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Critical review

The importance of cyclooxigenase in dentistry: a narrative review

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Aim: Cyclooxygenase enzymes (COX) catalyze the conversion of arachidonic acid to prostaglandins and thromboxanes during pain and inflammation conditions. These enzymes have also been linked to several other conditions and diseases, and hence, in dentistry, it is crucial to identify the processes that increase the levels of these mediators. This paper aims to describe the significance of COX in dental practice through a narrative review. **Methods:** Articles relating to COX upregulation published in English and Spanish over the last 51 years in databases such as EBSCO, Google Scholar, Science Direct, PubMed, and Web of Science; were analyzed. **Results:** A total of 115 articles demonstrating the relationship between COX upregulation and multiple conditions and diseases of importance in prosthodontics, periodontics, oral pathology, orthodontics, and endodontics were included. **Conclusions:** COX upregulation is related to inflammatory and malignant diseases in oral tissues, such as periodontitis, pulpitis, and oral cancer, nevertheless, its expression is advantageous in other fields of study such as orthodontics. Additionally, is well documented that dental materials provoke an undesired increase in COX expression, which could be a significant factor that directly affects pulpal health.

Keywords: Prostaglandin-endoperoxide synthases. Dinoprostone. Periodontitis. Mouth neoplasms.

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Introduction

Cyclooxygenases are enzymes that regulate the production of prostanoids such as prostaglandins (PG) and thromboxanes which are potent lipid messengers synthesized from arachidonic acid. Cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), and cyclooxygenase-3 (COX-3) are the three reported isoforms of this enzyme, all of which are encoded by distinct genes[1]. Until recently, little was known about the function of the third isoform (COX-3)[2]. COX-1 is constitutively expressed in many tissues and is indispensable for normal cell functioning, whereas COX-2 is an inducible enzyme[3]. Both are essential in various physiological and pathophysiological processes such as inflammation and cancer. In addition, these proteins are responsible for producing prostaglandin E2 (PGE2), an inflammatory mediator involved in an extensive range of effects such as vasodilation, potentiation of pain, and nociceptive responses[4]. The role of these enzymes in various oral disorders and pathologies has been widely studied. Increased COX-2 expression is associated with many conditions such as periodontitis, pulpitis, dental pain, and oral cancer.

This paper aims to provide an overview of the importance of cyclooxygenases in dentistry, the association of these enzymes with oral cavity pathologies and conditions, and the relevant aspects of their clinical implications.

Materials and methods

A literature search of the EBSCO, Google Scholar, Science Direct, PubMed and Web of Science databases for articles published in English and Spanish from 1971 to 2021 was performed. Search terms included: “Cyclooxygenase” and “Dentistry”, “COX-1” and “Dentistry”, “COX-2” and “Dentistry”.

Two hundred and thirteen duplicate studies were excluded from the articles retrieved. The search results were reviewed, the titles and abstracts were screened to remove studies outside the scope of this review, and 1962 articles were excluded. Then, the full text of all potentially eligible studies was obtained and further examined to exclude those that did not fulfill the inclusion criteria. In this step, 11 citations were removed. Ultimately, 115 studies were included, and the extracted information was organized in a spreadsheet (Excel, Microsoft Corporation, Redmond WA, USA) to facilitate analysis. A flow diagram of the literature is presented in Figure 1.

