Original Article

Effect of Celecoxib Alone or in Combination of Sitagliptin in Monoiodoacetate Rat Model of Osteoarthritis

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Abstract

Background: Osteoarthritis (OA) is considered an attractive research issue; as it is the most common musculoskeletal progressive condition with no cure yet. **Aims:** To evaluate effect of celecoxib alone or in combination of sitagliptin in monoiodo acetate rat model of OA. **Methods:** A total of 40 Sprague-Dawley male rats were divided into 4 groups, negative control (n=10), positive control group (OA induced by monoiodoacetate (MIA)) (n=10), celecoxib 50mg/kg (n=10), and celecoxib 50mg/kg plus sitagliptin 20mg/kg group (n=10). Serum levels of inflammatory biomarkers and serum CTX-II were assessed for all groups. Data were analyzed statistically by SPSS version 28.00. **Results:** group treated with celecoxib showed a significant reduction in the inflammatory biomarkers and CTX-II serum levels compared with the OA group (P<0.01). A significant reduction in CTX-II level in combination treated group relative to celecoxib treated group. **Conclusion:** Celecoxib imparted anti-inflammatory and cartilage protective effect in OA induced rat model. Sitagliptin combination with celecoxib added an extra cartilage protective effect by reducing cartilage degradation evident by lowering CTX-II serum levels.

Keywords: Celecoxib, CTX-II, osteoarthritis

Introduction

Osteoarthritis (OA) is considered an attractive research issue; as it is the most common musculoskeletal progressive condition with no cure yet. OA can affect any joint in the body but it is more common in the knee, hip, and hand joints. It is estimated that the prevalence of knee OA (KOA) for male over 60 is 10%, whereas for female over 60 is 13%.[1] With this increased prevalence, OA imposes an enormous burden on comprised lost wages, reduce economic productivity, medical care costs, and the significant low life quality of the sufferers.[2,3]

The exact mechanism of OA pathogenesis is still unknown, despite the advances in the analysis and diagnosis procedures.[4]

Pharmacological management for OA provides symptomatic pain relief without treating the condition.[5] Painkillers represented by nonsteroidal anti-inflammatory drugs provide pain relief through blocking COX enzyme and hence decreasing prostaglandins; several unwanted reactions are associated until selective COX-2 inhibitors have been developed circumventing COX-1 isoform inhibition, beside pain relief COX-2 inhibitors could be promising in preventing cartilage degradation and thereby slowing KOA progression.[6,7]

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Prostanoids inhibition by COX-2 inhibitors not only protect against cartilage degradation but also against synovial fibrosis and chondrocyte hypertrophy.[8,9]

The effect of these selective COX-2 inhibitors represented by celecoxib (the prototype of this group) on synovial inflammation, cartilage degradation, osteoclast metabolism cartilage degradation, synovial inflammation, and osteoclast metabolism have been reviewed previously.[10]

On the other hand, dipeptidyl peptidase inhibitors (DPP-IV inhibitors) represented in this study by sitagliptin are group of antidiabetic agents that are used alone or in combination with other antidiabetics in type II DM. They exert antidiabetic effect through the inhibition of incretin degradation. In recent years, growing evidence suggested pleiotropic cytoprotective

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effect of sitagliptin.[11-14] In this study, we investigated the effect of celecoxib alone or in combination of sitagliptin in monoiodoacetate rat model of OA.

Materials and Methods

Forty male Sprague–Dawley rats with weight average of 200–250 g were taken from the animal house of the Iraqi Center for Cancer and Medical Genetics Research in Baghdad/Iraq. All rats were housed in a well-ventilated room at 25°C ± 2°C, with 12/12 h dark/light cycle and under typical conditions with food and water provided *ad libitum*.

After acclimatization of the 40 rats, they were evenly and randomly divided into four groups: Negative control group (G−ve) normal untreated rats, positive control OA induced but not treated positive control group (G+ve), group one (G1) OA induced and treated with 50 mg/kg celecoxib orally via gavage, group two (G2) OA induced and treated with the combination of 50 mg/kg celecoxib and 20 mg/kg sitagliptin also via oral gavage. The study lasted for 4 weeks.

