by improving BMD and bone mass, reducing fracture risk (both osteoporotic and nonosteoporotic) and osteoporosis, while also improving fracture healing [235]. Actually, PTH is considered to be the only osteoanabolic therapy currently available for osteoporosis and bone fracture healing [235, 239]. In vivo studies also indicate that PTH administration increases bone density around implants and enhances implant anchorage and early fixation, which might lead to improved clinical results in future studies [240].

4.10.1.2 Calcitonin

Standard treatment for postmenopausal osteoporosis usually includes calcium supplementation and exercise along with the prescription of antiresorptive drugs, such as calcitonin [241]. Besides its use for treatment of postmenopausal osteoporosis, calcitonin is also used to treat hypercalcemia, Paget's disease, and other bone-related conditions [241]. The hormone participates in calcium and phosphorus metabolism, counteracting PTH [241]. In vivo, in vitro, and clinical studies demonstrated that calcitonin is a physiologic endogenous inhibitor of bone resorption that can decrease osteoclast number and osteoclast activity, leading to decreased bone resorption, increased BMD, reduced osteoporosis, and reduced risk of bone fractures [242, 243]. Due to its positive effects on bone metabolism, future studies should address the influence of calcitonin on bone healing, osseointegration, and dental implants.

4.10.1.3 Bisphosphonate

Bisphosphonates, such as clodronate and zoledronic acid, are used to inhibit bone resorption by regulating osteoclast function, particularly in the management of osteoporosis and Paget's disease [244]. In vivo, in vitro, and clinical studies indicate that bisphosphonates are used successfully in the treatment of osteoporosis to reduce bone resorption and hypercalcemia and prevent pathologic bone fractures [244]. Specifically, bisphosphonates bind to hydroxyapatite crystals and inhibit crystal growth and dissolution [245]. Besides, bisphosphonates also act directly on osteoclasts and interfere with specific intracellular biochemical processes such as isoprenoid biosynthesis and subsequent protein prenylation to inhibit cell activity [246]. However, there is growing concern regarding the fact that bisphosphonates, particularly nitrogen-containing bisphosphonates, may be associated with bisphosphonate-related osteonecrosis of the jaw (BRONJ) by inhibiting osteoclasts activity and over-suppressing bone remodeling [247]. BRONJ is an area of uncovered bone in the maxillofacial region that did not heal within 8 weeks after identification by healthcare provider, in a patient who was receiving or had been exposed to bisphosphonate therapy without previous radiation therapy to the craniofacial region [248]. Literature is conflict regarding the association between BRONJ and dental implants. In 2007, the American Association of Oral and Maxillofacial Surgeons recommended that dental implants should be avoided in patients receiving bisphosphonates treatment because an increased risk of BRONJ is associated with dental implants [249]. But other studies observed no association or found out a late complication of BRONJ in those dental implant patients but not related to the oral surgery [250]. However, it is necessary for the need of an extended follow-up of patients who are taking bisphosphonates and also undergo dental implant placement, and their dental implants should be removed only if the antibiotic treatment fails to alleviate the signs and symptoms of BRONJ [250]. Future studies are necessary for the deeper explanation

on this topic, as well as the effects of bisphosphonates on bone healing, osseointegration, and dental implants.

4.10.1.4 Sclerostin Inhibitors

Sclerostin is a protein encoded by the symbol for the protein sclerostin (SOST) gene. Sclerostin is a secreted glycoprotein with a C-terminal cysteine knot-like (CTCK) domain and sequence similarity to the DAN (differential screening-selected gene aberrative in neuroblastoma) family of BMP antagonists [251]. In vivo and in vitro studies indicate that sclerostin is produced by the osteocyte and has anti-anabolic effects on bone formation by binding to low-density lipoprotein receptor-related protein 5/6 (LRP5/6) and inhibiting Wnt signaling [252]. The absence of sclerostin results in the high bone mass clinical disorder sclerosteosis [252]. Antibodies to sclerostin increase bone formation dramatically and improve bone strength without affecting bone resorption [252]. Therefore, sclerostin inhibitors are currently being explored as a potential anabolic treatment of osteoporosis [253]. However, future studies are still needed to confirm the effects of sclerostin inhibitors on bone healing, osseointegration, and implants.

4.11 Hypercholesterolemia Medications

Hypercholesterolemia, also called dyslipidemia, is the presence of high levels of cholesterol in the blood, which needs anticholesterol drugs for the treatment [254]. Underneath we discuss statins, the medication widely used for hypercholesterolemia which also can exert effects on bone and dental implants.

4.11.1 Statins

Statins, also known as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are a class of lipid-lowering medications that reversibly inhibit the enzyme HMG-CoA reductase which plays a central role in the production of cholesterol [255]. Statins are currently used for clinical treatment of hypercholesterolemia [255]. Besides their action as lipid-lowering agents, statins can also regulate bone metabolism [256].

