Effects of Nonsteroidal Anti-inflammatory Drugs on Osseointegration: A Review

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The purpose of this study was to review the effects of nonsteroidal anti-inflammatory drugs on osseointegration and determine whether they cause failures in dental implants and whether patients who use them chronically can receive dental implants safely. A bibliographic electronic search was performed using the Cochrane Library, PubMed, and Medline databases, selecting articles published between January 1982 and December 2012. The search included the following keywords, either alone or combined: "nonsteroidal anti-inflammatory drugs," "dental implants," "bone healing," and "osteoprogenitor cells." The inclusion criteria were the following: randomized, double-blind, placebo-controlled clinical studies, in vivo animal model studies of osseointegration, and in vitro studies of the effects of these agents on osteoprogenitor cells. The literature search revealed 360 references. A total of 31 articles met the inclusion criteria, including 2 clinical trials, 20 animal studies, and 9 osteoprogenitor cell studies. The clinical trials revealed that cyclooxygenase-1 (COX-1) inhibitors did not impair osseointegration. The animal studies showed that any drug that is capable of inhibiting COX-2 may impair the osseointegration process. The in vitro studies showed that COX-2 inhibitors are the most potent depressors of osseointegration at the cellular level. Caution must be taken when selecting COX-2 nonsteroidal anti-inflammatory drugs during the postoperative period.

Key Words: osseointegration, nonsteroidal anti-inflammatory drugs, dental implants

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the management of acute and chronic inflammation and pain.[1] These anti-inflammatory agents function by suppressing the enzyme cyclooxygenase (COX), which has 3 isoforms: COX-1, COX-2, and COX-3.[2] COX-1 is constitutively expressed in most cells, and COX-2 is considered to be induced by inflammation and by the presence of pro-inflammatory cytokines and mitogens, although it exerts important physiological effects on the cardiovascular system. COX-3 is an alternatively spliced variant of COX-1 that exists predominantly in the central nervous system.[3–5]

Bone tissues are abundantly supplied with prostaglandins (PGs), mainly prostaglandin E2 (PGE_2), which plays a stimulatory or inhibitory role in bone metabolism, depending on physiological and pathological conditions. Several clinical, animal, and in vitro studies have demonstrated impaired osseointegration and bone healing in the presence of conventional NSAIDs.[6] Osseointegration is well known to be a prerequisite for the rehabilitation of patients with oral implants who are completely or partially edentulous.[7] Many researchers have studied the factors that influence osseointegration.

An important issue is whether NSAIDs have unfavorable effects on osseointegration. Variables such as the dose, duration of administration, and selectivity of NSAIDs can impair osseointegration, raising the question of whether they can be used safely for pain relief after dental implant surgery.[8] Thus, because this issue remains controversial, the present review seeks to determine whether the use of NSAIDs diminishes bone healing and osseointegration when administered after dental implant surgery. An important question is whether patients who use NSAIDs chronically can receive dental implants safely.

MATERIAL AND METHODS

A bibliographic electronic search was performed using the Cochrane Library, PubMed, and Medline databases, selecting articles published between January 1982 and December 2012. The following search terms were used, either alone or combined: "nonsteroidal anti-inflammatory drugs," "dental implants," "bone healing," and "osteoprogenitor cells." The

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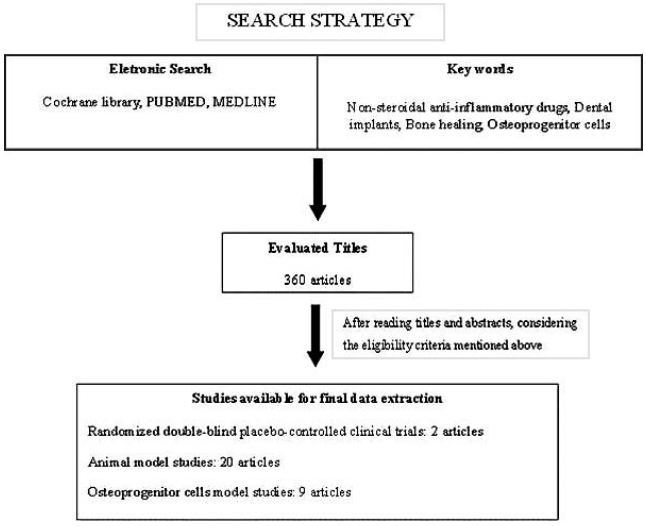

Figure 1. Search strategy.

initial inclusion criteria were randomized, double-blind, placebo-controlled clinical studies that analyzed the effects of nonsteroidal anti-inflammatory drugs on dental implant osseointegration in humans. In vivo animal studies of bone healing/osseointegration and in vitro studies of the effects of these agents on osteoprogenitor cells were also included. The exclusion criteria included publications in languages other than English, studies using a periodontal disease model, and case reports (Figure 1).

Results

The search yielded 360 articles, and the titles and abstracts were analyzed. Considering the inclusion and exclusion criteria, 31 studies were selected, including 2 clinical trials, 20 animal studies on osseointegration, and 9 osteoprogenitor cell studies. We analyzed the full text of these articles and sought to determine whether these drugs diminish osseointegration and bone repair, causing failure when administered postoperatively after dental implant surgery, and whether patients who use them chronically can receive dental implants safely.