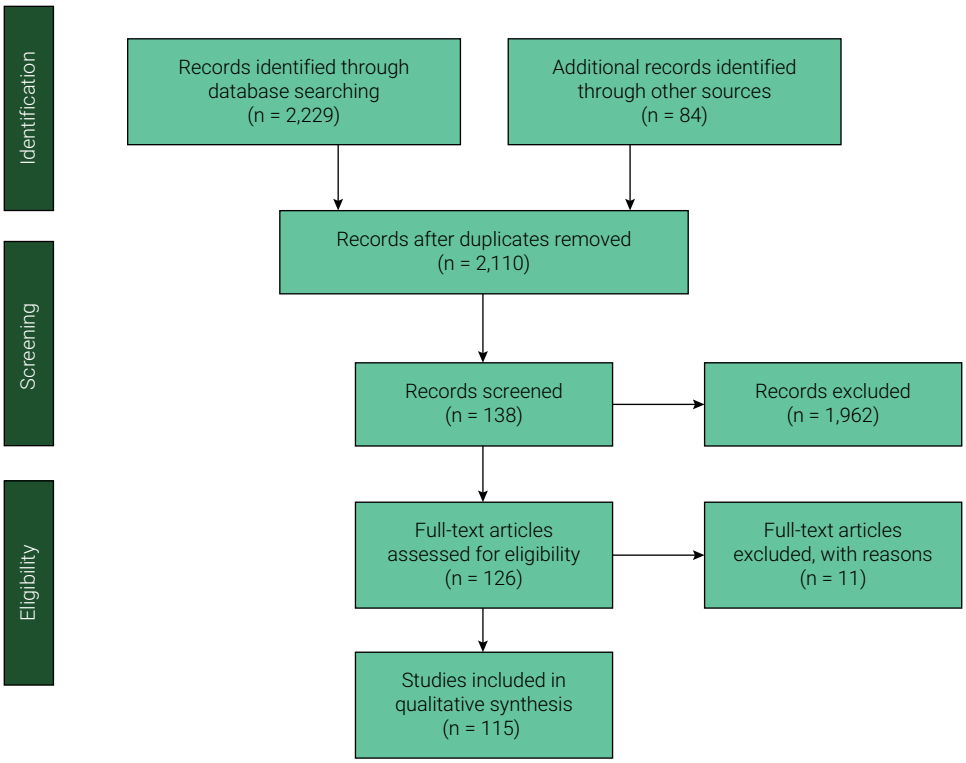

Figure 1. Flow diagram of the literature search and included studies

The inclusion criteria for the selection of articles were clinical case studies, review articles, and original articles with experimental studies, especially in humans and in vitro. Papers on perspectives and opinions, commentary articles, and book reviews were excluded.

Results

Cox in periodontitis progression

Understanding the mechanisms of COX expression in periodontal disease and its susceptibility to nonsteroidal anti-inflammatory drugs (NSAID's), selective COX inhibitors, or other drugs could be important in the development of more effective treatments for periodontitis.

The gingival tissue of patients with the periodontal disease contains prostaglandins[5], with exceptionally high levels of PGE2 in purulent exudates[6]. COX-2 overexpression in periodontal tissues is related to chronic periodontitis, bleeding index, inflammatory infiltrate, loss of connective tissue in the lamina propria, reduced clinical attachment, decrease radiographic alveolar bone mass, and inflammation[7,8]. In addition, high levels of PGE2 stimulate osteoclast bone resorption, and thereby promote the progression of periodontal disease[9]. These findings point to a link between COX, PGE2, and periodontitis, and the possibility that local production of these mediators contributes

to the inflammatory changes seen in periodontal disease, particularly attachment loss mechanisms such as the breakdown of extracellular matrix and support structures as the disease progresses.

COX-2 expression is linked to the severity of periodontitis, and pharmacological suppression of this enzyme may have a beneficial effect on periodontitis progression. Consequently, some studies have focused on the use of NSAIDs or selective COX inhibitors for the treatment of periodontitis. Flurbiprofen, meclofenamate, naproxen, and ketoprofen were shown to suppress periodontitis-related COX activity in the human gingiva[10], and celecoxib and rofecoxib inhibited PGE2 in gingival fibroblasts from patients with severe periodontitis[11]. Moreover, nimesulide decreased PGE2 levels in the gingiva of patients with chronic periodontitis[12], and flurbiprofen reduced PGE2 expression in the crevicular fluid of patients with gingivitis[13]. The local reduction of PGE2, as well as positive outcomes in periodontal health, is attributed to the use of these anti-inflammatory drugs.