OA induction, 30 rats were anesthetized with diethyl ether (Thomas Baker, India). Then, a freshly prepared monoiodoacetate 3 mg/kg (9 Ambeed, USA) intra-articularly was injected into the knee joint pocket using 26G syringes. The rats were carefully monitored after induction of OA for 1 week. This procedure was performed as in Feng *et al*.'s study.[15]

At the end of the experiment interval (4 weeks), the rats were euthanized; blood was collected and then centrifuged at 3000/rpm. The serum was stored at −20°C in a specific refrigerator till the time of analysis.

Inflammatory cytokines, represented by tumor necrosis factor-alpha (TNF-α), interleukin one beta (IL-1β), IL-2, and IL-6, were analyzed by ELISA kit methods (LABISKOMA, Inc. Korea). Furthermore, C-telopeptide of the fragment of type II collagen (CTX-II) serum level also was measured using the ELISA kit method (MyBioSource). Procedures of ELISA kits were performed according to manufacture protocol and instructions.

Resulted data were statistically analyzed by SPSS (Statistics for Window version 26.00, Armonk, NY, IBM, Corp, USA). One-way analysis of variance was used to compare data that were expressed as mean ± standard deviation. The level of significance was applied when $P < 0.05$.

Results

Inflammatory cytokine levels of the G+ve were significantly higher than that of the G−ve. The same for the cartilage degradation marker (CTX-II) is shown in Figures 1 and 2 and Table 1.

Discussion

The result of this study demonstrated that celecoxib therapy significantly reduced inflammatory biomarkers and CTX-II relative to G+ve. This reduction could be imposed by celecoxib through its well-known anti-inflammatory property; furthermore, emerging evidence suggested that it could have disease-modifying properties. Celecoxib has been approved to affect all joint tissues involved in the disease progression bone, synovium, and cartilage.[16-18] Besides COX-II inhibition celecoxib modulates signal transduction pathways independent of COX-II signaling pathway.[19]

Normally, the chondrocyte maintains an equilibrium between the degradation and synthesis of the extracellular

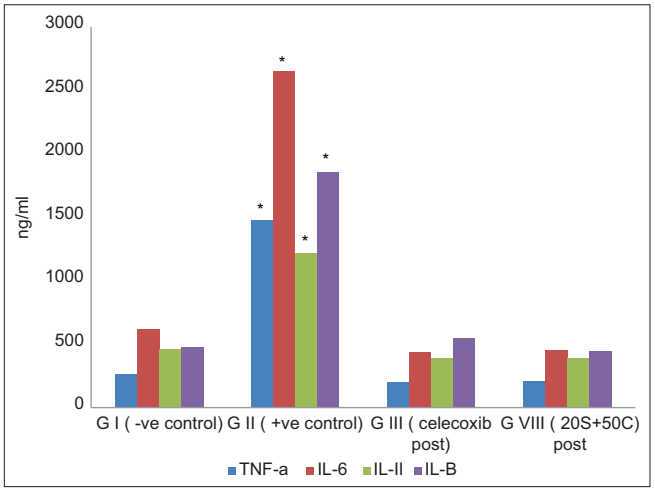

Figure 1: Effect of celecoxib alone or in combination of sitagliptin on inflammatory serum level (ng/ml) in rats with experimental OA. $P < 0.001$. OA: Osteoarthritis

Table 1: Effect of celecoxib alone or in combination of sitagliptin on serum level of inflammatory cytokines and C-telopeptide of the fragment of Type II collagen in a rat model of osteoarthritis all data are expressed as mean±standard deviation in ng/mL

Groups	*n*	TNF-α	IL-Iβ	IL-6	IL-II	CTX-II
G −ve	10	265.59±87.88	475.69±175.14	618.24±68.03	457.56±138.07	1.72±0.34
G +ve	10	1579.79±883.27*	1858.34±583.82*	2654.30±595.14*	1220.60±237.21*	5.95±1.59*
Group I	10	205.1±9.9	549.05±21.97	436.32±55.32	547.87±12.49	1.79±0.08
Group II	10	205±9.2	448.65±21.08	453.67±20.06	391.21±19.83	0.66±0.099

