Drug Metabolism Reviews

ISSN: 0360-2532 (Print) 1097-9883 (Online) Journal homepage: http://www.tandfonline.com/loi/idmr20

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**To cite this article:** Dragos Apostu, Ondine Lucaciu, Gheorghe Dan Osvald Lucaciu, Bogdan Crisan, Liana Crisan, Mihaela Baciut, Florin Onisor, Grigore Baciut, Radu Septimiu Câmpian & Simion Bran (2016): Systemic Drugs That Influence Titanium Implant Osseointegration., Drug Metabolism Reviews, DOI: 10.1080/03602532.2016.1277737

**To link to this article:** http://dx.doi.org/10.1080/03602532.2016.1277737

Accepted author version posted online: 28 Dec 2016.

# Systemic Drugs That Influence Titanium Implant Osseointegration.

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**Abstract**

Titanium implants are widely used on an increasing number of patients in orthopedic and dental medicine. Despite the good survival rates of these implants, failures that lead to important socio-economic consequences still exist. Recently, research aimed at improving implant fixation, a process called osseointegration, has focused on a new, inovative field: systemic delivery of drugs. Following implant fixation, patients receive systemic drugs that could either impair or enhance osseointegration; these drugs include anabolic and anti-catabolic bone-acting agents in addition to new treatments. Anabolic bone-acting agents include parathyroid hormone (PTH) peptides, simvastatin, prostaglandin EP4 receptor antagonist, vitamin D, and strontium ranelate; anti-catabolic bone-acting agents include compounds like calcitonin, biphosphonates, RANK/RANKL/OPG system, and selective estrogen receptor modulators (SERM). Examples of the new therapies include DKK1- and anti-sclerostin antibodies. All classes of treatments have proven to possess positive impacts such as an increase in bone mineral density and on osseointegration. In order to prevent complications from occurring after surgery, some post-operative systemic drugs are administered; these can show an impairment in the osseointegration process. These include nonsteroidal anti-inflammatory drugs, proton pump inhibitors, and selective serotonin reuptake inhibitors. The effects of aspirin, acetaminophen, opioids, adjuvants, anticoagulants, and antibiotics in implant fixations are not fully understood, but studies are being carried out to investigate potential ramifications. It is currently accepted that systemic pharmacological agents can either enhance or impair implant osseointegration; therefore, proper drug selection is essential. This review aims to discuss the varying effects of three different classes of treatments on improving this process.

Keywords: drug-supported osseointegration, drug-enhanced osteoblast activity, drugs that down-regulate osteoclast activity, drugs that influence titanium implant osseointegration, titanium implant.

## Introduction

Although pure titanium is one of the most abundant metals on Earth (Peters et al. 2003, Oshida 2013) it could not be isolated in large amounts until the invention of the Kroll process by a metallurgist named William Kroll, in 1946 (Lütjering and Williams 2007). Superior mechanical and physical properties, such as corrosion resistance and high modulus of elasticity in tension, and their excellent biocompatibility have made pure titanium and its alloys widely used in medicine (Long and Rack 1998).

Nowadays titanium implants are used in the orthopedic and dentistry fields, for joint arthroplasties, spinal and maxillofacial reconstructions, and dental prostheses. The large scale use of these screws in day-to-day medical practice makes research in this field very important.

Titanium implant-bone host interface is the key factor for implant success. As a bioinert material, titanium allows for bone apposition, this procedure is called osseointegration (The glossary of prosthodontics terms 2005), and leads to bone anchorage (see Figure 1). The osseointegration process begins with the absorption of ions, proteins, polysaccharides, and proteoglycans by the Ti-oxide layer (Albrektssonet al. 1983, Puleo and Nanci 1999). Afterwards, macrophages, neutrophils, and osteoprogenitor cells (mainly osteoblasts) migrate on the bone-implant interface and lead to bone apposition in close contact with the implant surface (see Figure 2).

**Figure 1. Histological section of bone (B) detached from a titanium implant after 7 years of clinical function. The implant was removed in spite of an undisturbed bone anchorage. Bone Marrow = BM. (Albrektssonet al. 1983)**

**Figure 2. Electron micrographs of the bone-titanium contact close to the cortical bone of young rats on the 28$^{th}$ day after operation. Some of the epithelial cells facing the titanium are removed during specimen preparation, but remain normally in some parts (arrows). Below the epithelial cells, an osteoblast (Ob) surrounded by collagen fibrin layer (CL) and mature bone matrix (M) can be seen. Original magnification x 19,000. (Murai et al. 1996)**

Although macroscopically there is direct contact between implant and host bone, microscopically there is a thin amorphous zone or lamina limitans which appears to have a thickness of 20–50 nm, or according to other studies it is larger and does not exceed 400 nm (Murai et al. 1996, Thomsen et al. 1997) (see Figure 3). The osseointegration process takes time over a period of at least 3–5 months to be adequate. Research carried out in time regarding the titanium implant-bone tissue interface, has highlighted the limits of the osseointegration process, the apparition of the inflammatory response at the interface level. Problems like these which arise in clinical practice require in vivo and in vitro research on animals. Studies carried out in the specialized literature considered interventions at the level of the implant surfaces in order to improve the biocompatibility and to modify the cellular activity at the level of the bone receptor site receiving the implant, in order to improve the osseointegration process. The longevity of a titanium implant depends on the quality of the tissue at the titanium-bone interface.