There are reports on how patients taking NSAIDs or COX-inhibitors, such as phenylbutazone, aspirin, etoricoxib, naproxen, ibuprofen, nimesulide, flurbiprofen, or meclofenamate, as a treatment for periodontal disease showed clinical improvement with decreased gingival index values, probing pocket depth, loss attachment, plaque index, gingival fluid volume, bleeding on probing, redness and bone loss[12-19]. Since the effectiveness of NSAIDs and COX-2 inhibitors on the inflammatory response of periodontal tissues can be clinically detected and may therefore help to avoid further disease progression, it can be considered COX-2 inhibition could be a helpful treatment for periodontal disease, with favorable clinical outcomes.

Because inflammatory mediator by-products synthesized by cyclooxygenase are responsible for periodontitis progression, this enzyme has potential use as a pharmaceutical target for treatment and as a biomarker of periodontal disease progression. NSAIDs or selective COX-2 inhibitors as adjuvants to traditional mechanical periodontal therapy may be a preferable option for a more effective treatment. Since the progression of periodontitis can be slowed by pharmacological modulation of COX-2 and PGE2 production, this mode of therapy could be regarded as a supplementary therapeutic option for periodontal disease; however, further research is required.

Cox association with cancer and precancerous lesions

Cancer lesions in the oral cavity can display aggressive behavior. Hence, identifying biomarkers that facilitate early diagnosis is key to developing more appropriate treatments options and improving the prognosis. There is evidence that COX-2 expression plays essential roles in cancerous and precancerous lesions in the head such as participating in malignant transformation, proliferation, cellular adhesion, immune surveillance, apoptosis, invasiveness, angiogenesis, metastasis, and tumor development[20,21]. The increased energy demand of these malignant processes causes lipid metabolism disorders which in turn allow cancer cells to survive and proliferate. Consequently, aberrant levels of proteins and lipidic mediators associated with this pathway are linked to the risk or poor prognosis of a various malignancies[22]. Since COX-2 is an enzyme involved in lipid metabolism, any disruption in lipid synthesis, such as an increase in lipid utilization in cancer, will impact its upregulation.

The relationship between COX-2 expression and the progression of malignant and premalignant pathologies in the oral cavity can be understood by some common signaling pathways shared by growth factors[23]. The findings of some studies suggested that COX-2 and PGE2 promote carcinogenesis and tumor recurrence in head and neck squamous cell carcinoma through cross-activation and the signaling loop of the epidermal growth factor receptor (EGFR), using a signaling pathway involving Akt activation[24,25]. This indicates that the EGF/AKT/COX-2/PGE2 signaling pathway may play an important role in the development and invasion of head and neck squamous cell carcinoma.

COX-2 overexpression has been linked to the severity or progression of various oral cancerous and precancerous lesions, including oral leucoplakia[26] and tongue squamous cell carcinoma[27]. Additionally, COX-2 overexpression in the epithelium of oral lichen planus has been correlated with clinical severity, burning sensation, and pain symptoms[28]. Moreover, COX-2 expression is significantly upregulated in radicular cysts, ameloblastomas, ameloblastic carcinomas, ameloblastic fibromas, and dentigerous cysts[29-31]. COX-2 overexpression, which is involved in the carcinogenic process of these lesions, could be used as a possible indicator of the severity of malignancy of these conditions.

Information on COX-1 and its relationship with cancer is scarce. Nonetheless, there is evidence that benign salivary gland tumors, such as Whartin's tumor, have high COX-1 and COX-2 protein expressions[32]. Additionally, COX-1 expression increases progressively from normal oral mucosa to hyperplasia, dysplasia, and finally, carcinoma. COX-2 is also expressed in hyperplasia, with maximum activation observed in dysplasia[33]. Epidermal growth factor (EGF)-stimulated oral squamous cell carcinoma cell lines overexpressing COX-2 showed elevated PGE2 levels; however, COX-1 expression was unaffected[24]. These results reveal an association between severity and increasing levels of cyclooxygenase expression, with COX-1 being linked to precancerous lesions and COX-2 overexpression being associated with cancerous lesions.

