

## Prostaglandins and bone: potential risks and benefits related to the use of nonsteroidal anti-inflammatory drugs in clinical dentistry

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**Abstract:** In the skeleton, prostaglandins, mainly PGE<sub>2</sub> produced by osteoblasts under COX-2 stimulation, play either a stimulatory or an inhibitory role in bone metabolism, depending on the physiological or pathological conditions. The anabolic effect occurs largely in response to mechanical forces and in bone fracture healing, whereas PGE<sub>2</sub>-mediated resorption contributes significantly to bone loss in inflammatory diseases and in response to prolonged immobilization. Many reports have shown that conventional nonsteroidal anti-inflammatory drugs (NSAIDs) may delay fracture healing and negatively interfere with spinal fusion in both humans and other animals, whereas the alleged inhibitory effects of COX-2-selective NSAIDs still lacks experimental and clinical evidence. Pertaining to clinical dentistry, recent studies have suggested a potential adjuvant role for NSAIDs in periodontal therapy. There are few experimental reports addressing the deleterious effects of conventional NSAIDs on alveolar bone healing; clinical reports, relating mostly to short-term administration of NSAIDs for management of post-extraction edema and pain, are just as rare and have noted no clinically perceptible delay in bone healing. Additional studies are necessary in order to elucidate whether patients who require reparational bone formation can safely receive

prolonged treatment with NSAIDs, and which drug types are less harmful. (J. Oral Sci. 50, 247-252, 2008)

Keywords: bone; prostaglandins; COX-1; COX-2; nonsteroidal anti-inflammatory drugs; NSAIDs.

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### Introduction

The cyclooxygenase enzymes COX-1 and COX-2 catalyze the conversion of arachidonic acid to prostaglandins (PGs). COX-1 is a constitutive enzyme normally expressed in a variety of tissues and organs, leading to formation of PGs with physiological functions, such as protection of gastrointestinal mucosa, control of renal blood flow and homeostasis. COX-2 is an inductive enzyme induced mainly by pro-inflammatory mediators and leads to formation of PGs involved in pathophysiological processes such as edema formation, hyperalgesia, fever and carcinogenesis (1-3).

The participation of PGs in a great variety of human pathologies was the motive for development of nonsteroidal anti-inflammatory drugs (NSAIDs), frequently used in the control of edema, fever and pain, in acute post-surgical or post-traumatic pain, and for relief of chronic pain associated with muscle-skeletal disorders, rheumatoid arthritis and osteoarthritis (2,4). Furthermore, NSAIDs are among the most commonly used drugs for management of acute and chronic pain in clinical dentistry (5).

The beginning of the 1970s was distinguished by the discovery of the action mechanism of NSAIDs, which inhibit COX activity, and consequently PG synthesis. Since then, a diverse array of drugs has become available,

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currently identified as conventional or non-selective NSAIDs, which in addition to providing effective therapeutic activity, exert adverse side effects, largely in the gastrointestinal system and kidney, when under prolonged use. Only in the early 1990s was the existence of two isoforms of COX confirmed, and it has since been hypothesized that while the isoenzyme COX-1 is responsible for the synthesis of constitutive PGs, COX-2 catalyzes the synthesis of inductive PGs. Thus, the therapeutic action of NSAIDs results from COX-2 inhibition, while their undesirable side effects are provoked by COX-1 inhibition (1).

In order to improve the benefit/risk ratio of NSAIDs, the pharmaceutical industry was urged to invest massively in the development of drugs that selectively inhibit COX-2. Thus, a new class of selective COX-2 inhibitors, collectively denominated COXIBs, was developed for the treatment of pain and inflammation. These medicaments – celecoxib (Celebrex<sup>®</sup>, Pfizer, New York, USA), rofecoxib (Vioxx<sup>®</sup>, Merck, New Jersey, USA) and valdecoxib (Bextra<sup>®</sup>, Pfizer) – have anti-inflammatory effects that are at least comparable to conventional NSAIDs, but with less gastrointestinal toxicity. They were made available for use in 1999 (6), with the promise of solving the morbidity associated with prolonged NSAID use.

