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# Use of nonsteroidal anti-inflammatory drugs in diabetic retinopathy

## Zastosowanie niesteroidowych leków przeciwzapalnych w leczeniu retinopatii cukrzycowej

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<b>Abstract:</b>	<p><b>Introduction:</b> Diabetic macular edema, a manifestation of diabetic retinopathy, occurs more frequently in type 2 diabetes mellitus. There is evidence that inflammation plays a prominent role in the pathogenesis. A number of pro-inflammatory cytokines are consistently elevated in the vitreous of patients with advanced stages of diabetic retinopathy. Nonsteroidal anti-inflammatory drugs inhibit the catalytic activity of the cyclooxygenase isoenzymes COX-1 and COX-2, the key enzymes in inflammatory processes.</p> <p><b>Purpose:</b> To present current knowledge of benefits and limitations of using nonsteroidal anti-inflammatory drugs in diabetic retinopathy.</p> <p><b>Conclusions:</b> Nonsteroidal anti-inflammatory drugs may be considered as an adjuvant treatment in diabetic retinopathy especially in patients with diabetic macular edema.</p>
<b>Key words:</b>	diabetic retinopathy, diabetic macular edema, nonsteroidal anti-inflammatory drugs.
<b>Abstrakt:</b>	<p><b>Wstęp:</b> cukrzycowy obrzęk plamki, jeden z objawów retinopatii cukrzycowej, występuje częściej w przebiegu cukrzycy typu 2. Uważa się, że reakcje zapalne odgrywają główną rolę w jego patogenezie. W ciele szklistym pacjentów z zaawansowaną retinopatią cukrzycową stwierdzono podwyższone stężenie cytokin. Niesteroidowe leki przeciwzapalne hamują katalityczną aktywność izoenzymów cyklooksygenazy COX-1 i COX-2, kluczowych enzymów procesów zapalnych.</p> <p><b>Cel:</b> przedstawienie aktualnego stanu wiedzy na temat zalet i ograniczeń niesteroidowych leków przeciwzapalnych w leczeniu retinopatii cukrzycowej.</p> <p><b>Wnioski:</b> niesteroidowe leki przeciwzapalne mogą być rozważane jako dodatkowe w leczeniu retinopatii cukrzycowej, zwłaszcza z obrzękiem plamki.</p>
<b>Słowa kluczowe:</b>	retinopatia cukrzycowa, cukrzycowy obrzęk plamki, niesteroidowe leki przeciwzapalne.

### Introduction

Diabetic retinopathy (DR) is one of the most common complications of diabetes and remains the most prevalent cause of visual impairment in the working-age population in industrialized countries despite established screening programs, early diagnosis and treatment of the condition. Diabetic macular edema (DME), a manifestation of DR, occurs more frequently in type 2 diabetes mellitus, and appears to be more prevalent as the duration of diabetes increases, and as the severity of DR worsens. Decades of research into the pathophysiology and management of DR have revolutionized our understanding of the disease process. There is evidence that inflammation plays a prominent role in its pathogenesis. Inflammatory cytokines such as Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) and Interleukin-1 $\beta$  (IL-1 $\beta$ ) have been implicated in the pathogenesis of diabetic retinopathy (1, 2). The induction of endothelial adhesion molecules by pro-inflammatory cytokines is often mediated via the activation of nuclear factor  $\kappa$ B (NF- $\kappa$ B) (3). NF- $\kappa$ B upregulates intercellular adhesion molecule-1 (ICAM-1) and related inflammatory genes; for example, cyclooxygenase 2 (COX-2) (3). Cyclooxygenase 1 (COX-1) and COX-2 are key enzymes in the conversion of arachidonic

acid to prostaglandin H<sub>2</sub> (PGH<sub>2</sub>), the common precursor for all other eicosanoids (4). Although there is no pathogen in the diabetic retina, risk factors of DR such as hyperglycemia, hypertension and dyslipidemia are all involved in retinal inflammation in DR through a variety of mechanisms including oxidative stress, nitric oxide synthase dysregulation, advanced glycation end products formation, renin-angiotensin system activation, and inhibition of endogenous anti-inflammatory pathways (5).

### Purpose

To present current knowledge of benefits and limitations of using nonsteroidal anti-inflammatory drugs in treatment of diabetic retinopathy.