Understanding the molecular mechanisms of the relationship between cyclooxygenase and cancer is essential for the development of novel diagnostic biomarkers and therapeutic targets[22]. Excessive lipid levels promote cancer development by inducing an inflammatory response and upregulating multiple mediators[34]. This results in unusual arachidonic acid metabolism, increasing COX-2/PGE2 activity and concentrations related to protumoral mechanisms, and poor outcome indicators in several types of cancer.

It is well known that early diagnosis is key to achieve a positive outcome in oral cancer. In this regard, COX-2 expression in cancerous and precancerous lesions in the oral cavity could be used as a prognostic biomarker; however, further research is needed. Additionally, COX-2 may represent a potential target for pharmacological approaches to manage these lesions.

Cox-related tissue destruction

As we delved further into the aforementioned topics, we found a common characteristic between the progression of periodontitis and cancerous lesions: an aggres-

sive behavior characterized by destruction of the adjacent tissues. This contributes to bone degradation which in turn facilitates the spread of tumor or resorption of periodontal tissues.

It has been proposed that up-regulation of COX and PGE2 is associated with bone resorption in inflammatory conditions and space-occupying lesions[9,35]. It promotes degradation, invasiveness and progression of the aforementioned pathologies in two ways: osteoclastic bone resorption and stimulation of other enzymes, such as matrix metalloproteinases (MMP), both of which involve a common endogenous pathway involving the receptor activator of NFkB ligand (RANKL)[36,37].

For example, COX-2 and PGE2 mediate osteoclastogenesis, bone resorption, and upregulation of RANK, RANKL, and NFkB in a variety of cells and tissues, including dental pulp fibroblasts, periodontal ligament cells, gingival fibroblasts, and alveolar bone[37-41]. These findings also support the hypothesis that decreasing PGE2 production by using COX-2 inhibitors may inhibit inflammatory bone resorption.

PGE2 increases RANKL expression in osteoblasts and fibroblasts, thereby enhancing osteoclastogenesis and bone resorption. A specific COX-2 inhibitor, NS-398, was shown to suppress this action, which can be reversed by adding exogenous PGE2 in vivo[42]. Furthermore, flurbiprofen prevents radiographic alveolar bone loss[43], while ketorolac rinse and orally-administered flurbiprofen was shown to reduce bone resorption and PGE2 levels in the gingival crevicular fluid of patients with periodontitis[44]. In periodontal disease induced in rats, meloxicam prevented alveolar bone and cementum loss, along with a reduction in the number osteoclasts[45]. These findings demonstrate the relevance of COX-2/PGE2 in bone resorption, as well as the efficacy of NSAIDs and selective COX-2 blockers drugs as potential treatments for periodontal disease.

It is critical to understand the mechanisms by which COX causes bone resorption. What other players, such as COX-regulated key enzymes, are involved in this phenomenon? MMPs are proteases involved in the physiological remodeling of extracellular matrix. An imbalance in the production and activity of these proteins could result in tissue destruction in the oral cavity[46]. Increased levels of COX-2, MMP-1, MMP-3, and MMP-9 are associated with chronic periodontitis, and PGE2 could have a role in the degradation of extracellular matrix by inducing MMP production that can be downregulated by glucocorticoids[47,48]. The potential regulatory effects of arachidonic acid metabolites such as PGs on MMPs could cause tissue destruction in periodontitis development.