**Figure 3. Young rats, 28$^{th}$ day. An amorphous zone (arrows) with high electron density is seen present on the lamina limitans-like structure. Osteocyte canaliculus (arrow-head). Original magnifixation x 8,000. (Murai et al. 1996)**

Failures of titanium implants occur due to inadequate qualitative and quantitative bone at the recipient site, implant insertion surgical trauma, titanium surface limits and to bone

metabolism modifications. At the present moment, research in the field has not been able to single out a modality for improving  the titanium surface, so as to increase the latter's integration rate.

In terms of titanium surface limits, it is widely accepted that there is need for new titanium alloys and surface treatments with the following characteristics:

(1) High corrosion resistance, lower modulus of elasticity, high mechanical strength, and wear resistance to avoid mechanical failures;

(2) Higher biocompatibility, without allergic reactions, cytotoxicity, and carcinogenicity, in order to avoid biological failures;

(3) More bioactive surfaces that will lead to faster and enhanced osseointegration;

(4) Increased antimicrobial properties that will reduce failures due to infection.

International literature is abundant in researche carried out aiming to improve the osseointegration process by new Surface Treatment Modifications:

- *Surface Modifications to Improve the Mechanical Properties of the Implant;*
- *Surface Modifications to Induce Bioactivity, Cell Growth, and Osseointegration;*
- *Surface Modifications with Antibacterial Effects;*
- *Cell seeding and proliferation at the level of the implant surface.*

Although significant progress has been achieved, there are still many improvements required. Titanium alloys fabrication methods appear to play a pivotal role on the mechanical properties, corrosion resistance, pore size, and distribution of the materials. Of paramount importance is the interaction of host cells with the titanium surface, process that depends on the

pore size. Furthermore it is very important to be able to stimulate bone metabolism in order to improve the cellular activity at the level of the implant recipient site.

In the last years research regarding the improvement of the osseointegration has focused on pharmacological agents that increase titanium implants fixation by three main mechanisms: increase osteoblast activity throughout the proliferative phase (anabolic agents), reduction in osteoclast activity within the maturation phase (anti-catabolic agents) or dual (anabolic and anti-catabolic mechanism). Most of these agents have been first described in the treatment of osteoporosis, because the same bone remodelling process is the main target in both osseointegration and osteoporosis.

On the other hand, orthopaedic joint replacements and dental implants are procedures that can cause pain. Consequently, there is need for pain relief drugs such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids or adjuvants (tricyclic anti-depressants and anticonvulsants). Other drugs such as proton-pump inhibitors, selective serotonin reuptake inhibitors (SSRIs), antibiotics and anticoagulants, also have certain indications in these groups of patients, either for treating or preventing comorbidities. Considering the large number of drugs in these procedures, with such diversity in mechanisms of action, it is important to know which ones interfere with the osseointegration process of titanium implants resulting in a lower survival rate and which do not.

The aim of this review is to provide an update on proper drug selection for an increase of implant life span and patient satisfaction.

## 1. Systemic Drugs That Enhance Titanium Implant Osseointegration

### *1.1 Anabolic Agents*

These consist of pharmacological agents which increase bone mass by augmenting osteoblastic activity. They include parathyroid hormone (PTH) peptides, simvastatin, prostaglandin EP4 receptor antagonist, vitamin D, strontium ranelate and newer therapies such as DKK1-antibody and anti-sclerostin antibody, also known as romosozumab.

*1-34 PTH* or *teriparatide* was the first anabolic agent proven to increase osseointegration of implants. 1-34 PTH is a fragment of endogenous PTH which is the main regulator of calcium and phosphate metabolism in bone and kidney(Stroup et al. 2008). Teriparatide's metabolic sites are liver and kidney, where it is degraded (Serada et al. 2012). The agent acts on PTH receptor (PTHR) in osteoblasts and increases the expression of M-CSF (Weir et al. 1993) and receptor activator of nuclear factor-κB ligand or RANKL (Yang et al 2015)(see Figure 4). It has been shown to increase both cortical and trabecular bone masswhen used intermittently (Brouwers et al. 2009).1-34 PTH is clinically used in the treatment of patients with osteoporosis which do not respond or tolerate other treatments (Lau et al. 2012). Skripitz and Aspenberg(2001)have demonstrated that intermittent human PTH (1-34) treatment injected subcutaneously may enhance early fixation of implants. PTH increases both bone-to-implant contact and pull-out force according to Dayer et. al (2010). Tao et al. (2015) showed that combined treatment of 1-34 PTH and simvastatin has a cumulative effect on osseointegration compared to each of the agents alone. Javed et. al (2016a) concluded in his review of PTH efficacity that intermittent PTH therapy is enhancing new bone formation around implants.

