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Review

Influence of nonsteroidal anti-inflammatory drugs on osseointegration

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Abstract: This paper reviews contemporary literature concerning the possible influence of nonsteroidal anti-inflammatory drugs (NSAIDs) on osseointegration. In vitro studies concerning the effect of NSAIDs on growth factors and bone-generating cells are the primary source of data pertaining to this issue because relatively few *in vivo* studies have been conducted. It is concluded that prescribing NSAIDs during the early postoperative period is likely not without negative effect, although any negative influence appears to be temporary and does not affect the final outcome of osseointegration. (J. Oral Sci. 50, 239-246, 2008)

Keywords: NSAID; osseointegration.

Introduction

Osseointegration is prerequisite for the rehabilitation of patients with oral implants who are totally or partially edentulous. Many researchers have dealt with the factors that influence osseointegration. One unanswered question is whether nonsteroidal anti-inflammatory drugs (NSAIDs) have an unfavorable effect on osseointegration. NSAIDs are widely prescribed for dental implant patients, not only for postoperative pain relief but also for concurrent cardiovascular diseases and muscular and skeletal disorders. NSAIDs are also ingredients of commonly available pain-killers. Given their frequency of use, likely cross-correlation of NSAIDs with implant failure could indicate that they cannot be used safely for pain relief during the early postoperative period.

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Review of the Literature

Neither clinical retrospective nor prospective studies regarding the possible effects of NSAIDS after placement of oral implants have been published. Therefore the only source of data is from experimental studies of implants in orthopaedic surgery (Table 1). Jacobsson et al. reported observing a weak interface at hydroxyapatite (HA)-coated Ti implants inserted in 10 rabbit femora 3 weeks after surgery, after treatment with diclofenac (1). They concluded that the negative effect of NSAIDs on bone healing would not be compensated by HA coating. It should be noted, however, that the dose used in their study was 3-4 times higher than the maximum dose for humans. In another *in vivo* experiment, Trancik et al. (2) reported a statistically significant decrease in bone growth in the pores of cobalt-chromium implants after administering indomethacin, ibuprofen and high-dose aspirin to rabbits. These implants used in both studies differed from those used in max-illofacial surgery in many aspects, including shape, material, surface and embiomechanics. Therefore these studies could not be used to establish a positive correlation between NSAIDs and oral implant failures.

Recently, Ribeiro et al. (3) noted an unfavourable effect of meloxicam (3 mg/kg) in the osseointegration of Ti implants in rats. The rats received meloxicam during the first 60 postoperative days at a dose of 3 mg/kg. There was a statistically significant reduction in the rate of bone-implant contact and in bone density for both cortical and cancellous bone. The authors suggested that patients who receive chronic treatment with selective inhibitors of cyclooxygenase-2 (COX-2) for osteoarthritis or rheumatoid arthritis should avoid implant treatment or, at least, have a longer healing time before loading.

On the other hand, some researchers have disproved any negative effects of NSAIDs on osseointegration. For example, in a prospective clinical study performed by Reddy et al. (4) it was observed that bone density increased

Table 1 *In vivo* studies

Authors	Subjects	Medication	Result
Jacobsson et al. (1)	10 New Zealand white rabbits	Study group: Diclofenac 30 mg for 7 days Control group: Saline	Low interface strength at HA-coated ti implants
Trancik et al. (2)	120 New Zealand white rabbits	a. Indomethacin 1 mg/kg/day b. Indomethacin 2 mg/kg/day c. Indomethacin 3 mg/kg/day d. Ibuprofen 17 mg/kg/day e. Ibuprofen 34 mg/kg/day f. Aspirin 17 mg/kg/day g. Aspirin 34 mg/kg/day h. Control group: Saline	Decrease in bone ingrowth into a porous-coated implant
Ribeiro et al. (3)	30 Wistar rats	Study group: Meloxicam 3 mg/kg for 60 days Control group: Saline	Reduced bone-to-implant contact, bone area and bone density in cortical and cancellous bone
Reddy et al. (4)	4 patients	Flurbiprofen 100 mg ×2 per day for three months	No negative influence
Jeffcoat et al. (5)	29 patients	a. Flurbiprofen 50 mg ×2 per day for three months b. Flurbiprofen 100 mg ×2 per day for three months c. Control group: Placebo	No negative influence
Chikazu et al. (20)	COX-$2^{+/+}$ and COX-$2^{-/-}$ mice	–	Reduced osteocalcin mRNA in bone surrounding implants in COX-$2^{-/-}$ mice. Minimal new bone formation in cortical bone adjacent to the implant in COX-$2^{-/-}$ mice.
Darmongsri et al. (23)	12 Wistar rats	Study group: NS-398 3 mg/kg/day Control group: Saline	Reduced BMP-6 expression and impaired osseous regeneration