MMPs are involved in the deterioration of tissues during inflammatory responses. Under inflammatory conditions, the expression of MMP-1, MMP-3 and MMP-8 increased in gingival fibroblasts, and dexamethasone, celecoxib, and the COX-2 inhibitor NS-398 inhibited their expression[49-51]. Furthermore, there is an association between PGE2 and MMP-8 overexpression in the crevicular fluid of patients with periodontitis, which could be reduced by meloxicam[52,53]. In addition, indomethacin significantly attenuates MMP-1 and MMP-8 upregulation in periodontal ligament cells[54].

Additionally, MMP-1, MMP-2, MMP-3, PGE2, and RANKL were overexpressed in odontogenic keratocyst fibroblasts under inflammatory conditions[36]. Celecoxib reduced inflammatory-induced activation of COX-2, MMP-9, and NFkB in the rat alveolar bone[37]. Conversely, COX-2 may exert anti-inflammatory effects in periodontal tissues through the downregulation of MMP-13 and MMP-14[51,55].

The interaction between COX and MMPs in tissue destruction is synergetic, where COX-2 initiates inflammation and promotes the activation of MMP, which subsequently triggers the tissue breakdown process, causing tissue damage and clinical inflammation. It is evident that COX-2 and PGE2 have regulatory effects on MMP expression and function, and that these effects can be affected by COX inhibitors.

Orthodonctic stimulation of COX

COX-related tissue destruction is present not only in pathological conditions or diseases, but can also be induced, in an advantageous way, for orthodontic purposes. Understanding the role of PGE2 in alveolar bone metabolism changes generated by orthodontic mechanical stress during tooth movement is essential to improve the comprehension of the bone biological response and its importance in orthodontics.

PGE2 is a proinflammatory mediator that is also one of the most effective osteoclast inducing agents (as previously stated); it is produced by a variety of cells in periodontal tissues. Therefore, it is essential to understand how the release of PGs in response to orthodontic mechanical stress promotes bone resorption and formation. Orthodontic tooth movement occurs as a result of therapeutic mechanical stress, causing bone remodeling that involves localized biochemical mediators, such as COX, which has been linked to the hyaline zone in the alveolar bone during orthodontic treatment[56,57].

Periodontal ligament cells respond to mechanical stress by increasing the levels of PGE2, RANKL, bone resorptive activity, and osteoclastogenesis[39,58]. PGE2 is synthesized by osteoblasts and gingival fibroblasts exposed to mechanical stress[59,60]. In rats, compressive pressure was shown to prevent osteoblast differentiation and stimulate osteoclastic bone resorption via PGE2 production, which could be prevented by COX inhibition[61,62]. In contrast, the bone formation mechanism induced by orthodontic forces can also be stimulated through PGE2 synthesis. Osteoblastic cells exposed to compressive forces induce mineralization due to the increase in COX-2/PGE2 production[63]. PGE2 levels could dictate the difference between bone resorption and formation in mechanical stress induced by orthodontic movements.

Some COX-related factors can improve orthodontic treatment outcomes. Mechanical vibration and local administration of PGE1 enhance alveolar bone resorption during orthodontic tooth movement via the cyclooxygenase pathway mechanism[64,65]. Other factors, such as the use of continuous light force or interrupted force do not show differences in PGE2 level changes in the gingiva; there is a sustained up-regulation in each kind of them[66].

Orthodontic treatment in the elderly is different because some of them are also treated for chronic inflammatory diseases and conditions, such as osteoporosis, which require pharmaceutical medications that could modify the outcomes of

orthodontic treatment. There are reports that people over 35 years of age exhibit an increase in age-related COX-2 and PGE2 expression in periodontal ligament cells exposed to compressive force[67]. The biphosphonate clodronate[68] and the COX inhibitor NS-398[69] reduced COX-2 and PGE2 synthesis overexpression in periodontal ligament fibroblasts exposed to mechanical stress. Furthermore, NSAIDs, such as etoricoxib, celecoxib, acetaminophen, rofecoxib, diclofenac, and aspirin inhibit orthodontic tooth movement in rats[70-72].