Discussion

Clinical studies

We found only 2 articles that evaluated the effects of selective COX-1 NSAIDs on dental implant osseointegration (Table 1), in which the time of administration and doses were determining factors. Jeffcoat et al[9] evaluated the effect of flurbiprofen (50 or 100 mg, twice daily), the selectivity of which is described in Table 2. They administered flurbiprofen for 3 months to patients who received dental implants. Patients in the 100 mg flurbiprofen group experienced approximately half the bone loss of the 50 mg flurbiprofen and placebo groups. However, after 1 year, the balance between bone loss and gain became stable in all of the groups. These results indicate that flurbiprofen at high doses may spare the bone around mandibular root-form dental implants. No significant changes in bone height or mass were found between 6 and 12 months, indicating that bone loss stabilized even after flurbiprofen treatment was discontinued.

Alissa et al[10] evaluated the efficacy of a 1-week postoperative course of 600 mg ibuprofen taken 4 times daily on marginal bone level around dental implants. They found no statistically significant differences between groups in the mean marginal bone level around dental implants at 3 and 6 months postplacement.

Although less or an absence of bone loss following NSAID exposure was reported, trials that investigated the effects of NSAID treatment on bone metabolism outcomes in human patients are limited, and the results have been controversial with regard to the association between NSAIDs and bone healing. Further research is required to confirm or refute the findings presented in this review.

Table 1

Clinical studies on osseointegration around titanium implants

Authors	Group	Posology	Analyzed Criteria	Outcome
Jeffcoat et al[9]	Low-dose flurbiprofen group High-dose flubirprofen group	Flurbiprofen, 50 or 100 mg twice daily for 3 months	Height and mass changes around root-form of titanium dental implants during 1-year observation	The 100-mg flurbiprofen group experienced approximately half of the bone loss of the low-dose flurbiprofen and placebo groups ($P < 0.001$)
	Placebo group			From the 6th to 12th month of the study, bone mass was stable in all groups
Alissa et al[10]	Ibuprofen group (31 patients) Placebo group (30 patients)	Ibuprofen, 600 mg taken 4 times over 1 week	Marginal bone level changes during 6-month observation period	No statistically significant differences in mean marginal bone level changes were found between groups at 3 or 6 months

TABLE 2

Selectivity of nonsteroidal anti-inflammatory drugs for cyclooxygenase enzymes[31]

Group	Description	Selectivity Proportion	Examples
I	High selectivity for COX-1	100–1000	ketorolac, etodolac
II	High selectivity for COX-1	10–100	flurbiprofen
III	Low selectivity for COX-1	1–10	indomethacin, naproxen, ibuprofen
IVA	Nonselective drugs; complete inhibition of both COX enzymes	1	fenoprofen, ketoprofen
IVb	Nonselective drugs; incomplete inhibition of both COX enzymes	1	salicylates
V	Low selectivity for COX-2	1–10	nimesulide, paracetamol, meloxicam, piroxicam, sulindac, diclofenac, celecoxib
VI	High selectivity for COX-2	10–100	valdecoxib, parecoxib, eterocoxib
VII	High selectivity for COX-2	100–1000	rofecoxib

Animal studies

The influence of nonsteroidal anti-inflammatory drugs on osseointegration is related to the duration of treatment, dose administered, and drug selectivity. Previous studies have sought to determine the effect of COX-1 inhibitors on bone healing. Keller et al[11] investigated the effect of indomethacin (12.5 mg/kg) administered for 6 weeks on surgical defects with different sizes (ie, 2, 3, and 8 mm) produced in the tibia in rabbits. Histological analysis revealed that the drug did not influence bone formation in the 2-mm surgical defects, but it did influence bone formation in 3- and 8-mm surgical defects, indicating that the inhibitory effects on bone remodeling depend on the extent of the trauma.

Senerby et al[12] reported that administration of different doses of indomethacin (1 and 4 mg/kg) for 3 weeks did not influence bone healing around implants in rabbits. Endo et al[13] showed that etodolac (20 mg/kg) administered for 3 weeks significantly affected bone healing in tibia fractures in rats. Martins et al[14] found that ketoprofen (12.5 mg/kg) administered for 30 days in rats with tibia fractures led to increased bone density in the first week of the study but significantly affected bone healing after 21 days of administration. These experiments suggest that the administration of COX-1-selective NSAIDs at low doses and for short periods of time does not affect osseointegration.

Chikazu et al[15] compared osseointegration in mice that carried the COX-2 gene (COX-$2^{+/+}$) and COX-$2^{-/-}$ knockout mice. In the COX-$2^{+/+}$ group, new bone formation was statistically significant, and larger amounts of COX-2 mRNA and osteocalcin mRNA were found in bone tissue around the implant. However, new bone formation was minimal in the COX-$2^{-/-}$ group.

