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Research Paper
TMJ Disorders

The action of anti-inflammatory agents in healthy temporomandibular joint synovial tissues is sex-dependent

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Abstract. This study evaluated the effects of dexamethasone, parecoxib, and glucosamine on cartilage thickness and cytokine levels in the temporomandibular joint (TMJ). Forty-eight rats (24 female, 24 male) were assigned to four treatments administered once daily for 7 days: control (saline intramuscularly), parecoxib (0.3 mg/kg intramuscularly), dexamethasone (0.1 mg/kg intramuscularly), and glucosamine (80 mg/kg orally). The thickness of TMJ cartilage and levels of four cytokines were measured. Median cartilage thickness was higher in males than in females in the control (253.2 vs. 240.4 μm, $P = 0.0036$), parecoxib (227.3 vs. 192.1 μm, $P < 0.0001$), and dexamethasone (227.1 vs. 170.5 μm, $P = 0.017$) groups, but was lower in males in the glucosamine group (214.5 vs. 239.6 μm, $P = 0.0001$). IL-1β was not detected. Median IL-1α levels differed between males and females in the parecoxib group (0.08 vs. 0.04 ng/ml, $P = 0.0055$), but not in the control (0.07 vs. 0.06 ng/ml), dexamethasone (0.06 vs. 0.04 ng/ml), or glucosamine (0.08 ng/ml vs. 0.06 ng/ml) groups (all $P > 0.05$). Only dexamethasone induced lower IL-6 levels in males than in females (median 4.6 vs. 2.1 ng/ml, $P = 0.0044$). Median TNF-α levels did not differ between males and females in the control (0.07 vs. 0.05 ng/ml) or parecoxib (0.07 vs. 0.05 ng/ml) groups (both $P > 0.05$), but dexamethasone (0.09 vs. 0.05 ng/ml, $P = 0.0002$) and glucosamine (0.09 vs. 0.07 ng/ml, $P = 0.0259$) induced higher TNF-α levels in females. Thus, the effects of the three treatments on the levels of cytokines and thickness of condylar cartilage were sex-dependent.

Key words: temporomandibular joint; cartilage; anti-inflammatory; cytokine.

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The temporomandibular joint (TMJ) consists of the mandibular fossa of the temporal bone and the mandibular condyle. The mandibular condyle is covered by cartilage composed of different cellular layers: fibrous, proliferative, mature, and hypertrophic. The TMJ also has an articular capsule, ligaments, and a thin articular disc located between the mandibular fossa and the condyle[1]. Pathologies of the TMJ manifest as pain in the condylar joint, leading to either physiological adaptation or derangement of the TMJ[2,3]. An influence of gonadal hormones has been observed in rats[4], and it is in fact well known that women are more prone to TMJ disorders than men[5].

Disorganization/destruction of the TMJ tissues induces the release of inflammatory mediators into the articular surroundings[6]. Inflammation has a considerable role in TMJ disorders, especially in arthritis, acute trauma, and articular cartilage derangement[7]. Increased cytokine (interleukin (IL)-1β, IL-6, and tumor necrosis factor alpha (TNF-α)) and prostaglandin (PGE2) levels in the synovial fluid have been found in internal derangement of the TMJ, such as anterior disc displacement and osteoarthritis[8].

PGE2 has been associated with articular pain[7], and is therefore the target of non-steroidal anti-inflammatory therapies aimed at controlling acute pain and inflammation. Non-steroidal anti-inflammatory drugs (NSAIDs) are amongst the most prescribed medications for the control of TMJ disorders[5]. NSAID treatment regimens vary from several days[9] to 1 month[10], mainly due to side-effects[11].

Non-cyclooxygenase 2 (COX-2) selective NSAIDs are known to cause serious side-effects, especially gastrointestinal irritation. Some selective COX-2 inhibitors have demonstrated fewer adverse effects[11], however selective inhibitors have been shown to increase the risk of life-threatening cardiovascular disorders. This has resulted in restrictions in the use of both rofecoxib and valdecoxib in the USA and Europe[12]. While short-term administration of most of the NSAIDs has been associated with allergic reactions, renal failure, coagulation disturbances, and asthma episodes, their long-term use has been associated with gastrointestinal adverse effects, renal failure, and congestive heart failure[13]. Parecoxib is the prodrug form of valdecoxib and is available in parenteral formulations. After intramuscular (IM) or intravenous (IV) injection, parecoxib is rapidly metabolized into its active form in the liver, and reaches significant plasma concentrations at between 30 min and 3.5 h. Its elimination half-life is approximately 8 h[14].