and bone height was stable in patients after a three-month course of flurbiprofen (100 mg ×2 per day). This dose is consistent with those approved for the chronic treatment of osteoarthritis. The effects of NSAIDs on osseointegration were assessed via digital subtraction radiography. There was no statistically significant difference during the buried healing period between subjects who received and those who did not receive flurbiprofen. In a second study by the same group of researchers, Jeffcoat et al. (5) reached the same conclusion for a 100-mg BID dose, but not for a lower dose (50 mg BID). Again, these doses are consistent with those associated with chronic use and not those used for postoperative pain relief.

Although the effects of NSAIDS in maxillofacial surgery have not been adequately delineated, their negative effect on bone healing has been confirmed in orthopaedics (6-8). In experimental studies it has been shown that healing of fractures is delayed, but not arrested, when selective or non-selective COX-2 inhibitors are used (9-13). Moreover, many clinicians recommend the use of NSAIDs after hip arthroplasty in order to prevent heterotopic ossification, a pathologic ectopic bone deposition that reduces the extent of joint motion (14). Finally, it has been observed that the results of spinal fusion surgery are inferior, with a higher incidence of non-union, when NSAIDs are used postoperatively (15). All these factors should be taken into consideration, since osseointegration is an example of bone healing.

In order to fully comprehend and possibly explain the potential effects of NSAIDs on osseointegration, one should first consider the biology of bone healing (16). The early stages of bone healing are characterized by inflammation. Specifically at the site of a fracture, a blood clot is formed and accumulation of leukocytes is observed during the first 6-8 hours. Inflammatory cells, and mainly platelets, secrete abundant cytokines and growth factors, such as the bone morphogenetic proteins (BMPs), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). During the first 10 days the blood clot becomes organised and granulation tissue is formed, while at the same time neovascularization is observed. Moreover, in inflamed tissues COX-2 expression is induced (13). Endogenous prostaglandins have a key role in the metabolism of bone, and are the main regulators of balance between composition and absorption during bone repair. Evidence of the importance of COX-2 and prostaglandins

is that knockout COX-$2^{-/-}$ mice (in which the gene responsible for the COX-2 has been deleted) show serious dysfunction in the healing of fractures (8). It is also reported that in samples of tissue collected from fractures with disturbed healing, the concentration of COX-2 is 13 times lower than that found at normally healing sites (17).

Regarding osseointegration, the process of bone repair after implant placement begins with the creation of a blood clot in the space between the bone and the implant (18,19). In the first 10 days, adsorption of plasma proteins, activation of platelets, cytokine secretion and chemotactic factors and an inflammatory response are observed. At the same time the productive phase of inflammation begins, which consists of revascularization of the region, attraction, differentiation, proliferation and activation of cells that are involved in bone healing (osteoblasts, osteocytes, osteoclasts, and mesenchymal stem cells) and production of an immature connective tissue matrix. COX-2 is essential not only for fracture healing, but also for osseointegration of dental implants, as Chicazu et al. (20) reported in their *in vivo* experimental study after insertion of Ti implants in COX-$2^{-/-}$ mice. The study authors observed reduced osteocalcin mRNA in bone surrounding the implants and minimal new bone formation in cortical bone adjacent to the implants. Contrary to fracture repair and formation of callus occurring at long bones, in peri-implant healing there is no endochondral ossification, and consequently, osseointegration has similarities with direct bone healing. In this review possible mechanisms via which NSAIDs could intervene with osseointegration are examined.

Effect of NSAIDs on BMPs

Experimental *in vitro* studies have shown negative effects of NSAIDs on growth factors that encourage osteogenesis, primarily bone morphogenetic proteins (BMPs) (Table 2).

Arikawa et al. (21) reported reduction of BMP-2 levels in cultures of human mesenchymal stem cells after addition of NS-398, a selective inhibitor of COX-2, via a mechanism that is related to reduction of prostaglandin E_2 (PGE_2) levels. The role of BMP-2 in osteoblastogenesis renders this reduction critical for the early stages of osseointegration.