In vivo, in vitro, and clinical studies have shown that administration of statins presents anabolic effects on bone by promoting osteoblast activity and suppressing osteoclasts, resulting in increased bone formation, increased BMD, improved fracture healing, decreased risk of bone fracture, and prevention of osteoporosis [257, 258]. Statins stimulate the expression of anabolic genes, such as BMP-2, COLLIA1, and osteocalcin, and also suppress osteoclast activity by decreasing RANKL/OPG ratio, leading to beneficial effects on bone [259, 260]. Moreover, in vivo studies also indicate that statins can promote osseointegration and bone healing around titanium implants, even in osteoporotic animals [261, 262]. However, its impact on implant success needs to be confirmed in epidemiological studies.

4.12 Antihistamine Drugs

Antihistamines are a type of pharmaceutical drug that opposes the activity of histamine receptors in the body and are used to treat allergic diseases [263]. In vivo, in vitro, and clinical studies indicate that antihistamine drugs can cause increased BMD and decreased bone resorption, but it inhibits bone healing [264]. Antihistamines increase the levels of serum calcitriol and directly enhance bone formation by stimulating calcitriol synthesizing enzyme [265]. Histamine seems to mediate the osteoclastic pathway by expression of RANKL in osteoblasts and bone marrow stromal cells [266–268]. Antihistamines then stimulate RANKL expression, but cannot develop osteoclastogenesis, resulting in increased BMD but delayed bone healing [265]. No data indicating there is association between antihistamines and increased risk of bone fracture, so more researches are needed for further investigation on this, as well as the association between antihistamines and other procedures, such as osseointegration and dental implant survival.

4.13 HIV Infection Therapy

Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is a spectrum of conditions caused by infection with the human immunodeficiency virus (HIV). Antiretroviral therapy is currently the most commonly used treatment for HIV/AIDS and also exerts effects on bone metabolism that are discussed underneath.

4.13.1 Antiretroviral Therapies

It seems that the use of antiretroviral therapies causes increased bone loss, decreased BMD, increased osteoporosis, and increased fracture rate, according to in vivo and clinical studies [269]. Patients with HIV/AIDS are living longer due to the success of highly active antiretroviral therapy [270], with dramatically reduced morbidity and mortality rates from the HIV infection [271]. There have been anecdotal reports of bone disorders such as avascular necrosis of the hip and compression fracture in HIV-infected patients receiving antiretroviral therapies, which are recognized complications of severe osteoporosis [271, 272]. The mechanisms underlying the bone loss with antiretroviral therapies initiation are not clear, because of the inability to replicate in vivo effects of that in vitro [273]. It might be because that these drugs increase osteoclastogenesis, induce osteoclastic function, and lead to increased bone resorption and loss [207, 271]. Future studies are needed to confirm the mechanism in vitro and also the effects of antiretroviral therapies on bone healing, osseointegration, and dental implants.

4.14 Anticoagulants

Anticoagulants are a class of drugs that work to prevent blood coagulation (clotting), among which heparin is one of the most frequently prescribed drugs. Heparin also has been proven to affect bone metabolism that is discussed underneath.

4.14.1 Heparin

Heparin, which works by activating antithrombin III and blocking thrombin from clotting blood, is a widely used injectable anticoagulant, to treat and prevent deep vein thrombosis and pulmonary embolism (collectively known as venous thromboembolism), and is also used as part of the treatment of myocardial infarction and unstable angina [274].

Epidemiological, in vivo, and in vitro studies reveal that heparin decrease BMD, increase bone fractures, and develop osteoporosis by enhancing bone resorption and hindering bone formation [275]. Heparin treatment leads to a reduction in bone density and an increased risk of fractures because it stimulates BMP signaling and possibly Wnt signaling, which results in enhanced mineralization in vitro [275]. Previous published protein data on the decoy effects of heparin on OPG binding to RANKL suggests that heparin stimulates osteoclastogenesis by downregulating the expression of OPG [276–278]. There is no significant correlation between bone density and the dose or duration of heparin [279]. Also there is no literature talking about the effects of heparin on bone healing, osseointegration, and dental implant survival, which may bring out more insight, especially that patients who receive heparin appear to have an increased risk of overall and major bleeding events [280].

4.15 Alcohol

Alcohol is a central nervous system depressant with detrimental systemic effects on central nervous system, gastrointestinal tract, immune system, cardiovascular system, and bone tissue [281, 282]. In vivo, in vitro, and clinical studies indicate that alcohol exert negative effects on bone metabolism by inhibiting osteoclast activities, leading to delayed bone healing and increased risk of osteoporosis and bone fracture [282, 283].

Studies also discover the negative effects of alcohol on osseointegration and dental implants in vivo, with less bone density around implants and reduced direct bone-to-implant contact [284].

Clinically, alcohol addiction seems to be significantly associated with higher risk of dental implant failure [285]. The possible mechanism might be due to suppression of T lymphocytes and impaired mobility, adhesion, and phagocytic capabilities of the innate immune system [286].

4.16 Final Remarks

In the above we have summarized the literature on drugs we know could affect bone and osseointegration. However, we cannot rule out many other possible drugs that have not been investigated yet. There are over 1400 FDA-approved drugs that are being used routinely all around the world. And future studies will have to be done to explain the effects of other drugs on bone, osseointegration, and implants.

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