### Discussion

Nonsteroidal anti-inflammatory drugs (NSAIDs) could constitute an attractive therapeutic tool for diabetes due to inflammatory nature of early diabetic retinopathy. A number of pro-inflammatory cytokines are consistently elevated in the vitreous of patients with advanced stages of DR and treatment with NSAIDs prevents or delays its progression in ani-

mal models (6). Schonberger et al. demonstrated elevated levels of PGE<sub>2</sub> in vitreous samples taken from patients with proliferative diabetic retinopathy (PDR) which correlate with vitreous levels of Vascular Endothelial Growth Factor (VEGF) and provides support for a pathogenic role of PGs in DR (7). NSAIDs act along the arachidonic acid cascade at a later stage than the corticosteroids, resulting in more specific antiinflammatory effects and fewer adverse events (8). The therapeutic efficacy of topical NSAIDs in stabilizing pupil dilation during intraocular surgery and treatment of allergic conjunctivitis and postoperative inflammation, pain and cystoid macular edema (CME) has been well established (1, 5). Chemically, NSAIDs can be grouped into six major classes: salicylates, fenamates, indoles, phenylalkanoic acids, phenylacetic acids and pyrazolones. Their classification as NSAIDs emphasizes that their chemical structures do not include a steroid nucleus derived biosynthetically from cholesterol. NSAIDs used in ophthalmology in a topical form are the derivatives of salicylic-, indole acetic-, aryl acetic-, aryl propionic and enolic acid (9).

NSAIDs inhibit the catalytic activity of the cyclooxygenase isoenzymes COX-1 and COX-2. As COX enzymes catalyze the production of five classes of PGs: PGE<sub>2</sub>, PGD<sub>2</sub>, PGF<sub>2</sub> $\alpha$ , PGI<sub>2</sub>, and Thromboxane A<sub>2</sub>, their inhibition has favorable effects on intraocular inflammation and retinal edema (7). Most NSAIDs act as nonselective inhibitors of COX-1 and COX-2 and are almost equally effective clinically as anti-inflammatory agents when used at equivalent doses. Differences are mainly found in their toxicity profile, route of administration, and elimination half-life.

Aspirin is a potent anti-inflammatory agent that acts not only by inhibiting the enzymatic activity of COXs by acetylation, but also by inhibiting the activation of some transcription factors, including NF- $\kappa$ B and CCAAT/enhancer binding protein (C/EBP) (10, 11). Aspirin effects vary with different doses: 80 mg/day has been regarded as a low dose in humans, based on average human body weight of 70 kg, 2–4 g/day as intermediate doses, and 6–8 g/day as high doses (12). It can irreversibly acetylate serine groups on COX-1 to inhibit platelet thromboxane A<sub>2</sub> generation at a low dose, globally inhibit COX-1 and -2 and block prostaglandin production at intermediate doses, and has unknown mechanism(s) at high doses (12). The therapeutic benefit of systemic NSAIDs in DR has been evaluated in a few clinical studies. It was first observed a half century ago that rheumatoid arthritis patients taking salicylates had a reduced incidence of DR (13). This observation was later examined in two large multicenter clinical trials, the Early Treatment Diabetic Retinopathy Study (ETDRS) and the Dipyridamole Aspirin Microangiopathy of Diabetes (DAMAD) Study (14, 15). While no benefit was found in patients with more advanced DR in ETDRS, a significant effect was seen in the DAMAD study, where higher doses of aspirin were found to slow the development of retinal microaneurysms. The low doses of aspirin were sufficient only to inhibit platelet and thromboxane production (14, 15). Zheng et al. demonstrate that three different salicylate-based anti-inflammatory drugs (aspirin, sodium salicylate, and sulfasalazine) were able to significantly inhibit the degeneration of retinal capillaries (one of the key markers of early lesions of DR) and prevent ganglion cell loss in diabetic rats. They also postulate that

the salicylate-mediated inhibition of early stages of DR is at least in part due to inhibition of the diabetes-induced activation of NF- $\kappa$ B and other transcription factors in the retina (16). A second effect of aspirin exerted at micromolar concentrations is the inhibition of ribosomal protein S6 kinase, which phosphorylates and activates the transcription factor C/EBP (17). C/EBP- is involved, in a complex fashion, in multiple cellular activities, including inflammatory responses (18). Aspirin can inhibit C/EBP- phosphorylation in the diabetic retina and thus work by limiting the consequences of the small increase in the level of the transcription factor induced by diabetes. Aspirin reduces ICAM-1 protein levels, the retinal TNF- $\alpha$  levels, the retinal endothelial nitric oxide synthase (eNOS) and retinal NF- $\kappa$ B activities.

Administration of other NSAIDs (meloxicam, celecoxib) has also been reported to inhibit diabetes-induced retinal microvascular disease and prevent early DR (19). A prospective, controlled trial conducted by the National Eye Institute demonstrated that oral celecoxib significantly reduced vascular leakage in patients with DR despite premature treatment discontinuation due to concerns regarding cardiovascular toxicity (20). A randomized 3-year pilot study revealed that another NSAID, sulindac, prevented development and progression of DR (21).