Moreover, Takiguchi et al. (22), studying BMP-2 as a possible factor that promotes regeneration of periodontal tissues, observed that simultaneous treatment of human periodontal ligament cells with BMP-2 and interleukin-1β (IL-1β) enhanced the activity of alkaline phosphatase (ALP) and production of PGE_2, and promoted the differentiation of osteoblasts. Addition of indomethacin to the culture suppressed this action. However, these observations concern the response of cells to exogenous treatment with BMP-2 and IL-1b, and consequently may

Table 2 Effect of NSAIDs on growth factors. *In vitro* studies

Authors	Subject	Medication	Results
Arikawa et al. (21)	Human mesenchymal stem cells (hMSCs)	NS-398 0.1 μM	↓BMP-2
Takiguchi et al. (22)	Human periodontal ligament cells (HPLC)	a. BMP-2 500 ng/ml and IL-1β 0.025-25 ng/ml b. + Indomethacin 1 μM	a.↑ALP, PGE_2 and osteoblastic differentiation b. Inhibition of the above effect
McAllister et al. (24)	Human gingival fibroblasts	a. EGF and PDGF b. + Bradykinin c. + Indomethacin 30 μM	a. ↑ DNA synthesis b. Inhibition of the above effect c. Restoration
Koide et al. (25)	Mouse bone marrow cells	a. BMP-2 100 ng/ml and IL-1a 1 ng/ml b. + Indomethacin 0.1 μM and 0.5 μM or NS-398 0.01 μM and 0.1 μM	a. ↑Osteoclast formation b. Inhibition of the above effect
Kawaguchi et al. (26)	Neonatal mouse calvarial culture	a. FGF-2 at high concentrations (>10^{-9} M) b. + Indomethacin or NS-398 0.01 μM	a. ↑Osteoclast formation b. Inhibition of the above effect
Harada et al. (27)	RTC-3 cells from fetal rat calvaria	PGE_2 10^{-8}-10^{-6} M	Rapid and transient increase in VEGF mRNA
Szabó et al. (31)	Human dermal microvascular endothelial cells (HMVECs)	Indomethacin 500 μM or NS-398 100 μM	Decrease in VEGF-induced Egr-1 mRNA expression
Miura et al. (32)	Human gastric fibroblasts	a. IL-1β b. +Indomethacin or NS-398 10 μM	a. ↑ VEGF and COX-2 b. Restoration

not be pertinent to peri-implant healing.

In an *in vivo* experimental study of growth factors, Damrongsri et al. (23) reported reduced expression of BMP-6 and impaired osseous regeneration after COX-2 inhibition by NS-398 in a rat GBR (guided bone regeneration) model. In addition, it was also shown that levels of COX-2, BMP-2 and PDGF (platelet-derived growth factor) reach a peak during the 3rd postoperative day, compared to the 7th, 21st and 28th days, suggesting an important role of COX-2 in new bone formation.

Contrary to the aforementioned studies, some researchers have also argued in favour of NSAID use, since they have observed that in the presence of inflammation, NSAIDs restore the levels of growth factors that promote bone healing. However, it should be noted that in these studies the growth factors were added exogenously, and not secreted by cells.

For example, McAllister et al. (24) reported an increase of DNA synthesis in human gingival fibroblasts after addition of epidermal growth factor (EGF) and PDGF to the culture. The presence of bradykinin arrested this increase, while addition of indomethacin restored it. Also, Koide et al. (25), contrary to Takiguchi et al. (22), observed promotion of osteoclastogenesis in bone marrow cells by BMP-2 and IL-1α, which was arrested by addition of indomethacin or NS-398. These opposing effects could be attributed to differences in the concentrations of growth factors or to the different types of cells used. Moreover, increased osteoclastogenesis does not necessarily mean increased bone absorption, since the activity and level of differentiation of the osteoclasts was not verified. Finally, Kawaguchi et al. (26) showed that high concentrations of FGF-2 (fibroblast growth factor-2) enhanced osteoclastogenesis and increased the release of Ca, whereas indomethacin or NS-398 suppressed this effect.

Effect of NSAIDs on VEGF (angiogenesis)

Vascular endothelial growth factor (VEGF) has been recognized as important for angiogenesis, proliferation of endothelial cells and increased vascular permeability. Any influence on this growth factor may impair angiogenesis during osseous repair (Table 2). Harada et al. (27) showed that VEGF is expressed *in vitro* in osteoblasts, with a potential role in bone metabolism. They observed an abrupt and brief increase of VEGF after adding PGE_2 to cultures of RTC-3 cells, which express osteoblastic features. Consequently, NSAIDs, by decreasing the level of PGE_2 may bring about a reduction of VEGF, although this conclusion has not been confirmed. Notably, however, an *in vivo* study assessing osteotomy sites 2 weeks after surgery in guinea pigs that had received indomethacin (28) found reduced blood flow at the osteotomy sites. In addition, Murnaghan et al. (29) demonstrated that rofecoxib had a significant negative effect on blood flow across fracture gaps in mice. The NSAID-treated group exhibited a lower blood flow from day 4 onward (significant at days 4, 16, and 24) and poorer healing in terms of all studied parameters.