Subsequently, growing experimental and clinical evidence has suggested that it is not possible to clearly separate the functions of PGs produced by COX-1 and COX-2, as COX-1 also appears to play a significant role in the inflammatory process, while COX-2 is constitutively expressed in a variety of organs, exerting a number of physiological functions in the gastrointestinal mucosa, endothelial cells and kidneys. Thus, although COX-2 inhibitors proved to be clinically effective against certain chronic inflammatory diseases and in reducing the incidence of gastrointestinal lesions, prolonged use has unexpectedly caused a significant increase in the incidence of thrombosis and myocardial infarcts (1,6).

In reaction to these cardiovascular events, rofecoxib (Vioxx<sup>®</sup>, Merck) was taken off the market in September 2004, valdecoxib (Bextra<sup>®</sup>, Pfizer) was withdrawn in April 2005, and a black-box warning was designated for celecoxib (Celebrex<sup>®</sup>, Pfizer). A second generation of coxibs have subsequently emerged for use in the USA, UK and 45 other countries: lumiracoxib (Prexige<sup>®</sup>, Novartis), etoricoxib (Arcoxia<sup>®</sup>, Merck), and parecoxib (Dynastat<sup>®</sup>, Pfizer) (6). Although the selective NSAIDs available at present have the same active principle and action mechanisms, and despite the persistent controversy between the scientific community and health professionals, these drugs continue to be prescribed, and are considered by some to be the best

option for treatment of certain chronic conditions.

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COX-1 is expressed in normal bone, while COX-2 expression is up-regulated during bone repair and under pathological conditions such as inflammation and neoplasia. Thus, the skeleton is abundantly supplied with PGs, mainly PGE<sub>2</sub>, which plays either a stimulatory or an inhibitory role in bone metabolism, depending on the physiological or pathological circumstances. The anabolic effect occurs mainly in response to mechanical forces and in the healing of long bone fractures, whereas PGE<sub>2</sub>-mediated resorption contributes significantly to bone loss related to inflammatory diseases and in response to prolonged immobilization (2,3,7-9).

The anabolic effect of PGs on bone has been demonstrated by systemic administration of PGE<sub>2</sub>, which stimulates bone formation and increases bone mass in infants and animals (3). Under physiological conditions, particularly in response to mechanical forces, PGs produced by activation of COX-2 can stimulate bone formation by increasing multiplication and differentiation of osteoblasts, an effect related to the production of growth factors. In this context, the bone response to mechanical loading may be decreased by NSAIDs, including selective COX-2 inhibitors (3,7,10,11). In addition, PGs in association with hormones, cytokines and growth factors play an important role in the complex and dynamic process of bone healing; thus, NSAIDs, mainly the conventional non-selective drugs, have been shown to impair the healing of animal and human long bone fractures (2,3,12-14).

In contrast, under specific pathological conditions, PGs (mainly PGE<sub>2</sub>) can stimulate bone resorption by increasing the amount and functional activity of osteoclasts. It has been shown that hormones and cytokines involved in bone resorption can stimulate COX-2 expression and PG synthesis. Experimental animals carrying genes that have been made inoperative for COX-2 and PG receptors (knockout mice) have impaired osteoclastogenesis and decreased bone resorption. Elevated secretion of inflammatory cytokines and PGE<sub>2</sub> is related to the bone loss taking place in some inflammatory diseases, including arthritis and periodontitis (3,7,9,10,15,16) and the role of PGs in the pathogenesis of osteoporosis is supported by studies in human and animal models (17).