Topical administration of drugs is the most preferred route for management of ocular inflammation as it provides higher ocular drug concentrations, avoiding the systemic side effects associated with the oral administration. However, due to the physiologic constraints of the eye only few of the anti-inflammatory agents which possess certain physicochemical properties can be formulated into a suitable dosage form. Several topical NSAIDs are commercially available for ophthalmic use: ketorolac, bromfenac, diclofenac, and nepafenac. Nepafenac is the only NSAID prodrug, having less anti-inflammatory activity without conversion to its more active state (22).

Upon topical ocular instillation, the molecule penetrates the cornea, where nepafenac is metabolized into the more potent NSAID amfenac through the intraocular enzymatic hydrolysis (23). Ocular penetration and potency are critically important for the activity of a drug, as suggested in a study that measured aqueous humor drug concentration and correlated it with its effect (24). Nepafenac demonstrated significantly greater ocular bioavailability than any other drug tested, possibly providing a reservoir within the aqueous humor for continued amfenac production. Study conducted by Kern et al. demonstrates that administration of nepafenac inhibits functional and structural alterations typical of early stages of diabetic retinopathy. The most unique aspect of this study is that local drug delivery via eyedrops exerted this beneficial effect. Topical ocular administration of nepafenac was also found to inhibit leukostasis within retinal microvessels (19). Takadera et al. found that nepafenac partially inhibits the diabetes-induced activation of executioner caspases, such as caspase-3 and -6, within the retina (25). Both PGE<sub>2</sub> and superoxide have been reported to induce caspase-dependent apoptosis; thus, the inhibition of caspases and apoptosis in human retina by nepafenac might occur via the inhibition of these biochemical abnormalities (25).

There is a deficiency of human studies measuring NSAID levels in the vitreous after topical application. Heier et al. measured vitreous drug levels in patients who received ketorolac 0.4% four

times daily, bromfenac 0.09% two times daily, or nepafenac 0.1% three times daily for three days before vitrectomy surgery (26). Only ketorolac resulted in significantly lower vitreous PGE2 levels as compared to placebo. Bromfenac is structurally identical to amfenac with the exception of bromine content, which makes it more lipophilic, facilitating corneal penetration, increasing the duration of action and enhancing its COX-2 inhibitory activity (9). Aqueous and vitreous concentrations of NSAID would likely have a direct effect on the anterior (ciliary body and iris) and posterior (retina and choroid) PG production, respectively.

There were studies evaluating intravitreal diclofenac or ketorolac in DME. Soheilian et al. eight weeks after intravitreal injection of diclofenac (500 mcg/0.1 mL) in five eyes with DM noted that the VA improved in two eyes, worsened in two eyes, and remained stable in one eye, while the mean central macular thickness (CMT) was actually worse than at baseline (27). Elbendary and Shahin revealed that after intravitreal administration of diclofenac (500 mcg/0.1 mL) CMT decreased by 148.7 microns at three months (28). Reis et al. treated twenty patients with bilateral DME refractory to laser therapy with intravitreal ketorolac (500 mcg/0.1 mL). At one month, a significant VA improvement was observed in the treated eyes relative to controls, but there was no change in foveal thickness or macular volume (29). Maldonado et al. treated 25 patients with DME refractory to laser with a single injection of ketorolac (3000 mcg/0.1 mL). At one month, 28% of patients had the VA gain of at least five letters, while there was no significant difference in macular thickness (30).

One should be aware of some limitations of treatment with NSAIDs. Like any daily regimen, NSAIDs require compliance and continued use. They do not reverse the disease process, but merely attempt to control vascular damage. The edema would likely return with drug cessation if no other intervention is applied. Blood glucose level control must be emphasized. Long-term administration also creates an issue of cost. If medical therapy is required for years, the upfront cost of focal laser could actually save money for the patient after all costs are considered.

Unlike corticosteroids, which can reduce macular edema by several mechanisms, nonsteroidal anti-inflammatory drugs act mainly through one way, which is a potent inhibition of prostaglandins synthesis by suppression of the arachidonic acid transformation catalyzed by COX-1 and COX-2 (31). Since corticosteroids inhibit both pathways (cyclooxygenase and 5 lipoxygenase), they can theoretically be expected to be more effective than NSAIDs in decreasing inflammation and angiogenesis. However, one study reported that diclofenac can also inhibit the lipoxygenase pathway. This unique quality of diclofenac gives it a spectrum of activity more similar to corticosteroids and may contribute to its improved anti-inflammatory efficacy (32). Furthermore, corticosteroids have many well-documented adverse effects, including cataract formation or increased IOP in susceptible patients.

## Conclusion

Nonsteroidal anti-inflammatory drugs may be considered as an alternative or adjuvant treatment in diabetic retinopathy especially in patients with diabetic macular edema.

### Conflict of Interest

The authors declare no conflict of interest.

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