Inhibition of angiogenesis has been confirmed in other studies as well. It is known that NSAIDs delay the healing of gastric ulcers and the growth of tumors, via mechanisms that are related to angiogenesis (30). More specifically, Szabó et al. (31) have reported that addition of indomethacin or NS-398 to cultures of endothelial cells prevents the VEGF-induced increase in expression of the egr-1 gene. Additionally, Miura et al. (32) have reported that, while the presence of IL-1β increased production of VEGF and COX-2 by gastric fibroblasts, addition of indomethacin or NS-398 restored the VEGF to basic levels.

Effect of NSAIDs on osteoblastic function

NSAIDs possibly exert a negative effect on the proliferation and differentiation of osteoblasts (Table 3).

According to Zhang et al. (33), COX-2-/- mice showed (a) a notable delay in the healing of tibia fractures and (b) 75% less production of new bone, after implantation of titanium particles onto the calvaria. In cultures of bone marrow stromal cells from COX-2-/- mice, there were 50% fewer mineralized bone nodules than in cultures from normal mice. The transcription factors cbfa1 and osterix, which are related to the differentiation of mesenchymal stem cells to osteoblasts, were also reduced. Zhang et al. concluded that COX-2 participates in the regulation of osteoblast differentiation via a mechanism related to the expression of cbfa1 and osterix. However, they did not confirm this hypothesis using a control group of healthy mice.

In another *in vitro* study by Ho et al. (34), it was found that ketorolac and indomethacin caused reduction in the proliferation of primary osteoblasts. The effects were dose- and time-dependent. It is speculated that this action occurred via a mechanism independent of PGE2 production and related to the cell cycle. However, there was also a concurrent increase of alkaline phosphatase (ALP) activity and production of type I collagen 10 days after the start of the experiment. The authors considered that the unfavourable effect of NSAIDs was limited to the initial stages of cellular differentiation. Evans and Butcher (35) performed a study using cells obtained from human trabecular bone. Culture of osteoblasts with indomethacin or DFU (a selective COX-2 inhibitor) resulted in a reduction

of cell number and a statistically non-significant increase of ALP activity and collagen synthesis. In contrast, 24-hour incubation of cells with NSAIDs had the opposite effect. Alternatively, according to Daluiski et al. (17), in human osteoprogenitor cells there was a decrease of ALP activity after addition of celecoxib, even with simultaneous addition of rhBMP-2. This result agreed with that of Khokher and Dandona (36), according to whom in culture of osteoblasts, aspirin or indomethacin caused a reduction of basic, as well as vitamin D3- or insulin-induced, ALP activity and incorporation of thymidine. Moreover, Scutt and Bertram (37) reported an explicit anabolic action of PGE_2 in bone marrow cells after the first 48 hours of culture.

Effect of NSAIDs on the relationship between surface roughness and osseointegration

It is widely accepted that implants with a rough surface show better biological behavior. The higher success rate is attributed to increased adhesion of cells to the implant surface and to increased levels of cytokine and growth factor production, implying a phenotype with increased differentiation (38). Among them, the levels of PGE_2 were six-fold greater on a TPS (Ti plasma-sprayed) surface in comparison with plastic (39). In cultures of MG63 osteoblast-like cells, isolated from a human osteosarcoma, on SLA (sand-blasted, large grit, acid-etched) and TPS disks, in the presence of indomethacin), there was a reduction in the levels of osteocalcin, transforming growth factor β (TGF_β) and ALP activity (40). The result was similar when indomethacin was added to already established cultures for 4 days (41). Therefore, indomethacin may arrest the favorable effects of increased roughness on cells at the bone-implant interface.

Effect of NSAIDs on other cells (monocytes - macrophages)

Sun et al. (42) studied the influence of indomethacin on monocytes in contact with Ti particles and observed a reduction of PGE_2 levels, but also an increase of IL-6. The authors considered that the NSAIDs potentially contributed to implant failure via a mechanism related to IL-6. It should be mentioned that during the early postoperative period, the presence of Ti particles has been detected in the periimplant tissues, mainly round TPS implants and near their neck, which can be explained by the friction between bone and implant during placement (43-45).