*Prostaglandin EP4 receptor agonist* increases prostaglandin E2 (PGE2) activity on bone turnover in rats, resulting in a higher cancellous and cortical bone mass (Hayashi et al. 2005). It activates osteoblasts directly and osteoclasts indirectly (Graham et al. 2009). PGEP4 receptor activation on osteoblasts stimulates the production of RANKL (Graham et al. 2009), thus increasing osteoclast differentiation (see Figure 4). Hayashi et al. (2005) were the first to describe its action on implant fixation in rats by subcutaneous injections. The study demonstrated an increase in bone mineral density and bone-implant attachment strength. The same author showed that EP4 receptor agonist may increase early fixation of rough-surface implant (Hayashi et al. 2010).

*Vitamin D* ($1,25(OH)_2D$ or calcitriol) has the ability to promote calcium and phosphate intestinal absorption, thus providing adequate levels needed in bone turnover (Bikle 2014). Vitamin D undergoes 25-hydroxylation in liver and 1α-hydroxylation in kidney, all performed by cytochrome P450 in endoplasmic reticulum or mitochondria, resulting in a biologically active form of vitamin D (Bikle et al. 2014). By acting on Vitamin D receptor (VDR) on osteoblasts, it inhibits the production of osteoprotegerin (OPG) and increases the production of RANKL (Tang et al. 2008)(see Figure 4). Improvement of implant osseointegration by vitamin D has been established in 2008, in subcutaneous administration in rats, resulting in an increase in bone mass density and implant stability (Nakamura et al. 2008). Zhou et al. (2012) showed the same result on a larger number of rats and using oral gavage administration of vitamin D. However, a systematically review by Javed et al. (2016b) showed that the efficacy of vitamin D3 on osseointegration of implants still remains controversial. Nakamura et al. (2008) compared fixation of femoral implants in ovariectomized rats in alendronate, calcitriol and alendronate plus calcitriol treated groups. The authors showed an increase in bone mineral density in alendronate

group and an increase in implant stability only in alendronate plus calcitriol group (Nakamura et al. 2008).

*DKK1 antibody* is one of the newer therapies in osteoporosis and acts by inhibiting the Wnt/β-catenin signaling pathway (see Figure 4) which is necessary for the formation of osteoblasts from osteoblast precursors (Agholme et al. 2011, Pinzone et al. 2009). DKK1 antibody has proven its possible role in osseointegration when Olivares-Navarrete et al. (2010) pointed out the major role of DKK1 in early-stage differentiation during osseointegration on tissue cultures. The first experiment on animals was done by Agholme et al. (2011) when under subcutaneous administration, rats receiving DKK1 antibody had an increase in bone volume fraction.

Sclerostin is a protein produced mainly in osteocytes and acts similar to DKK1 by inhibiting theWnt/β-catenin signaling pathway (see Figure 4) and therefore down-regulating osteoblast differentiation (Nellie 2008). *Sclerostin antibody* (Scl-Ab) or romosozumab` denies sclerostin action on the signaling pathway which results in an enhanced osteoblast differentiation. Its role in implant osseointegration was first described by Virdi et al. (2012)in a study on subcutaneously injected rats which showed an accelerated and enhanced fixation of medullary implants by increasing both trabecular and cortical bone. Liu et al. (2015)showed that in a rat model of severe osteoporosis sclerostin antibody leads to an increased osseointegration of implants. In a study which compared Scl-Ab with PTH on osseointegration in metaphyseal bone, Agholme et al. (2014) demonstrated that PTH stimulates implant fixation specifically, whereas Scl-Ab has a wide-spread effect, mainly on cortical bone.

### *1.2 Anti-Catabolic Agents*

This group consists in factors which down-regulate osteoclast activity, resulting in a decrease in bone resorbtion process. They include calcitonin, biphosphonates, RANK/RANKL/OPG system and selective estrogen receptor modulators (SERM).

*Calcitonin* was the first anti-catabolic agent to be studied for its' osseointegration properties. It acts initially by inhibiting osteoclast motility, followed by modification of the cell's structure (Masi and Brandi 2007, Stevenson 1990), targeting calcitonin receptor (CTR) on osteoclasts (Masi and Brandi 2007) (see Figure 4). Furthermore, calcitonin inhibits differentiation of osteoclasts from precursors (Masi and Brandi 2007, Stevenson 1990). Nociti et al.(1999)outlined the increase in periosteal bone length and periosteal bone area in rabbits injected imtramusculary with calcitonin. The study also showed a minor negativ effect on the initial phase of osseointegration. The same author conducted another study showing no effect of subcutaneously-injected calcitonin rats in bone-to-implant contact and bone area (Nociti et al. 2002)compared to control. A more recent study published by Chen et al.(2011) showed an enhancement in bone mass surrounding the implant and osseointegrated implant surface, with an inferior effect compared to orally administrated alendronate.