*Significant elevation in all of the measured biomarkers in G +ve. CTX-II: C-telopeptide of the fragment of type II collagen, TNF: Tumor necrosis factor, IL: Interleukin, G +ve: Positive control group, G −ve: Negative control group

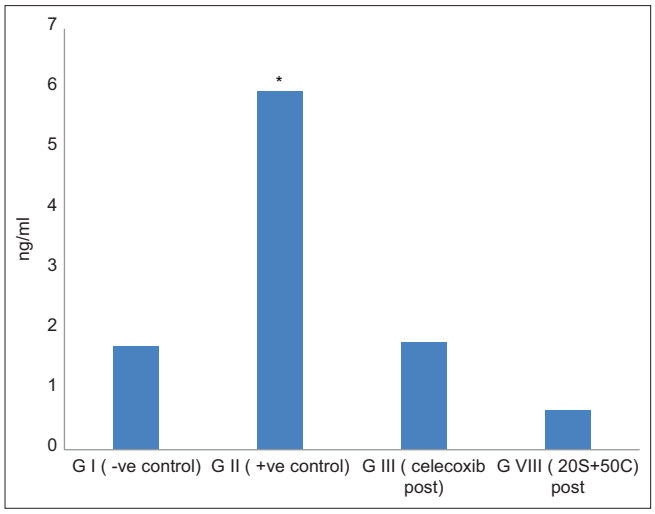

Figure 2: Effect of celecoxib alone or in combination of sitagliptin on CTX-II serum level ng/ml in OA rat model $P < 0.001$. OA: Osteoarthritis

matrix. When OA develops chondrocyte fail to preserve this equilibrium leading to disturbance in the integrity of cartilage. In the beginning, chondrocytes increase the synthesis of proteoglycans and collagens to maintain joint equilibrium; however, as disease progress catabolism cannot be counteracted and it will prevail.[20]

Major key players in this destructive process are IL-1β and TNF-α (both were significantly decreased by celecoxib use in this study), in OA these proinflammatory mediators stimulate the expression and release of collagenases and aggrecanases, and also stimulate the synthesis of nitric oxide (NO) and PGE2.[21] COX-2 was found to be upregulated in chondrocyte in the case of OA.[22,23]

Furthermore, in OA cartilage explants, celecoxib preserves cartilage through stimulation of proteoglycan synthesis and retaining the newly formed proteoglycans.[17] Moreover, the expression of PGE2 and COX-2 in OA cartilage is strongly inhibited by celecoxib.[24-26] This explains the decreased serum level of CTX-II obtained. C telopeptide fragment of type II collagen (CTX-II) is used to diagnose the integrity of cartilage as it represents a biomarker that could be measured in urine (noninvasively) or in blood.[27]

Celecoxib and through inhibiting JNK and nuclear factor-κB (NF-κB) (as were approved previously [16]) suppresses NO production and hence decreases apoptosis resulted [Figure 3][28] NF-κB has a pivotal role in the pathogenesis of OA as it upregulates cytokine, Matrix metalloproteinases (MMP), and A Disintegrin and Metalloproteinase with Thrombospondin motifs (ADAMTS) expression and decrease extracellular matrix secretion.

Sitagliptin as DPP-IV inhibitor controls blood glucose level through the incretin effect in a glucose-dependent manner it is usually used to treat type II DM. Previous studies proved its ability to prevent oxidative stress in several organs such as the heart, kidney, brain, and liver in OA.[28,29]