Effect of NSAIDs and duration of their use

In the previously mentioned studies, the effect of a short course of NSAIDs, such as those prescribed for post-operative pain, was not investigated. Goodman et al. (46) observed that when rofecoxib was used for 6 weeks there was less bone ingrowth in the inner core of a BHC (bone harvest chamber) implanted in the tibia of New Zealand rabbits. However, when the medication was given for only the 2 first weeks, at the end of 6 weeks there was no statistically significant difference from the control group. Recently, Karachalios et al. (47) evaluated the effect of short-term administration of low therapeutic doses of indomethacin, meloxicam or rofecoxib in rabbits. The medication was administered for five days, and at six weeks there was a minor negative effect on bone healing

Table 3 Effect of NSAIDs on cell functions. *In vitro* studies

Authors	Subjects	Medication	Results
Ho et al. (34)	Fetal rat calvaria cells	Ketorolac up to 1000 μM and indomethacin up to 100 μM	↓ Cell proliferation ↑ ALP activity and collagen I synthesis
Evans and Butcher (35)	Human osteoblasts	Indomethacin or DFU a. 0.3 μM for 4 days b. 0.003-0.3 μM for 1 day	a. ↓ Cell number [Not statistical significant ↑ ALP activity and collagen synthesis] b.Reversible decrease in cell number
Daluiski et al. (17)	Human osteoprogenitor cells (Saos-2)	Celecoxib	↓ ALP activity
Khokher and Dandona (36)	Human bone cells	Aspirin or indomethacin 1-1000 μg/l	↓ ALP activity and thymidine incorporation
Batzer et al. (40)	MG63 cells SLA and TPS Ti disks	Indomethacin (0.1 μM)	↓Osteocalcin and TGF_β production and ALP activity
Sun et al. (42)	Human monocytes in contact with Ti particles	Indomethacin 5 μM	↓PGE_2, ↑IL-6

in the rofecoxib group. In another *in vivo* study, Simon and O'Connor (48) determined how variations in NSAID therapy ultimately affect fracture-healing. They concluded that, although therapy during the early stages of fracture repair significantly reduced the mechanical strength of fracture callus, celecoxib therapy prior to fracture or started fourteen days after fracture did not significantly increase the proportion of nonunions. Moreover, from the studies of Trancik et al. (2) as well as Evans and Butcher (35) it is evident that the effects of NSAIDs are temporary and reversible

Discussion

Most studies that have assessed the effects of NSAIDs on osseointegration and bone healing have been performed *in vitro*. The concentration of NSAIDs in the periimplant bone, when the medication is taken *per os* postoperatively, is not known. Thus, one cannot reproduce *in vitro* a model of osseointegration influenced by oral administration of NSAIDs. For example, the concentration of indomethacin that has been used in experiments varies between 0.01 and 500 mM (Table 1). This range of concentration is very wide, and the concentration approximating that *in vivo* is not known. This means that the studies are not comparable with each other or with clinical conditions.

Likewise, the concentration and the precise action of growth factors secreted in healing bone are not known. The concentrations used by the study authors may not correspond to real conditions. Moreover, some of the growth factors have a biphasic action, for example PGE2, encouraging bone production at lower concentrations, but promoting bone resorption at higher concentrations. Furthermore, usually the action of a single growth factor is studied, without taking into consideration the interaction, synergy or competitiveness, among the growth factors that coexist in the periimplant bone.

Finally, it is not known whether the cell lines that were used exhibit the same behavior as osteoblasts during osseointegration. However, given their phenotypic resemblance, one can assume that the results of *in vitro* studies can be applied to clinical conditions.

As far as *in vivo* studies are concerned, it should be mentioned that there are pharmacokinetic differences between species. Previous authors have generally used doses of medication that correspond to doses recommended for humans. However, it is estimated that the half-life time of celecoxib and rofecoxib in guinea-pigs is 4 and 5 hours, compared to 11 and 10-17 hours, respectively, in human patients (48). Consequently, the effects of these medications on patients may be underestimated. Additionally, it is also unknown whether the same dose of medication inhibits COX-2 in both humans and animals (rabbit or rat).

Apart from the fact that the results of experimental *in vitro* or even *in vivo* studies cannot be applied to clinical conditions, some unanswered questions remain. For example, do different medications of the same category have different biological behavior? Is there any difference in the influence of selective and non-selective inhibitors of COX-2? If the effect of NSAIDs is transient and reversible, from which point onwards, or for how long in the early postoperative period, is their use safe? Are there patients at increased risk of complications in osseo-integration after receiving NSAIDs, and if so, which factors should be taken into consideration?

In summary, there is insufficient evidence to establish a positive correlation between NSAIDs and early implant failure. However, there has been a lack of prospective studies in humans, and therefore it is essential to further investigate this issue in order to develop protocols for the safe use of NSAIDs in this population.

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