*Biphosphonates* are the most frequently used drugs for the treatment of osteoporosis. They mainly act by inhibiting resorbtion of bone by osteoclast (Rosen 2016). They inhibit geranyl pyrophosphate (GPP) conversion to farnesyl pyrophosphate (FPP) in the mevalonate pathway (Gong etal. 2011), resulting in insuficient production of proteins necessary for osteoclast function and survival (see Figure 4). Moreover it has been shown that biphosphonates induce osteoblast apoptosis, decrease osteoclastogenesis and increase function of osteoblasts (Rosen 2016). The biphosphonates we focused on are more potent nitrogen-containing. They are

not metabolized and excreted unmodified by the kidney (Gong et al. 2011). The biphosphonates class contains several agents, the main difference between them being the affinity to calcium hydroxyapatite (Russell et al. 2008). The following have been studied regarding osseointegration of implants: alendronate, ibandronate, zoledronic acid, pamidronate and risendronate.

*Alendronate* has been first shown to improve removal torque values of titanium implants in subcutaneously injected rats by Narai and Nagahata (2003). Further studies concluded the same improvement in osseointegration (Duarte et al. 2005, Viera-Negron et al. 2008, Giro et al. 2008). Regarding oral administration of alendronate, Chacon et al. (2006) found on rabbits that the torque removal values did not differ significantly between alendronated and control group. On the other hand, Jensen et al. (2007) showed an increase in bone ongrowth, ultimate shear strength and periprosthetic bone in orally administred alendronate dogs. Mardas et al. (2011) showed that alendronate may impair new bone formation within early healing period in rabbits. Tallarico et al. (2015) showed no difference in implant survival of dental implants in forty patients treated with alendronate, but more studies are needed in order to confirm this result. As mentioned before, alendronate was compared in terms of osseointegration to calcitriol and alendronte plus calcitriol groups (Nakamura et al. 2008). Another comparative study (Ramalho-Ferreira et al. 2015) showed that alendronate had a lower effect on bone-to-implant contact and reverse torque compared to orally administred raloxifene.

*Ibandronate* was first introduced as a systemic enhancer of implant fixation by Skoglund et al. (2004) on subcutaneously injected rats. The study found an increase in pull-out force. Kurth et al. (2005) showed that ibandronate is capable of reversing the negative effect of osteoporosis on implant osseointegration, whereas Eberhardt et al. (2005) showed the importance of dosage in implant fixation, a higher dosage of 25 microg/kg/day (tumor dose) resulting in an improved

osseointegration compared to a lower dosage of 1 microg/kg/day (osteoporosis dose). The same author (Eberhardt et al. 2006) showed that an equivalent-dose single injection of ibandronate had the same effect on implant fixation as daily injections.

*Zoledronic acid's* or *zoledronate's* propriety of reducing particle-induced osteolysis has been demonstrated by von Knoch et al. (2005) after a subcutaneous single dose administration in mice. Same positive effect was proven in dogs by Bobyn et al. (2005) in terms of higher bone ingrowth and larger bone formation within implant pores. Experiments performed on rabbits showed the same enhancement in osseointegration but no difference in removal torque values compared to control group (Yildiz et al. 2010). Systemic zoledronic acid has a better effect on implant fixation compared to local administration, and both have an inferior effect compared to a combination of systemic and local administration (Qi et al. 2012). According to Cardemil et al. (2013), bone tissues react differently after zoledronate administration based on location. For the mandible, the study suggests a negative effect on the late phase of healing leading to a lower bone-to-implant contact, whereas tibia has a better osseointegration. Zoledronic acid has a better effect on bone-to-implant and peri-implant bone fraction compared to alendronate and strontium ranelate as stated by Chen et al. (2013).

*Pamidronate* has first been described as a systemic agent capable of improving osseointegration by Dayer et al. (2007). The authors had shown that pamidronate prevents loosening in low protein diet rats.

*Risedronate* administrated systemically has been first studied in orthopaedic implants. First, Sköldenberg et al. (2011) showed a lower rate in periprosthetic bone resorbtion in patients with total hip arthroplasty. Saari et al. (2014) showed no beneficial effects of systemic

risendronate regarding acetabular component fixation and bone mineral density (BMD) in revision arthroplasty.