In addition to NSAIDs, corticosteroids, especially dexamethasone, have been used to treat the pain and inflammation caused by TMJ disorders[10]. The protective effects of dexamethasone against cartilage degeneration have been observed in clinical and animal studies, and corticoids are considered key agents for the induction of chondrogenesis in mesenchymal stem cells[15,16]. Other strategies for the pharmacological control of condylar resorption have been described. These strategies include omega-3 fatty acids, tetracyclines, statins, and IL-6 receptor inhibitors (denosumab, tocilizumab), among others[17].

TMJ disorders are also characterized by collagen degeneration and a reduced quantity of proteoglycans[6]. Glucosamine is an amino-monosaccharide present in connective and cartilaginous tissues that contributes to the maintenance, resistance, flexibility, and elasticity of these tissues. Glucosamine has been used to treat osteoarthritis in humans[18]. Osteoarthritis animal models have supported the therapeutic potential of glucosamine. Glucosamine has been found to help retain proteoglycans, to inhibit type I collagen degradation, and to improve type II collagen synthesis in the articular cartilage[18]. In addition, when associated with chondroitin sulfate, glucosamine has been found to improve the symptoms of TMJ disorders, to decrease IL-1β and IL-6 in the synovial fluid, and to promote pain relief similarly to tramadol[6].

The main hypothesis of this study was that the effect of anti-inflammatory drugs on the rat TMJ is determined by sex. The aim of this study was to evaluate the effects of two anti-inflammatory agents (parecoxib and dexamethasone) and glucosamine on the articular cartilage of the TMJ in healthy male and female rats. In order to test the effects, a histomorphometric analysis of the articular cartilage layers was performed, as well as an evaluation of the levels of four cytokines.

Materials and methods

This study was approved by the Ethics Committee for Animal Research of the University of Campinas in Piracicaba, Brazil.

Forty-eight 3-month-old Wistar rats (*Rattus norvegicus* var. *albinus*), 24 female and 24 male, were assigned randomly to eight groups: group 1 comprised the control females (0.1 ml saline given intramuscularly (IM) once daily); group 2 comprised females treated with parecoxib (0.3 mg/kg IM once daily); group 3 comprised females treated with dexamethasone (0.1 mg/kg IM once daily); group 4 comprised females treated with glucosamine (80 mg/kg orally once daily); group 5 comprised control males (0.1 ml saline IM once daily); group 6 comprised males treated with parecoxib (0.3 mg/kg IM once daily); group 7 comprised males treated with dexamethasone (0.1 mg/kg IM once daily); and group 8 comprised males treated with glucosamine (80 mg/kg orally once daily). Figure 1 shows the experimental design.

The treatments were saline (0.9% sodium chloride; Laboratório Sanobiol, São Paulo, Brazil), parecoxib 20 mg/ml (Bextra injectable; Pfizer Laboratories Ltd, São Paulo, Brazil), dexamethasone 4 mg/ml (Decadron injectable; Ache Laboratórios

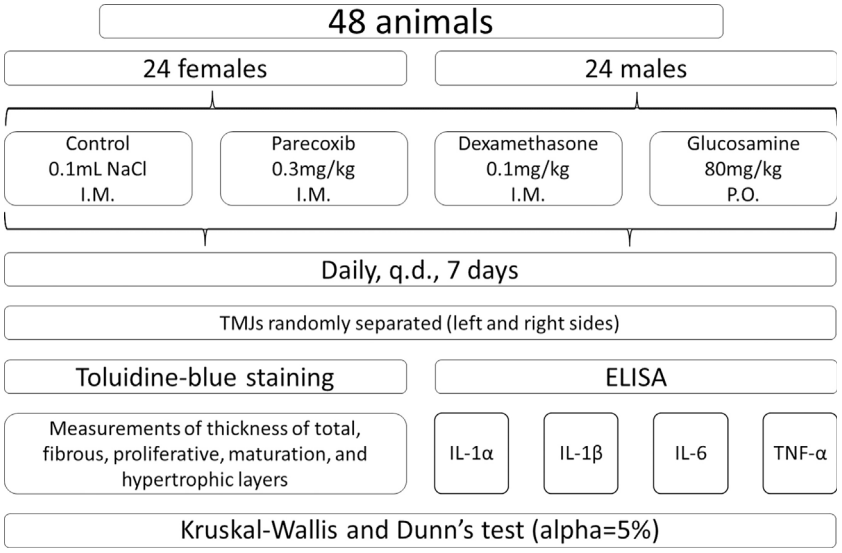

Fig. 1. Experimental design and animal distribution into groups.