PGE2 modulation of bone metabolism may explain, at least in part, why optimal orthodontic force stimulates mineralization and bone resorption in an equilibrated way, resulting in the most effective tooth movement with fewer side effects, such as unwanted bone or root resorption.

Compression and tension stimulate bone metabolism through COX-2 induction, leading to increased PGE2 production and upregulation of RANKL expression, which is involved in the normal functioning of bone cells. PGs are helpful in clinical orthodontic treatment, and their manipulation may be the key to accelerating orthodontic tooth movement, whereas NSAIDs and selective COX-2 inhibitors could be considered for reducing pain and preventing undesired bone resorption.

Cox changes in pulpal and periapical disease

Changes in COX-2 production during pulpal inflammation can be used to predict disease prognosis and endodontic treatment outcomes. PGE2 levels rise throughout the transition from healthy pulp to reversible pulpitis, but decrease substantially when the pulpitis is irreversible[73]. The increase in PGE2 levels occurs not only in inflamed pulp blood, irritated/painful pulpal tissues, and periapical lesions, but also in pulps of asymptomatic teeth with extensive restorations or cavities[74-76]. Its overexpression in irreversible pulpitis is caused by pulpal fibroblasts and macrophages[77]. These studies suggest that PGE2 levels can be used to indicate the difference between symptomatic teeth with reversible and irreversible pulpitis when clinical endodontic diagnosis is in doubt; this measurement could be considered a parametrical value.

COX-2 triggered by endodontic pathogens and cytokines may play a role in the etiology of pulpal inflammation. Black-pigmented bacteria, IL-1β, IL-1α, TNF-α and TLR2 can upregulate COX-2 and PGE2 expression in pulp cells[78-81]. In addition, lipopolysaccharide (LPS)-induced inflammation increased the expression of PGE2 membrane transporter proteins, microsomal PGE synthase, COX-2 dependent MMP-3, and PGE2 synthesis in rat dental pulp[82,83].

PGE2 levels are lower in the pulp of patients taking NSAIDs[73]. Indomethacin has been demonstrated to reduce PGE2 levels, vascular permeability, and periapical bone loss in rats with induced pulp inflammation[84,85]. Bradykinin and thrombin stimulate PGE2 production in dental-pulp fibroblasts, which can be inhibited by flurbiprofen, hydrocortisone, and dexamethasone[86]. Moreover, meloxicam promotes proliferation, differentiation, and mineralization in LPS treated pulpal cells[87]. Clinical trials are needed to evaluate whether NSAIDs and selective COX-2 inhibitors could be used to treat pulpitis and bone resorption in periapical lesions, decrease PGE2 levels, and promote the regeneration of dental pulp cells.

Regarding intracanal medication protocols, the addition of ciprofloxacin or chlorhexidine to calcium hydroxide was shown to be highly effective in lowering PGE2 levels[88,89]. In addition, there are some reports that, in rat pulps and pulpal cells, treatment with mineral trioxide aggregate (MTA) enhance the expression of PGE2 transporters and receptors in odontoblasts, endothelial cells, and nerve fibers, while also inducing the upregulation of COX-2 and PGE2 and activation of NFkB[90,91]. Furthermore, the reparative dentinogenesis that occurs after MTA treatment involves mild inflammatory changes through COX-2/PGE2 and NFkB via a signaling pathway.

When immediate endodontic treatment is not possible for symptomatic pulpal diseases, the only option for temporary pain relief is to prescribe strong analgesics. However, pain associated with irreversible pulpitis is typically severe and difficult to tolerate. Therefore, it is necessary to consider other pharmacological therapies that could be used in such instances. Some reports have shown that intraosseous injection of the corticosteroid methylprednisolone decreases pulpal concentrations of PGE2, pain, and percussion pain in teeth with irreversible pulpitis while taking significantly fewer pain medications[92,93]. This therapy can be used temporarily alleviate the symptoms of irreversible pulpitis until definitive treatment can be perform.