Considering the role of COX-2 in osseointegration, selective COX-2 inhibitors may exert more severe negative effects than selective COX-1 inhibitors, although the time of administration should be considered. Goodman et al[16] examined the effects of naproxen sodium (110 mg/kg) and rofecoxib (12 mg/kg) on bone healing in defects produced in the tibia in rabbits after 4 weeks of administration. Both drugs decreased bone formation, but only rofecoxib significantly reduced the area of osteoblasts per section. The authors concluded that any drug that is capable of inhibiting COX-2 will have a negative effect on osseointegration. O'Connor et al[17] compared the effects of rofecoxib (12.5 mg, once daily) and ibuprofen (50 mg, 3 times daily) administered for 28 days after surgical trauma of the tibia in rabbits. Rofecoxib significantly reduced the mechanical properties of the trauma site compared with ibuprofen.

Gerstenfeld et al[18] showed that ketorolac (4 mg/kg) and valdecoxib (5 mg/kg) administered for 7 and 21 days affected the rate of bone fracture union in the tibia. When administered for 21 days, the group that received valdecoxib exhibited a lower rate of fracture union, and PGE_2 levels were 2 to 3 times lower in the group treated with ketorolac. Furthermore, this same group exhibited reductions of bone formation and remodeling of calcified cartilage compared with the group treated with ketorolac. O'Keefe et al[19] also showed that celecoxib (25 mg/kg) administered for 2 weeks in rats significantly reduced the fractured tibia bone growth compared with ketorolac (4 mg/kg).

Conflicting results were found in the study by Fracon et al.[20] Administration of ketorolac (4 mg/kg), paracetamol (80 mg/kg), and etoricoxib (10 mg/kg) did not affect osteogenesis after tooth extraction. Such discrepancies between studies may be explained by differences between the species studied, the methodology used, and the pharmacokinetics of the drugs that can be affected by local or systemic compensatory factors.

Gerstenfeld et al[21] evaluated the mRNA levels of COX-1 and COX-2 for 35 days in surgical defects of bone tissue in the rat tibia. The authors found that the levels of COX-1 mRNA remained constant after 21 days, but the levels of COX-2 mRNA reached a maximum level after 14 days, confirming the importance of COX-2 in bone repair.

The time of administration should be considered an important factor in the use of selective COX-2 inhibitors. Goodman et al[22] evaluated the effect of rofecoxib (12.5 mg/day) administered for 6 weeks on bone growth in surgical trauma of the tibia in rabbits during 3 different time periods: the initial 2 weeks, the final 2 weeks, and continuously for 6 weeks. The results showed that a reduction of bone ingrowth occurred when the drug was administered continuously, but the effect on bone healing was not pronounced at 2 weeks of administration. Teofilo et al[23] reported that nimesulide (3 mg/kg) administered for 2 weeks did not significantly reduce the volume of new bone formation in the alveolar socket. Dimmen et al[24] showed that parecoxib (0.5 mg/kg) and indomethacin (0.625 mg/kg) administered for 7 days did not affect the properties of the tibia, but parecoxib had a higher potential for reducing bone mineral density. These results led to the

conclusion that short periods of selective COX-2 inhibitor administration did not adversely affect bone healing.

Gurgel et al[25] found that meloxicam (3 mg/kg) administered for 15 and 45 days reduced bone healing in the calvarias in rats. Ribeiro et al[26,27] also reported that treatment with meloxicam (3 mg/kg) for 60 days after application of a titanium implant in the rat tibia reduced the contact area between the implant/bone, area of bone formation, and bone density.

Akritapoulos et al[28] studied the dose-dependent effects of selective COX-2 inhibitors and found that high-dose parecoxib (1.06 mg/kg) treatment for 7 days had an inhibitory effect on bone repair in a fractured tibia in rats. Gerstenfeld et al[21] found that treatment with ketorolac at 4 mg/kg and parecoxib at 2 different doses (0.3 and 1.5 mg/kg) for 35 days altered the mechanical properties of the tibia in rabbits subjected to surgical trauma. The effects of the higher dose of parecoxib were more pronounced than the effects of ketorolac, in which it impaired the union of fractures at 21 days, whereas the lower dose was associated with no statistically significant differences.

Pablos et al[29] examined the effects of meloxicam (0.3 mg/kg) and diclofenac sodium (1.07 mg/kg) administered for 5 days post-surgery on the osseointegration of implants. Meloxicam did not negatively affect the contact area of the implant/bone area or cortical bone at the dose and time tested, but diclofenac sodium significantly affected these parameters. Jacobsson et al[30] found a reduction of the mechanical properties of the tibia in rabbits that received titanium implants after administration of diclofenac (30 mg, once daily) for 7 days. Both the time and dose influenced bone formation compared with the results of studies that used short- and long-term drug administration, although the use of diclofenac at different doses caused bone loss. Ribeiro et al[24,25] used a 10-fold higher dose of meloxicam than Pablos et al,[29] resulting in significant impairment of osseointegration. Tables 3 and 4 summarize these studies and show the relationships between the drugs, effects, and time of administration.