*RANKL/RANK/OPG system* is a target for novel therapies in osseointegration improvement. In order for osteoclasts precursors to differentiate into mature osteoclast cells, receptor activator of nuclear factor-κB ligand (RANKL) and receptor activator of nuclear factor-κB (RANK) need to bind (Coetzee and Kruger 2004) (see Figure 4). Therefore, any factor that can suppress this binding can lead to an increased implant fixation. Such a factor is o*steoprotegerin (OPG).* It interferes with the binding resulting in an impaired osteoclastogenesis (Coetzee and Kruger 2004). OPG and immunoglobulin Fc can form OPG-Fc complex for an increased half-life (Sköldenberget al. 2016). Aspenberg et al. (2011) showed a significant protection against resorbtion and a reduced osteoclast density, resulting in a more potent effect compared to alendronate. OPG-Fc also increases osseointegration of implant in subcutaneously injected rats according to Bernhardsson et al. (2015). The authors showed an increased pull-out force and bone density. OPG level can be increased by naringin as Tong et al. (2016) showed in an in vitro study resulting in a possible increase of implant osseointegration. Human anti-RANKL antibodies are available, such as *denosumab,* but they do not react with animal RANK for studies to be conducted (Bernhardsson et al. 2015). Sköldenberg et al. (2016) has started a trial in which he tests patients with subcutaneously injected denosumab for improvement in previously diagnosed osteolytic lesions around uncemented implants. A clinical trial is also undergoing regarding denosumab administration after total hip replacement in postmenopausal women (Turku University Hospital 2013). Another inhibitor of RANK is intravenous astragaloside, as shown by Li et al. (2015), which can attenuate titanium particle-induced osteolysis in mice.

*Selective Estrogen Receptor Modulator (SERM)* is another factor in the improvement of implant fixation. SERM inhibits both short and long-term bone resorbtion (Rey et al. 2009), leading to an increased bone mass and strength. SERM have an agonist effect on estrogen receptor alpha and estrogen receptor beta in osteoblasts and osteoclasts (Rey et al. 2009) (see Figure 4). They improve osteoblast function and differentiation and increase oscteoclast apoptosis (Galea et al. 2013). The only SERM approved for treatment of osteoporosis is raloxifene (Eriksen 2006). Ramalho-Ferreira et al. (2015) demonstrated that orally administrated raloxifene, increases peri-implant bone mass in osteoporotic rats, also restoring the reverse torque and bone-to-implant contact to levels found in non-osteoporotic group. Moreover, the same study showed an enhanced osseointegration of implants compared to orally administrated alendronate.

### *1.3 Dual Anabolic And Anti-Catabolic Mechanism Agents*

There is a high probability that many of the factors mentioned above in the anabolic and anti-catabolic groups have a dual mechanism, but the ones proved so far to affect osseointegration by acting both on osteoblasts and osteoclasts are simvastatin and strontium ranelate.

*Simvastatin* is a lipid-lowering agent being a potent competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase (Wolozin et al. 2007) in the mevalonate pathway (see Figure 4). It is metabolized and eliminated in the liver by billiary excretion, and to a lesser extent, in the kidney (Mangravite et al. 2012). A less known anabolic mechanism of action is that it supresses the synthesis of FPP and GGPP factors, which down-regulate osteblastogenesis (Ruan et al. 2012)(see Figure 4). In addition, simvastatin supresses osteoclast formation induced by BMP-2 and RANKL (Yamashita et al. 2010). Other anabolic mechanisms are inhibition of

osteoblast apoptosis through TGF-β receptor (Ruan et al. 2012). Therefore, there is both an anabolic and anti-catabolic effect of simvastatin on bone metabolism. It was first introduced as an adjuvant factor in osseointegration by Ayukawa et al. (2004) increasing bone density around the implant and bone-to-implant contact in intraperitoneally treated rats. The same author found subsequently that a dose of 5mg/kg or more promotes osseointegration around implants (Ayukawa et al. 2010). Oral administration of simvastatin was proven effective as well resulting in a improvement in bone density, bone area and bone to implant contact (Du et al. 2009).

*Strontium ranelate* (SR) is an option in the treatment of osteoporosis. It is supposed to have a dual mechanism: 1) increase osteoblast differentiation and activity; 2) decrease osteoclast differentiation (by lowering RANKL levels and increasing OPG production) and activity (Fonseca and Brandi 2010) (see Figure 4), but sufficient evidence for anabolic effects in humans does not exist (Stepan 2013). On osteoblasts, SR acts on calcium sensing receptor (CaSR) thus increasing $Ca^{+2}$ intracellular levels from internal storage (Cannata-Andia et al. 2010, Purroy and Spurr 2002) (see Figure 4). On osteoclasts, it acts on the same receptor (CaSR) resulting in an increase of apoptosis through NF-κB. On osteoclast precursor it inhibits differentiation to osteoclasts. Li et al. (2010) showed that following an oral administration of strontium ranelate in rats there is an enhancement of bone volume ratio, percentage of osseointegration and maximum push-out force. On the other hand, an article published by Linderback et al. (2012) showed that the effect is weak in case of early implant fixation. A comparative study between strontium ranelate (oral administration), zoledronic acid (intravenous administration) and alendronate (oral administration) showed a superior effect of zoledronic acid group compared to similar effects of SR and alendronate groups (Chen et al. 2013).