PGs exert this range of actions through a variety of receptors expressed in the target cells. The PGE<sub>2</sub> receptors (EP1, EP2, EP3 and EP4 subtypes) belong to the G-protein-coupled receptor family. A vast and still inconclusive range of studies, developed in knockout mice or carried out by administration of specific agonists and

antagonists, have confirmed the subtypes EP2 (18) and EP4 (19) as important mediators of PGE<sub>2</sub> anabolic action in bone. Conversely, there have also been reports that PGE<sub>2</sub>-induced bone resorption is mediated chiefly by EP4 and partially by EP2 (20). A recent review on the role of PGE<sub>2</sub> and EP receptors in the pathogenesis of bone destruction observed in rheumatoid arthritis showed that PGE<sub>2</sub> binding to EP4 can stimulate osteoclastogenesis or activate osteoblastogenesis by increasing the specific transcriptional factors required for bone resorption or formation, respectively (21).

### **Potential risks and benefits for bone due to prolonged use of NSAIDs**

Although PGs modulate osteoblastic and osteoclastic function under physiological conditions, it appears that NSAIDs, even under prolonged use, cause only marginally adverse effects on normal bone. The beneficial effects of NSAIDs pertain to prevention of heterotopic ossification, an ectopic bone deposition that can adversely affect patients subjected to total hip arthroplasty. Furthermore, clinical observations have led to indications for NSAIDs to prevent bone loss and treat osteoporosis in elderly women (2,3,7,13,14). Conversely, clinical studies have largely confirmed that conventional NSAIDs can interfere negatively with long bone fracture healing and spinal fusion rate (22-26).

Considerable experimental evidence has indicated that conventional non-selective NSAIDs (indomethacin, ibuprofen, naproxen, ketorolac) have inhibitory effects on long bone fracture healing (2,3,13) although an absence of this deleterious effect has also been reported (27-30). It has been suggested that factors such as dosage and duration of treatment could affect the results, as well as intra- and inter-species differences regarding sensitivity to drugs, compensatory local and systemic factors, rate of bone remodeling and pharmacokinetics of drugs in laboratory animals compared to humans (3,29). However, most experimental studies have utilized rodent models, and despite the methodological differences in evaluating newly formed bone (mechanical test, clinical, radiographic, histological or histometric assessments) and variations in dosages, administration route and treatment duration, it appears that the controversies could not be explained only by the diversity of these experimental parameters. For instance, two independent groups of investigators evaluated the effects of ibuprofen (30 mg/kg/day, given orally for up to 12 weeks) on rat femoral fracture healing by mechanical testing and histological examination, and while Altman et al. (31) reported an inhibitory effect on fracture repair even after cessation of treatment, Huo et al. (30)

reported no significant difference between treated and control animals.

Data pertaining to selective NSAIDs (celecoxib, rofecoxib, parecoxib) and experimental bone growth are much more recent and less numerous, and despite the importance of COX-2 and PGE<sub>2</sub> for bone formation, the results remain controversial, as are reports referring to the long-term use of selective NSAIDs and impaired reparational bone formation in humans (3,13,14,26,29,32-37). As mentioned for conventional NSAIDs, these apparent controversies cannot be explained by the diversity of experimental parameters alone. For example, while mechanical, radiographic and histological examination revealed the interruption of femoral fracture healing in rats treated with celecoxib (4 mg/kg/day given orally for 2 to 8 weeks) (34), treatment of rats with the same drug (3 mg/kg/day for 4 to 12 weeks, orally) apparently did not interfere with femoral fracture healing, as confirmed by mechanical and radiographic examinations (35). Criticism of experimental models showing deleterious effects by the use of selective NSAIDs on reparative bone formation include the need of further information related to pharmacological dosages for comparison with human-intended therapies, as well as the use of high doses for very long periods, considering their clinical use for intraoperative acute pain control (4,27). Nevertheless, the long-term use of these drugs for controlling the chronic pain associated with musculoskeletal disorders, osteoarthritis and rheumatoid arthritis remains necessary in clinical medical practice (4,27).