In vitro studies

The effects of NSAIDs on the dynamics of bone metabolism have been studied at the molecular pharmacology level in an attempt to determine how these drugs can alter the cellular response (Table 5). Ho et al[32] evaluated the effects of indomethacin and ketorolac (1–1000 mM) in cell cultures of the rat calvarias. Ketorolac reduced the number of cells by 14.3–50.7%. After 6 hours of treatment, ketorolac and indomethacin reduced the levels of PGE_2 by 12.1–97.5% and 24.1–93.1%, respectively. After 24 hours, ketorolac and indomethacin decreased these levels by approximately 92.2% and 94.6%, respectively. Additionally, ketorolac increased intracellular collagen type 1 levels about 1.1 to 4.4 fold, and 1.5 to 3.3 fold after 10 and 15 days, respectively. Indomethacin increased intracellular collagen type 1 levels about 0.5 to 4.8 fold, and 1.0 to 1.5 fold after 10 and 15 days, respectively.

Arpornmaeklong[33] found that cell cultures of the rat calvarias treated with indomethacin (0.1 μM) and celecoxib (1.5, 3.0, and 9.0 μM) had fewer cells than the control group. The effect was dose-dependent in the cultures that were treated with celecoxib. Prostaglandin E2 levels were also significantly lower in the groups that were treated with anti-inflammatory drugs.

Chang et al[34] subjected human and mouse mesenchymal cell cultures to different pharmacological challenges (ie, indomethacin, ketorolac, diclofenac, piroxicam [all 10^{-5} to 10^{-4} M] and celecoxib [10^{-6} to 10^{-5} M]), with various treatment times (ie, 24 hours, 1 week, 2 weeks, and 3 weeks). The percentage of the cell population in the G0/G1 phase of the cell cycle was significantly higher in the groups that were treated with these drugs, suggesting that they led to arrest of the cell cycle process. This study also sought to further explore the effect of drug treatment on the expression of cell cycle regulatory proteins (ie, p21, p27, and cyclins E1 and E2). Indomethacin increased the expression of p21 and p27 but did not significantly alter the expression of cyclins E1 and E2 in human mesenchymal cells after 24 hours of treatment. Celecoxib, however, increased the expression of p27, but did not affect the expression of other regulators. When considering the influence of these drugs on mineral deposition in mesenchymal cells in mice, only 2- to 3-week indomethacin treatment and 3-week ketorolac treatment significantly decreased this process. Nevertheless, no cytotoxic effects were seen with the use of these drugs after 24 hours of treatment.

Another study by Chang et al[35] evaluated the response of cultured human osteoblasts treated with indomethacin, ketorolac, diclofenac, piroxicam (all 10^{-5} to 10^{-4} M) and celecoxib (10^{-6} to 10^{-5} M). The drugs dose-dependently suppressed cell proliferation after 24 hours of treatment. Additionally, the increased proportion of cells in the G0/G1 phase of the cell cycle reflected a reduced number of cells in the S phase in the treated groups compared with controls. Toxicity tests showed no significant toxicity of celecoxib. Celecoxib, however, was able to induce apoptosis after 24 hours treatment and induced necrosis at higher concentrations (10^{-5} M). The expression of the pro-apoptotic regulators *Bak* and *Bad* also increased.

Evans and Butcher[36] found that cultured human osteoblasts treated with indomethacin and DFU (5,5-dimethyl-3-[3 fluorophenyl]-4-[4 methylsulphonyl]phenyl-2[5H]-furanone), a selective COX-2 inhibitor, at concentrations of 3.0×10^{-9} and 3.0×10^{-7} M, respectively, for 5 days reduced the number of osteoblast cells by 13% and 22%, respectively. Moreover, the results revealed a decrease in cell number with increasing drug concentration. Both drugs led to an increase in collagen synthesis (85% and 48%, respectively), but no statistically significant difference was found between groups, with no difference in alkaline phosphatase activity.

Wang[37] assessed the effects of celecoxib (10–100 mM) on human osteoblasts. A dose-dependent decrease in cell proliferation was found. The data suggested that celecoxib increased the intracellular concentration of Ca^{2+} at a dose of 10 mM. The influence on calcium channels and increase in the intracellular concentration of this ion led to increased cytotoxicity of the drug.

Yoon et al[38] assessed the effects of celecoxib (10, 20, and 40 μM) and naproxen (100, 200, and 300 μM) administered for 14 days on mesenchymal cell cultures derived from bone marrow. The addition of IL-1, simulating inflammatory conditions, dose-dependently inhibited osteogenic differentiation. However, the expression of COX-1 and COX-2 was not consistently altered by

TABLE 3

Studies on bone healing and osseointegration around titanium implants in animal models