### *1.4 Future Directions*

Currently, it is widely accepted that systemic pharmacological agents enhance implant osseointegration (Table 1). These factors are considered to be one of the great potential advances in the field of dental implants and orthopaedics within the coming years. Nevertheless, due to overlapping of mechanisms in implant osseointegration, osteoporosis and fracture healing, improvement in this field can apply to a wider range of patients.

The future lies in selecting those systemic agents with highest implant fixation and lowest adverse reaction rate, to be identified in comparative studies. Still, the positive effect on implant fixation had been shown mostly on animal models, therefore clinical trials are needed in order to test their efficacy in clinical situations and set up guidelines regarding patient selection, timing and duration of administration.

Upcoming molecular and genetic research on osteoblasts and osteoclasts can discover new targets for systemic drugs in order to promote implant fixation by regulating differentiation, function or apoptosis.

Due to recent advances in implant surface biocompatibility and local factors that promote osseointegration, there is a high probability of a staged combination of all these approaches following dental and orthopaedic implant surgery.



**Figure 4.Mechanism of action for systemic drugs that influence osseointegration.**

**Table 1.** Discovery of systemic drugs interaction that enhance osseointegration on animal models (publications)

## 2. Systemic Postoperative Drugs That Influence Titanium Implant Osseointegration

### *2.1 Pain Management Drugs*

*Aspirin* is used to treat pain and inflammation in patients with orthopaedic and dental implants. Altough an NSAID, we will talk about aspirin separately because it is the first choice in the pain management ladder. It acts by inhibiting cyclooxygenase-1 (COX-1) in low doses (Abramson et al. 2016). In intermediate doses it inhibits both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) (Abramson et al. 2016). As a result, arachidonic acid conversion will be suppressed and the levels of tromboxane $A_2$, prostaglandine $E_2$ and prostacycline are lowered (Gasparyan et al. 2008). Abdelhamid (2011)found on screw-shaped titanium implants in rabbits that bone-to-implant contact is significantly higher in aspirin treated group compared to control. On the contrary, Trancik et al. (1989) showed that aspirin might have a negative effect on implant fixation. We consider that further studies on a higher number of subjects need to be conducted in order to support this result.

*Acetaminophen* or *paracetamol* is prescribed to treat fever and pain and has a reduced anti-inflammatory effect due to decreased effect on (COX-1) and (COX-2), when compared to NSAIDs (Botting 2003). This results in a low effect on prostaglandin production. It is supposed to act on different form of cyclooxygenase, called COX-3, found in brain and spinal cord(Botting and Ayoub 2005). We have found no studies regarding the impact of acetaminophen on osseointegration. In theory, acetaminophen should be a lesser threat for implant fixation compared to NSAIDs (Bryce et al. 2014), but studies need to be conducted.

*NSAIDs* are commonly used drugs for the treatment of pain in this group of patients and act by inhibiting COX-1 and COX-2 in the arachidonic acid pathway (Gomes et al. 2015). The most important aspect in this mechanism regarding implant fixation are the prostaglandins, which are mostly reduced under the action of NSAIDs on COX-2. Prostaglandins promote inflammation, thus resulting in an increase supply of cells needed for bone formation. The importance of COX-2 was shown by Chikazu et al.(2007) when he found that COX-2 deficient mice had minimal bone formation around implant compared to control. Other animal and in vitro studies also outlined the importance of COX-2 in implant fixation (Gomes et al. 2015). One of the first studies to prove the negative effect of NSAIDs on bone formation was carried out by Trancik et al.(1989). He concluded that indomethacin and ibuprofen may be contraindicated postoperatively in patients with cemetless joint replacements(Trancik et al. 1989). Other NSAIDs shown to reduce implant fixation were diclofenac (Jacobsson et al. 1994), meloxicam (Ribeiro et al. 2006) and flurbiprofen (Reddy et al. 1990). In a review by Fu et al. (2012), the authors concluded that continued use of NSAIDs is associated with a lower bone density around implants, bone area and bone-to-implant contact. Gomes et al. (2015)stated in his review that clinical trials showed no reduction in osseointegration of titanium implants regarding COX-1 inhibitors, but there is no conclusion yet regarding selective COX-2 inhibitors (Jeffcoat et al. 1995, Alissa et al. 2009). On the other hand, Lionberger and Noble (2005) showed on patients undergoing cementless total hip replacement, that celecoxib, a COX-2 specific inhibitor, does not affect periprosthetic bone density and bone specific alkaline phosphatase (BSAlkP) levels compared to control group. In addition, another study on rats showed that meloxicam, another COX-2 specific inhibitor, did not interfere with implant fixation (Pablos et al. 2008). In terms of dental implants, a study conducted by Alissa et al. (2009)on patients, concluded that short-term

administration of ibuprofen may not have a significant effect on implant fixation. A common NSAID used in the prophylaxis of heterotopic ossification in orthopedic surgery is indomethacin. Cook et al. (1995) noted on dogs that indomethacin only affects implant fixation in early stages of osseointegration, but no significant difference compared to control group can be found after 24 postoperative weeks. In patients following hip replacement surgery, no statistically significant radiologic changes are to be found in indomethacin group compared to control group (Wurnig et al. 1993).