PGE2 levels fluctuate during endodontic therapy. Spontaneous pain, sensitivity to percussion, pus, radiolucent area, sinus tract, and swelling, are significantly associated with high PGE2 concentrations in periapical exudates during root canal treatment[94,95]. PGE2 levels and the clinical manifestation of periapical periodontitis decreases markedly following endodontic therapy[96]. These results suggest the central role of PGE2 in pulpitis and periapical diseases. However, concentrations of PGE2 in apical tissue fluid and postoperative pain were higher after the second endodontic treatment visit than after the first treatment visit, especially in teeth with large restorations and without pus discharge[95,97]. The reported increase in PGE2 could have resulted from periodontal ligament injuries related to canal instrumentation.

The proinflammatory function of PGE2 has been well documented; however, it has been described in *in vitro* experiments that through the augmentation of hepatocyte growth factor, a potent stimulator of regeneration, and the downregulation of MMP1[98,99], PGE2 could exert a protective effect against dental pulp degeneration and inflammation.

PGE2 plays a key role in the pathogenesis of inflammatory pulpal diseases and may control disease manifestation and healing response following root canal therapy. COX-2 or PGE2 levels may help determine the severity of pulpal or periapical disease and treatment outcomes. As a therapeutic adjuvant, NSAIDs could be an excellent strategy to treat pulpal or periapical inflammation.

Dental materials and other substances that modulate COX expression

Some substances commonly used in dentistry that trigger cytotoxicity; which in turn could induce an inflammatory responses. For example, eugenol an endodontic obtu-

ration material, enhances COX-2 protein expression in human osteoblasts through the activation of NFkB, which can be inhibited by N-acetylcysteine[100]. TEGDMA and BisGMA, both monomers of composite resin, induce the overexpression of COX-2 and PGE2 in dental pulp cells[101,102]. Dental bonding agents induce COX-2 overexpression in gingival fibroblasts[103]. Tannin fluoride suppresses COX-2 and PGE2 expression induced by glass ionomer cement in dental pulp cells[104].

Other substances that are not frequently used in dentistry can modulate COX/PGE2 expression. For example, the substance emdogain (EMD), which is composed of enamel matrix proteins, elicits a proliferative response of periodontal ligament fibroblast through COX-2 upregulation, which can be inhibited by celecoxib[105]. Retinoids inhibit both basal expression and EGF-mediated induction of COX-2 transcription and PGE2 production in squamous carcinoma cells; however, they do not affect levels of COX-1 expression[106]. Pilocarpine reduces COX-2 dependent PGE2, and MMP-3 production in LPS-induced dental pulp inflammation in rats[82]. PGE2 levels in incisors exposed to dentinal injury increased moderately, whereas intradentinal administration of endotoxins or capsaicin resulted in a highly significant increase[107]. Cyclosporine A reduces the expression of COX-2 in rat gingival fibroblasts[108]. Multiple materials used in dentistry have been shown to increase COX expression, although further research is needed to fully understand these correlations.

Discussion

The effect of COX in conditions such as inflammation and pain has been extensively studied in dentistry[109]; however, this enzyme also has a significant association with oral diseases, as discussed in this review. For this reason, we focus on other less well-known COX implications in dentistry that may have potential significance.

Since the majority of consultations in dentistry are related to pain[110-114], dentists are well trained to treat it primarily with COX inhibitors[115]. However, it is necessary to understand how to modulate and interpret COX levels for the treatment of diseases related to COX upregulation. This may hold the key to complementary and preventive care of various oral disorders.

There are limitations in using COX inhibition as a treatment for many diseases or conditions such as those that are not pain-related, that are relevant in prosthodontics, periodontics, oral pathology, orthodontics, and endodontics. Therefore, this topic requires more exploration and research, especially regarding its clinical applications.