Authors	Animal	Drug Administration	Analyzed Criteria	Results
Keller et al[11]	Rabbits	Indomethacin, 12.5 mg/kg for 6 weeks	Histological analysis	No effects on activated remodeling process in cortical bone neighboring a small drill hole (2 mm) but not at 3 and 8 mm
Senerby et al[12]	Rabbits	Indomethacin, 1 and 4 mg/kg for 3 weeks	Bone ingrowth	No statistical significance
Endo et al[13]	Rats	Etodolac, 20 mg/d for 3 weeks	Radiograph analysis	Fracture healing was significantly poorer than placebo group
Martins et al[14]	Rats	Ketoprofen, 12.5 mg/d for 30 days	Optical density	Increase in optical density during first week and delayed new bone formation after 21st day in ketoprofen group
Chikazu et al[15]	COX-$2^{-/-}$ and COX-$2^{+/+}$ mice	No drug was administered	Bone formation, COX-2 and osteocalcin mRNA	Expression of COX-2 and osteocalcin mRNA was induced in bone surrounding implants in COX-$2^{+/+}$ mice but not COX-$2^{-/-}$ mice New bone formation was minimal in COX-$2^{-/-}$ mice
Goodman et al[16]	Rabbits	Naproxen sodium, 110 mg/kg for 4 weeks	Bone ingrowth	Naproxen sodium: 15.9% Rofecoxib: 18.5%
		Rofecoxib, 12.5 mg/kg for 4 weeks	Area of osteoblasts per section	Only rofecoxib decreased area of osteoblasts per section
O'Connor et al[17]	Rabbits	Ibuprofen, 50 mg, 3 times daily for 28 days after surgery	Histological analysis	No significant differences between placebo, ibuprofen, and rofecoxib treatment groups after 3 weeks
		Rofecoxib, 12.5 mg once daily for 28 days after surgery	Mechanical tests	Rofecoxib reduced mechanical properties after 6 weeks
Gerstenfeld et al[18]	Rats	Kerotolac, 4 mg/kg for 7, 21, and 35 days	Rate of nonunion bone	Both drugs reduced the rate of nonunion bone at 7 days Valdecoxib reduced PGE_2 levels at high rate at 21 days No significant difference at 35 days
			PGE_2 levels	Valdecoxib led to two- to three-fold lower levels of PGE_2 compared with ketorolac
		Valdecoxib, 5 mg/kg for 7, 21, and 35 days	Histological analyses	Valdecoxib reduced bone formation and delayed remodeling of calcified cartilage
O'Keefe et al[19]	Rats	Celecoxib, 25 mg/kg for 2 or 5 weeks	Bone ingrowth	Celecoxib reduced bone ingrowth by 45% at 2 weeks and 60% at 5 weeks
		Ketorolac, 4 mg/kg for 2 or 5 weeks		Ketorolac did not affect bone ingrowth at 2 weeks and reduced it by 60% at 5 weeks

TABLE 3

Continued

Authors	Animal	Drug Administration	Analyzed Criteria	Results
Fracon et al[20]	Rats	Paracetamol, 80 mg/kg/day for 2 weeks Ketorolac, 4 mg/kg/d for 2 weeks Eterocoxib, 10 mg/kg/d for 2 weeks	Percentage of trabecular bone in alveolar socket	Treatment with all drugs did not negatively interfere with alveolar bone healing
Gerstenfeld et al[21]	Rats	Ketorolac, 4 mg/kg for 1, 3, 5, 7, 10, 14, 21, 35, and 42 days	Expression of COX-1/COX-2 mRNA during bone healing	Levels of COX-1 mRNA remained constant over a 21-day period COX-2 mRNA levels showed peak expression during the first 14 days of healing
		Parecoxib, 0.3 and 1.5 mg/kg for 1, 3, 5, 7, 10, 14, 21, 35, and 42 days	Mechanical properties	Ketorolac reduced mechanical properties compared with controls at 21 and 35 days Parecoxib at a high dose led to failure to unite fractures by 21 days Parecoxib at a low dose let to inhibition that was not statistically significant
Goodman et al[22]	Rabbits	Rofecoxib, 12.5 mg/kg/day for 2 or 6 weeks	Bone ingrowth	Reduction at 6 weeks No effect at 2 weeks
Teofilo et al[23]	Rats	Nimesulide, 5 mg/kg for 2 weeks	Volume of neoformed bone inside alveolar socket	Volume fraction of new bone in treated rats was not significantly different from control rats
Dimmen et al[24]	Rats	Parecoxib, 0.5 mg/kg for 7 days	Bone density	Parecoxib reduced mechanical strength after 3 weeks and bone density after 2 weeks
		Indomethacin, 0.625 mg/kg for 7 days	Mechanical properties (moment, total energy, stiffness, deflection) of tibia 2 and 3 weeks after surgery	Indomethacin reduced mechanical strength and bone density after 3 weeks
Gurgel et al[25]	Rats	Meloxicam, 3 mg/kg for 15 and 45 days	Bone filling	Meloxicam groups presented significant reduction of bone healing compared with respective controls
Ribeiro et al[26]	Rats	Meloxicam, 3 mg/kg for 60 days	BIC,* BA,† BD‡ ($P < 0.05$)	Zone A¶ Meloxicam: 35.93%,* 61.58%,† 91.06%‡ Saline: 47.01%,* 86.42%,† 96.86%‡
		Saline for 60 days		Zone B‖ Meloxicam: 16.86%,* 25.66%,† 7.73%‡ Saline: 30.76%,* 34.83%,† 15.76%‡
Ribeiro et al[27]	Rats	Meloxicam, 3 mg/kg for 60 days Saline for 60 days	BIC, BA, BD ($P < 0.05$)	Meloxicam: 25.23%,* 42.94%,† 49.30%‡ Saline: 39.48%,* 60.62%,† 56.31%‡
Akritopoulos et al[28]	Rats	Parecoxib, 1.06 mg/kg for 7 days	Radiographic analysis 28 and 42 days after fracture	Parecoxib given at a high dose for a short duration appeared to have a transient inhibitory effect on bone healing, but the long-term effects did not appear to be significant