*Opioids*, which are recommended for moderate to severe pain, adjuvants for pain management such as t*ricyclic anti-depressants* (nortriptyline, desipramine or amitriptyline) and a*nticonvulsivants* (gabapentin, pregabalin, and carbamazepine) have not been yet studied in terms of influence upon osseointegration, but further are required.

Our opinion is that NSAIDs are the least safe of the pain management drugs in terms of implant survival, due to the most potent inhibition of COX-2. We therefore recommend the use of acetaminophen for mild to moderate pain and opioids for moderate to severe pain with or without adding adjuvants.



### *2.2 Drugs For Preventing Post Implant Surgery Comorbidities*

*Proton pump inhibitors* (PPI) are usually prescribed in patients after implant surgery in order to prevent adverse reactions of NSAIDs on digestive system. They bind to gastric $H^+/K^+$-ATPase and restrict gastric acid secretion (Shin and Kim 2013). Subaie et al. (2016) showed on rats that omeprazole impairs osseointegration, mostly due to a decreased number of osteoclasts. The mechanism of action is yet unknown, being supposed to be related to gene expression (Subaie et al. 2016). Further studies need to be done to confirm the result.

*Selective serotonin reuptake inhibitors* (SSRIs) are administrated in some patients for treatment of depression. SSRIs inhibit serotonin reuptake sites at the level of the synapses, increasing the concentration of serotonin at 5-HT postsynaptic receptors (Wu et al. 2014). In a study on 490 patients with 916 dental implants, treatment with SSRI WAS associated with an increased failure risk for implants due to mechanical loading (Wu et al. 2014).

*Anticoagulants* such as low molecular weight heparin (LMWH), unfractionated heparin, oral anticoagulants and fondaparinux are used in preventing blood clot formation which can lead to pulmonary embolism. They inhibit factors in the coagulation cascade, both on intrinsic and extrinsic pathways. Therefore, LMWH inhibit IIa and Xa factors, fondaparinux inhibits Xa factor, unfractionated heparin inhibits XIIa, XIa, IXa, Xa, IIa factors and oral anticoagulants inhibit factor II and X (II, VII, IX and X if warfarin or acenocumarol). A study on warfarin showed that it reduces cobalt alloy implant fixation and does not interfere with hydroxyapatite coated implants (Callahan et al. 1995). Matziolis et al. (2003) compared the effect of fondaparinux, unfractionated heparin, dalteparin and enoxaparin on osteoblast cultures. Fondaparinux was found to have no inhibitory action on osteoblasts, in contrast to the other tested drugs (Matziolis et al. 2003, Mavrogenis et al. 2009). Further studies on animal models and clinical trials need to be done in order to confirm this result.

Considering *antibiotics,* we have found no studies to assess osseointegration of titanium implants when administrated systemically. Further studies are needed to test their effect on implant fixation.

Special attention should be kept on proton pump inhibitors, selective serotonin reuptake inhibitors and heparins due to studies supporting their negative effect on implant fixation. More studies to support their result need to be conducted and no final conclusion can be admitted yet.

On the other hand, fondaparinux and warfarin did not seem to interfere with the survival of hydroxyapatite-coated implants.

### *2.3 Future Directions*

We consider that more attention should be given on the influence of postoperative drugs on ossteointegration of titanium implants. Comparative studies between drugs should be performed in order to be able to choose the one with least chances to jeopardize implant survival (Table 2). Moreover, drugs that have not been tested by now, need studies to confirm or deny their effect on implant fixation. Genetic and molecular research is important in order to find explanation of drugs influence on bone formation and further develop better agents with neutral or positive effect on implant osseointegration. Together with implant surface biocompatibility, application of local factors and systemic agents which enhance implant fixation, postoperative drugs are an important aspect of a successful implant surgery.

**Table 2.** Drugs administrated after implant surgery - effect on osseointegration of titanium implants.



**Declaration of interest**

The authors report no declaration of interest.