Conclusions

In many oral disorders, COX expression may hold the key to fundamental knowledge of disease processes and could be used to develop novel diagnostic and therapeutic procedures for multiple oral diseases (Figure 2). Although the exact role of COX in various conditions is not fully understood, it is clear that its upregulation is related to inflammatory and malignant diseases in oral tissues, such as periodontitis, pulpitis, and oral cancer, nevertheless, its expression is advantageous in other fields of study such as orthodontics.

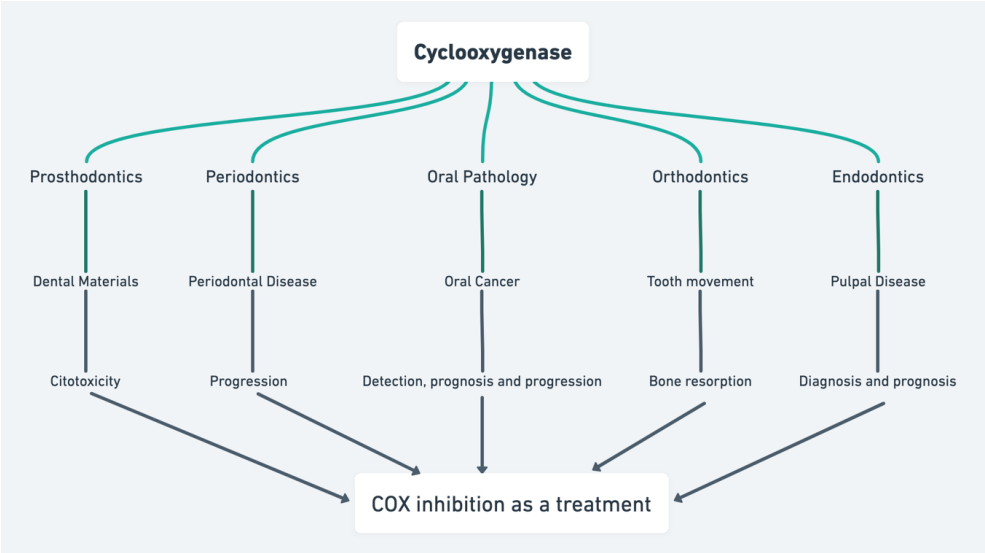

Figure 2. Cyclooxygenase and their importance in dentistry

We suggest using COX levels to track periodontal disease progression, endodontic prognosis, differential diagnosis, and detection of periodontal ligament injury. In addition, this enzyme could be employed as a biomarker for early detection, prognosis, and progression of oral cancer. Finally, COX inhibition with drugs such as traditional NSAIDs or selective COX-2 inhibitors could provide an option for combining drug therapy and conventional treatments for periodontitis, pulpitis, and probably oral cancer.

COX-mediated bone resorption is one of the multiple factors involved in orthodontic tooth movement; its levels could be used for prognosis treatment and its utilization for tooth movement enhancement or inhibition to reduce bone and root resorption. Additionally, is well documented that dental materials provoke an undesired increase in COX expression, which could be a significant factor that directly affects pulpal health. Therefore, considering different materials could contribute to decreasing these complications and improving outcomes.

Although the importance of COX in dentistry is widely studied, there is a need for further research to understand its modulation from a clinical perspective and to identify substances other than NSAIDs and COX-2 selective inhibitors that can modulate COX levels in the oral cavity.

Conflicts of interest

None.

Data availability

Datasets related to this article will be available upon request to the corresponding author.

Authors Contribution

Sara Delgadillo Barrera: actively participated the authorship; conception and design; acquisition, analysis, and interpretation of the data; drafting the work and reviewing, and final approval of the version to be published. **Lilia Jadith Bernal Cepeda:** actively participated the authorship; conception and design; acquisition, analysis, and interpretation of the data; drafting the work and reviewing, and final approval of the version to be published. **Jaime Eduardo Castellanos Parra:** actively participated the authorship; conception and design; acquisition, analysis, and interpretation of the data; drafting the work and reviewing, and final approval of the version to be published.

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