Table 3

Continued

Authors	Animal	Drug Administration	Analyzed Criteria	Results
Pablos et al[29]	Rats	Diclofenac sodium, 1.07 mg/kg for 5 days	BIC, CBA,¶ TBA,# ($P < 0.001$)	Diclofenac sodium: 49.6%,* 63.7%,§ 36.3%‖
		Meloxicam, 0.2 mg/kg for 5 days		Meloxicam: 67.1%,* 82.7%,§ 17.3%‖
Jacobsson et al[30]	Rabbits	Diclofenac, 30 mg/d for 7 days	Pullout test in fractured tibia	Reduction compared with control group

* Bone-to-implant contact
† Bone area
‡ Bone density
§ Cortical bone regions
‖ Cancellous bone regions
¶ Cortical bone area
# Trabecular bone area

the drugs, whereas PGE_2 synthesis was significantly inhibited by both drugs at the doses tested. Moreover, dose-dependent reductions of the expression of transcription factors related to osteogenesis (*Runx2/Cbfα*, *Dlx5*) and osteogenic differentiation markers (osteocalcin) were found under inflammatory conditions.

Kolar et al[39] reported that celecoxib (2, 10, 50 μM) administered to cultured human osteoblasts altered cell viability by stimulating O_2 consumption and increasing the expression of glucose-transporter 1 after 24 hours of treatment. Another effect of the drug was the reduced secretion of osteoprotegerin by osteoblasts.

Zhang et al[40] examined the area of mineralization nodules in cultures of bone marrow cells in COX-1 and COX-2 knockout mice compared with treatment with bone morphogenetic protein 2 (BMP-2) and PGE_2. After 21 days, a 50% reduction of the areas of mineralization nodules was observed in COX-$2^{-/-}$ cell cultures compared with controls, but this effect was reversed by the addition of PGE_2. The addition of BMP-2 to the cultures induced the formation of mineralization nodules in both wildtype and COX-$2^{-/-}$ cultures. This study also showed that the combination of BMP-2 and PGE_2 led to a further increase in mineralization.

Limitations and bias

Limitation to find clinical studies concerned to impact of NSAIDs on osseointegration must be detached. There are few

Table 4

Animal studies: relationship between NSAIDs and presented effect and time of administration

	COX-1 Selectivity	COX-2 Selectivity	Short-term Administration (< 2 weeks)	Long-term Administration (> 2 weeks)
Impaired osseointegration				
Etodolac	High			Endo et al[13]
Ketoprofen				Martins et al[14]
Ketorolac	High			Gerstenfeld et al[21]
Naproxen sodium	Low			Goodman et al[16]
Rofecoxib		High	O'Connor et al[17]	Goodman et al[16,22]
Valdecoxib		High	Gerstenfeld et al[18]	Gerstenfeld et al[18]
Celecoxib		Low	O'Keefe et al[19]	O'Keefe et al[19]
Parecoxib		High	Akritopoulos et al[28] Dimmen et al[24]	Gerstenfeld et al[21]
Meloxicam		Low	Pablos et al[29]	Gurgel et al[25] Ribeiro et al[26,27]
Diclofenac		Low	Jacobsson et al[30]	
Diclofenac sodium		Low	Pablos et al[29]	
No effects				
Indomethacin	Low			Senerby et al[12] Kelleret al[11]
Ibuprofen				O'Connor et al[17]
Paracetamol		Low	Fracon et al[20]	
Ketorolac	High		Fracon et al[20]	
Eterocoxib		High	Fracon et al[20]	
Nimesulide		Low	Teofilo et al[23]	
Rofecoxib		High	Goodman et al[22]	