### **Potential risks and benefits of prolonged use of NSAIDs in clinical dentistry**

In recent decades, arachidonic acid metabolites have been recognized as important pro-inflammatory mediators of bone resorption in periodontal disease (16,38). Nyman et al. (39) presented the first evidence that a non-selective NSAID (indomethacin) could, in addition to ameliorating acute inflammatory reactions, decrease alveolar bone resorption in an experimental model of periodontitis in dogs. Since then, numerous experimental and clinical studies have confirmed the local production of arachidonic acid metabolites, particularly PGE<sub>2</sub>, its role in bone destruction and a significant correlation with the clinical expression of periodontal disease, thus suggesting NSAIDs as a therapeutic possibility for preventing alveolar bone resorption in progressive periodontitis (40,41). Nevertheless, some investigators recommend against the use of NSAIDs in the adjuvant treatment of periodontal disease until more consistent data became available (42). Given that PGE<sub>2</sub> has also been implicated in the periimplantitis process, the

possibility of controlling failing implants with NSAIDs has been suggested (38).

A recent systematic review was carried out in order to validate the beneficial effects of antiproteinase, anti-inflammatory and bone sparing host-modulating agents in the adjunctive treatment of gingivitis and periodontitis. Collected data have suggested that NSAIDs have a potential adjunctive role in periodontal therapy (43). The literature was also recently reviewed in order to compare the effects of selective and non-selective NSAIDs on periodontal treatment (15). The authors reported experimental and clinical evidence confirming the beneficial effects of both drug types by reducing the rate of alveolar bone resorption, but suggested that the serious side effects of selective COX-2 inhibitors might preclude their use as adjuncts to periodontal therapy.

Very few studies have been conducted to assess the possible deleterious effects of NSAIDs on alveolar bone healing. In the 1970s, the effects of acetylsalicylic acid (44) and indomethacin (45) were evaluated. A histological study was also conducted to investigate the effects on bone repair of long-term treatment with aspirin cones placed in the extraction sockets of dogs (46). The authors reported delayed bone formation in the sockets filled with aspirin cones in 2-week samples, but not after long-term treatment (4, 6 and 8 weeks). They admitted, however, limitations in the experimental model that allowed the drug to stay in the sockets only for a short time (2-3 days). In rats, short-term treatment (4 days) with diclofenac delayed alveolar socket healing by impairing blood clot remission and new bone formation (47).

Clinical investigations are equally scarce and pertain to short-term administration of NSAIDs to control edema and pain after removal of impacted third molars. Based on clinical postoperative assessment, some surgeons have reported no significant difference in the rate of bone healing following administration of ibuprofen (48), aspirin, diclofenac (49) and flurbiprofen (50). Regarding these clinical observations, Godden (51) contested a previous recommendation by Stone and Richards (52) that more clinical trials would be required to confirm or refute the alleged harmful effects of NSAIDs on bone healing. Godden affirmed that, in the face of the numerous studies concerning the effects of NSAIDs on pain relief after removal of third molars, if any adverse effects had occurred in alveolar bone healing, the clinicians would have been obliged to report it, which did not occur. The author advised against more clinical trials in this field as they would be unnecessary and ethically questionable.

In conclusion, recent literature data have suggested NSAIDs as a therapeutic possibility to prevent alveolar bone

resorption in progressive periodontitis and to control failing implants in periimplantitis. The adverse effects of NSAIDs, particularly the conventional non-selective drugs, have been confirmed by numerous experimental and clinical trials in the orthopedic domain, with reports of impaired spinal fusion and delayed fracture healing. In contrast, few investigations have been carried out to assess the possible deleterious effects of NSAIDs on alveolar bone healing. However, as the lack of evidence of an effect does not constitute evidence of the absence of an effect (53), it seems reasonable to infer that more experimental and clinical tests should be performed before discarding precautions or contraindicating the use of NSAIDs in clinical dentistry, under specific circumstances. Additional information remains necessary to resolve important questions, such as whether patients from a dental clinic who require reparational bone formation can be safely subjected to prolonged use of NSAIDs and what types of NSAID are less harmful in such situations.

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