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**Table 1.** Discovery of systemic drugs that enhance osseointegration on animal models.

| Drug | Year | Author | Title | Journal |
|---|---|---|---|---|
| **Anabolic drugs** | | | | |
| 1-34 parathyroid hormone (PTH) or teriparatide | 2001 | Skripitz R et al. | Implant fixation enhanced by intermittent treatment with parathyroid hormone. | Journal of Bone & Joint Surgery, British Volume |
| Prostaglandin E2 Receptor 4 (EP4) receptor agonist | 2005 | Hayashi K et al. | Prostaglandin EP4 receptor agonist augments fixation of hydroxyapatite-coated implants in a rat model of osteoporosis. | Journal of Bone & Joint Surgery, British Volume |
| Vitamin D | 2008 | Nakamura Y et al. | Effect of Preoperative Combined Treatment with Alendronate and Calcitriol on Fixation of Hydroxyapatite-Coated Implants in Ovariectomized Rats. | Journal of Bone & Joint Surgery, American Volume |
| Dickkopf WNT Signaling Pathway Inhibitor 1 (DKK1) antibody | 2010 | Olivares-Navarrete R et al. | The roles of Wnt signaling modulators Dickkopf-1 (Dkk1) and Dickkopf-2 (Dkk2) and cell maturation state in osteogenesis on microstructured titanium surfaces. | Biomaterials |
| Sclerostin antibody | 2012 | Virdi AS et al. | Sclerostin antibody increases bone volume and enhances implant fixation in a rat model. | Journal of Bone & Joint Surgery, American Volume |

| | | | | |
|---|---|---|---|---|
| **Anti-catabolic drugs** | | | | |
| Calcitonin | 1999 | Nociti FHJ et al. | Effect of calcitonin on bone healing following titanium implant insertion. | Journal of Oral Science |
| Alendronate | 2003 | Narai S et al. | Effects of Alendronate on the Removal Torque of Implants in Rats with Induced Osteoporosis. | The International Journal of Oral & Maxillofacial Implants |
| Ibandronate | 2004 | Skoglund B et al. | Systemic and local ibandronate enhance screw fixation. | Journal of Orthopaedic Research |
| Zolendronic acid | 2005 | von Knoch M et al. | The decrease of particle-induced osteolysis after a single dose of bisphosphonate. | Biomaterials |
| Pamidronate | 2007 | Dayer R et al. | Defective implant osseointegration under protein undernutrition: prevention by PTH or pamidronate. | Journal of Bone and Mineral Research |
| Risendronate | 2011 | Sköldenberg OG et al. | The effect of weekly risendronate on periprosthetic bone resorbtion following total hip arthroplasty: a randomized, double-blind, placebo-controlled trial. | Journal of Bone & Joint Surgery, American Volume |
| OPG-Fc | 2011 | Aspenberg P et al. | Targetting RANKL for reduction of bone loss around unstable implants: OPG-Fc compared to alendronate in a model for mechanical induced loosening. | Bone |
| Raloxifene | 2015 | Ramalho-Ferreira G et al. | Raloxifene enhances peri-implant bone healing in osteoporotic rats. | International Journal of Oral and Maxillofacial Surgery |

**Dual anabolic and anti-catabolic mechanism drugs**

| | | | | |
|---|---|---|---|---|
| Simvastatin | 2004 | Ayukawa Y et al. | Simvastatin promotes osteogenesis around titanium implants. | Clinical Oral Implants Research |
| Strontium ranelate | 2010 | Li Y et al. | Strontium ranelate treatment enhances hydroxyapatite-coated titanium screws fixation in osteoporotic rats. | Journal of Orthopaedic Research |

**Table 2.** Drugs administered after implant surgery and their effects on osseointegration of titanium implants.

| Drug | Animal model experiment | Clinical trials | Conclusion |
|---|---|---|---|
| Pain management drugs | | | |
| Aspirin | Trancik et al. (1989) | No studies found | Impairs osseointegration of implant |
| | Abdelhamid (2011) | | Enhances osseointegration of implant |
| Acetaminophen | No studies found | No studies found | No conclusion |
| Nonsteroidal anti-inflammatory drugs (NSAIDs) | Trancik et al. (1989) | | Indomethacin and ibuprofen may impair osseointegration of implant |
| | Reddy (1990) | | Flurbiprofen impairs osseointegration of implant |
| | Jacobsson et al. (1994) | | Diclofenac impairs osseointegration of implant |
| | | Jeffcoat et al. (1995) | Flurbiprofen impairs osseointegration of implant |
| | Ribeiro et al. (2006) | | Meloxicam impairs osseointegration of implant |
| | | Alissa et al. (2009) | Short course administration of ibuprofen does not affect |

| | | | |
|---|---|---|---|
| | | | osseointegration of implant |
| Opiods | No studies found | No studies found | No conclusion |
| Tricyclic anti-depressants | No studies found | No studies found | No conclusion |
| Anticonvulsivants | No studies found | No studies found | No conclusion |
| Drugs for preventing post implant surgery comorbidities | | | |
| Proton pump inhibitors (PPI) | Subaie et al. (2016) | | Omeprezole impairs osseointegration of implant |
| Selective serotonin reuptake inhibitors (SSRIs) | | Wu et al. (2014) | Impair osseointegration of implant |
| Anticoagulants | Callahan et al. (1995) | | Warfarin impairs osseointegration of implant |
| Antibiotics | No studies found | No studies found | No conclusion |