TABLE 5

In vitro studies on osseointegration

Authors	Cells	Drug Administration	Analyzed Criteria	Outcome
Ho et al[32]	Calvarial cell culture	Ketorolac, 1–1000 mM	1. Cell proliferation	1. Ketorolac decreased cell number by 14.3–50.7% ($P < 0.01$)
		Indomethacin 1–1000 mM	2. PGE_2 level	2. For 6 hours, PGE_2 levels were decreased by 12.1–97.5% and 24.1–93.1% compared with control cultures with ketorolac and indomethacin treatment, respectively. PGE_2 levels in cultures treated for 24 hours were decreased by 92.2–94.6% with ketorolac and indomethacin treatment, respectively.
			3. Type I collagen synthesis	3. Ketorolac increased the intracellular levels of Type I collagen 1.1- to 4.4-fold and 1.5- to 3.3-fold after 10 and 15 days, respectively. Indomethacin increased collagen synthesis by 0.5- to 4.8-fold and 1.0- to 1.5-fold at 10 and 15 days after cell plating, respectively.
Arpornmaeklong et al[33]	Mouse calvarial cell line (MC3T3-E1)	Group A: 0.1 μM indomethacin for 1, 3, and 5 days	1. Cell growth	1. Numbers of cells in Group A were significantly lower than in controls and tended to be lower than in Groups B, C, and D at day 3 ($P > 0.05$).
		Group B: 1.5 μM celecoxib for 1, 3, and 5 days Group C: 3.0 μM celecoxib for 1, 3, and 5 days Group D: 9.0 μM celecoxib for 1, 3, and 5 days Group E: Control	2. Secretion of PGE_2	2. Levels of PGE_2 in Groups A–D were significantly lower than in Group E ($P < 0.05$).
Chang et al[34]	Human bone marrow mesenchymal stem cells (hBMSCs)	Indomethacin, ketorolac, diclofenac, and piroxicam (10^{-5} to 10^{-4} M) for 24 hours, 1 week, 2 weeks, and 3 weeks	1. Cell cycle kinetics	1. Percentage of cell population in G0/G1 phase was significantly higher with treatment with all drugs in D1-cells after 24 hours ($P < 0.01$)
	Mouse cells (D1-cell)	Celecoxib (10^{-6} to 10^{-5} M) for 24 hours, 1 week, 2 weeks, and 3 weeks	2. Cytotoxicity	2. No significant cytotoxic effect was caused by 24 hours of treatment with NSAIDs ($P < 0.01$) in D1-cells
			3. Protein and mRNA expression of cell cycle regulators	3. Indomethacin increased the expression of p27 and p21; no significant effect on the expression of cyclins E1 and E2 was found in hBMSCs after 24 hours; celecoxib only increased the expression of p27 and did not alter the expression of the other genes in HBMSCs after 24 hours.

TABLE 5

Continued

Authors	Cells	Drug Administration	Analyzed Criteria	Outcome
			4. Mineralization	4. Only 2- and 3-week treatment with indomethacin and 3-week treatment with ketorolac significantly decreased mineral deposition in D1-cell cultures ($P < 0.05$).
Chang et al.[35]	Human osteoblast cultures (hOCs)	Indomethacin, ketorolac, diclofenac, and piroxicam (10^{-5} to 10^{-4} M)	1. Proliferation	1. Nonelective and selective NSAIDs dose-dependently suppressed cell proliferation at 24 hours ($P < 0.05$)
		Celecoxib (10^{-6} to 10^{-5} M)	2. Cell cycle	2. Increase in proportion of cells in G0/G1 phase was accompanied by decrease in the proportion of cells in S phase in drug-treated cultures compared with control cultures ($P < 0.01$)
			3. Cytotoxicity	3. Celecoxib had significant cytotoxic effects (10^{-6} M, $P < 0.05$; 10^{-5} M, $P < 0.01$).
			4. Cell death	4. Apoptosis was caused by 24 hours treatment with celecoxib ($P < 0.01$), and necrosis was only caused at higher celecoxib concentration (10^{-5} M, $P < 0.05$).
			5. Protein levels and mRNA expression of pro-apoptosis regulators	5. Celecoxib (10^{-6} and 10^{-5} M, $P < 0.01$) significantly increased mRNA expression of Bak; higher concentration of celecoxib (10^{-5} M) also increased Bad mRNA expression ($P < 0.01$).
Evans and Butcher[36]	Human osteoblast cultures (hOCs)	Indomethacin, 3×10^{-9} for 5 days	1. Cell number	1. Number of cells decreased with time (13% and 22% of controls) with indomethacin and DFU treatment, respectively ($P < 0.001$); dose-dependent decrease in cell numbers with increasing concentrations of NSAIDs
		5,5-dimethyl-3-(3-fluorophenyl)-4-(4 methylsulphonyl)phenyl-2(5H)-furanone (DFU), 3×10^{-7} M for 5 days	2. Collagen synthesis	2. DFU increased collagen synthesis by 85%, and indomethacin increased collagen synthesis by 48% compared with control cultures; no significant difference was found in the effect of the 2 NSAIDs on collagen synthesis ($P > 0.05$).
			3. Alkaline phosphatase production	3. Increases in alkaline phosphatase activity did not reach statistical significance

TABLE 5

Continued

Authors	Cells	Drug Administration	Analyzed Criteria	Outcome
Wang et al[37]	MG63 human osteoblasts	Celecoxib, 10–100 mM	1. Cell proliferation	1. In the presence of 40, 70, and 100 mM celecoxib, cell numbers significantly decreased by 18 ± 2%, 25 ± 10%, and 42 ± 2%, respectively ($P < 0.05$).
			2. Ca^{2+} channels activity	2. Celecoxib evoked concentration-dependent increase in $[Ca^{2+}]_i$ (EC_{50} = 10 mM).
Yoon et al[38]	Bone marrow-derived mesenchymal stem cells (MSCs)	Celecoxib, 10, 20, and 40 μM for 14 days	1. Osteogenic differentiation	1. Under inflammatory conditions, MSCs treated with interleukin-1β, alcaline phosphatase staining was dose-dependently reduced by high doses of NSAIDs; high doses of NSAIDs may inhibit osteogenic differentiation under inflammatory conditions in MSCs.
		Naproxen, 100, 200, and 300 μM for 14 days	2. Genetic expression of COX-1 and COX-2	2. Expression of COX-1 and COX-2 was not consistently changed by celecoxib or naproxen ($P > 0.05$).
			3. Synthesis of PGE_2	3. Synthesis of PGE_2 in MSCs was significantly inhibited by NSAIDs at all tested doses ($P < 0.05$).
			4. Expression of osteogenic transcription factors and markers during osteogenic differentiation	4. Expression of *Runx2/Cbfα1*, *Dlx5,* and osteocalcin was dose-dependently decreased by celecoxib and naproxen under inflammatory conditions.
Kolar et al[39]	Human osteoblast cultures (hOCs)	Celecoxib, 2, 10, and 50 μM	1. Cell viability	1. Cell viability was significantly reduced by celecoxib treatment at 50 μM ($P < 0.05$).
			2. Energy metabolism	2. Celecoxib at 50 μM stimulated oxygen consumption; after 24 hours, GLUT-1 mRNA expression was significantly increased ($P < 0.05$).
			3. Bone remodeling processes	3. Celecoxib at 50 μM significantly inhibited osteoprotegerin protein secretion ($P < 0.05$).
Zhang et al[40]	Bone marrow cells derived from COX-$1^{-/-}$ and COX-$2^{-/-}$ mice	This study used growth factors BMP-2, 200 ng/mL, added on day 5 and continued until day 21 PGE_2, 10^{-7} M	Area of mineralized bone nodules	1. After 21 days, 50% decrease in the number and area of mineralized bone nodules in COX-$2^{-/-}$ cultures. 2. The addition of PGE_2 to COX-$2^{-/-}$ cell cultures restored nodule formation to wildtype levels. 3. BMP-2 induced bone nodule formation in both wildtype and COX-$2^{-/-}$ cell cultures. 4. BMP-2 + PGE_2 led to additional increase in nodule formation compared with cultures that contained BMP-2 alone.

clinical studies about effects of these drugs on bone healing. Then, this review deviated from standard systematic reviews because inferences were largely based in animal studies model, and it is not enough to affirm how wide are the effects of drugs in human body.

Moreover, publication bias should be discussed. A large number of studies have shown negative effects of NSAIDs on osseointegration, although many of these used extensive administration time to NSAIDs, therefore, negative effects on osseointegration should be expected in these studies. Therefore, selection bias could not be avoided by researchers because a large number of studies have the same methodology about administration time.

Suggestions to the future and current problems

There are a large range of questions to be answered by researchers. How COX-2-dependent can the osseointegration process be? Is there any difference in dental osseointegration to another body site? How does pharmacokinetics interfere in osseointegration? Could osseointegration in smokers or diabetics be more affected by NSAIDs than in healthy? Future studies could research these questions more in depth to help us better understand the osseointegration process. A current limitation regarding osseointegration studies pertains to the limited number of clinical trials, which prevents us from being able to predict whether some NSAIDs diminish osseointegration in the same extent that has been observed in animal models.

Conclusions

Some conclusions may be drawn from the international literature reviewed in the present study. Clinical trials indicated that COX-1 inhibitors do not impair osseointegration with both short- and long-term administration. However, whether COX-2 inhibitors are safe to use during the postoperative period has not been determined.

Animal studies showed that any drug that is capable of inhibiting the COX-2 isoform may impair the osseointegration process, indicating that COX-2 plays a more important role than COX-1 in osseointegration. Furthermore, COX-2 inhibitors exert negative effects if administered for long periods of time. These findings allow us to infer that the chronic administration of NSAIDs can impair osseointegration, possibly leading to unsuccessful results.

In vitro molecular pharmacological studies showed that COX-2 inhibitors are the most potent depressors of osseointegration at the cellular level. These drugs reduced cell viability and proliferation, arrested the cell cycle, diminished prostaglandin synthesis, altered the synthesis of cell cycle regulators, and elevated cytotoxicity in a pathway that depends on calcium channels. Moreover, they elevated the protein levels and mRNA expression of pro-apoptosis regulators, elevated the expression of osteogenic transcription factors and markers during osteogenic differentiation, elevated energy metabolism, and diminished bone remodeling processes. Consistent with the animal studies, these findings suggest that administration of selective COX-2 inhibitors may lead to failure in the osseointegration process.

More caution should be taken with regard to administering selective COX-2 NSAIDs during the postoperative period. Clinically, the successful use of dental implants depends on the correct use of pharmacotherapy for pain and inflammation control. The prolonged use of COX-1 inhibitors should be avoided because of the risks to osseointegration. Moreover, patients who use NSAIDs chronically may experience reduced success after implant surgery because of the possibility that the osseointegration process may be impaired.

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