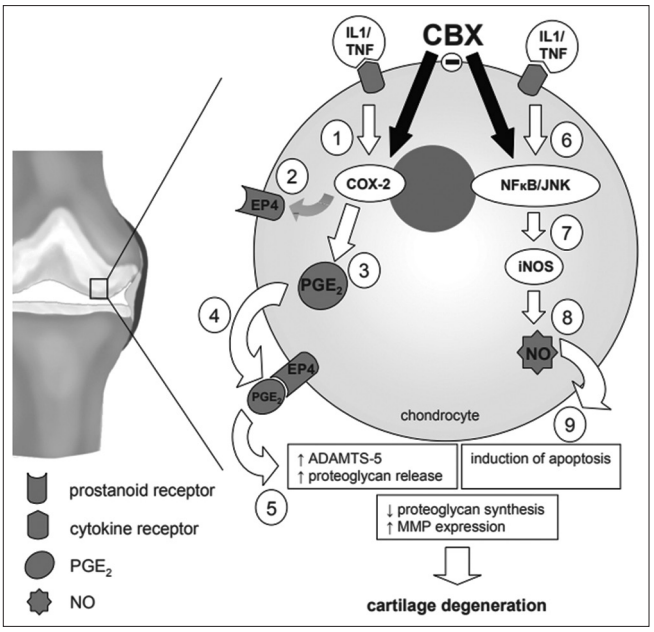

Figure 3: Celecoxib role in OA. OA: Osteoarthritis

Furthermore, it was previously provided that sitagliptin improves cell viability in human primary chondrocytes, and decreases collagen and aggrecan degradation via downregulating MMP-3, MMP-13, ADAMTS-4, and ADAMTS-5.[30] Similar previous study showed that vildagliptin (another DPP-IV inhibitor) reduces the expression of MMP-3, MMP-13, ADAMTS-4, and ADAMTS-5 and the subsequent collagen and aggrecan degradation.[31] an anti-inflammatory property of sitagliptin was reported in earlier studies results obtained in this study support the previously above mentioned.

The combination of celecoxib with sitagliptin resulted in an additional cartilage protective effect, as shown in Figure 2.[32,33]

Conclusion

Sitagliptin combination with celecoxib in monoiodoacetate rat model provided a significant cartilage protective effect.

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Conflicts of interest

There are no conflicts of interest.

References

1. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med 2010;26:355-69.
2. Zhao X, Shah D, Gandhi K, Wei W, Dwibedi N, Webster L, *et al.* Clinical, humanistic, and economic burden of osteoarthritis among noninstitutionalized adults in the United States. Osteoarthritis Cartilage 2019;27:1618-26.
3. Kotlarz H, Gunnarsson CL, Fang H, Rizzo JA. Insurer and out-of-pocket costs of osteoarthritis in the US: Evidence from national survey data. Arthritis Rheum 2009;60:3546-53.
4. Geyer M, Schönfeld C. Novel insights into the pathogenesis of

osteoarthritis. Curr Rheumatol Rev 2018;14:98-107.

5. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet 2019;393:1745-59.
6. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol 2011;31:986-1000.
7. Martel-Pelletier J, Pelletier JP, Fahmi H. Cyclooxygenase-2 and prostaglandins in Articular Tissues. Semin Arthritis Rheum 2003;33:155-67.
8. Bastiaansen-Jenniskens YM, Wei W, Feijt C, Waarsing JH, Verhaar JA, Zuurmond AM, *et al.* Stimulation of fibrotic processes by the infrapatellar fat pad in cultured synoviocytes from patients with osteoarthritis: A possible role for prostaglandin f2alpha. Arthritis Rheum 2013;65:2070-80.
9. Welting TJ, Caron MM, Emans PJ, Janssen MP, Sanen K, Coolsen MM, *et al.* Inhibition of cyclooxygenase-2 impacts chondrocyte hypertrophic differentiation during endochondral ossification. Eur Cell Mater 2011;22:420-36.
10. Zweers MC, de Boer TN, van Roon J, Bijlsma JW, Lafeber FP, Mastbergen SC. Celecoxib: Considerations regarding its potential disease-modifying properties in osteoarthritis. Arthritis Res Ther 2011;13:239.
11. Read PA, Khan FZ, Heck PM, Hoole SP, Dutka DP. DPP-4 inhibition by sitagliptin improves the myocardial response to dobutamine stress and mitigates stunning in a pilot study of patients with coronary artery disease. Circ Cardiovasc Imaging 2010;3:195-201.
12. Vaghasiya J, Sheth N, Bhalodia Y, Manek R. Sitagliptin protects renal ischemia reperfusion induced renal damage in diabetes. Regul Pept 2011;166:48-54.
13. Mega C, de Lemos ET, Vala H, Fernandes R, Oliveira J, Mascarenhas-Melo F, *et al.* Diabetic nephropathy amelioration by a low-dose sitagliptin in an animal model of type 2 diabetes (Zucker diabetic fatty rat). Exp Diabetes Res 2011;2011:162092.
14. Matsubara J, Sugiyama S, Akiyama E, Iwashita S, Kurokawa H, Ohba K, *et al.* Dipeptidyl peptidase-4 inhibitor, sitagliptin, improves endothelial dysfunction in association with its anti-inflammatory effects in patients with coronary artery disease and uncontrolled diabetes. Circ J 2013;77:1337-44.
15. Feng X, Pan J, Li J, Zeng C, Qi W, Shao Y, *et al.* Metformin attenuates cartilage degeneration in an experimental osteoarthritis model by regulating AMPK/mTOR. Aging (Albany NY) 2020;12:1087-103.
16. Alvarez-Soria MA, Herrero-Beaumont G, Sánchez-Pernaute O, Bellido M, Largo R. Diacerein has a weak effect on the catabolic pathway of human osteoarthritis synovial fibroblast – Comparison to its effects on osteoarthritic chondrocytes. Rheumatology (Oxford) 2008;47:627-33.
17. Mastbergen SC, Bijlsma JW, Lafeber FP. Selective COX-2 inhibition is favorable to human early and late-stage osteoarthritic cartilage: A human *in vitro* study. Osteoarthritis Cartilage 2005;13:519-26.
18. Katagiri M, Ogasawara T, Hoshi K, Chikazu D, Kimoto A, Noguchi M, *et al.* Suppression of adjuvant-induced arthritic bone destruction by cyclooxygenase-2 selective agents with and without inhibitory potency against carbonic anhydrase II. J Bone Miner Res 2006;21:219-27.
19. Tegeder I, Pfeilschifter J, Geisslinger G. Cyclooxygenase-independent actions of cyclooxygenase inhibitors. FASEB J 2001;15:2057-72.
20. Abramson SB, Attur M. Developments in the scientific understanding of osteoarthritis. Arthritis Res Ther 2009;11:227.
21. Goldring MB. Osteoarthritis and cartilage: The role of cytokines. Curr Rheumatol Rep 2000;2:459-65.
22. Hardy MM, Seibert K, Manning PT, Currie MG, Woerner BM, Edwards D, *et al.* Cyclooxygenase 2-dependent prostaglandin E2 modulates cartilage proteoglycan degradation in human osteoarthritis explants. Arthritis Rheum 2002;46:1789-803.
23. Mastbergen SC, Jansen NW, Bijlsma JW, Lafeber FP. Differential direct effects of cyclo-oxygenase-1/2 inhibition on proteoglycan turnover of human osteoarthritic cartilage: An *in vitro* study. Arthritis Res Ther 2006;8:R2.
24. Mastbergen SC, Bijlsma JW, Lafeber FP. Synthesis and release of human cartilage matrix proteoglycans are differently regulated by nitric oxide and prostaglandin-E2. Ann Rheum Dis 2008;67:52-8.
25. Watanabe Y, Namba A, Honda K, Aida Y, Matsumura H, Shimizu O, *et al.* IL-1beta stimulates the expression of prostaglandin receptor EP4 in human chondrocytes by increasing production of prostaglandin E2. Connect Tissue Res 2009;50:186-93.
26. Arunrukthavon P, Heebthamai D, Benchasiriluck P, Chaluay S, Chotanaphuti T, Khuangsirikul S. Can urinary CTX-II be a biomarker for knee osteoarthritis? Arthroplasty 2020;2:6.
27. Tsutsumi R, Ito H, Hiramitsu T, Nishitani K, Akiyoshi M, Kitaori T, *et al.* Celecoxib inhibits production of MMP and NO via down-regulation of NF-kappaB and JNK in a PGE2 independent manner in human articular chondrocytes. Rheumatol Int 2008;28:727-36.
28. Gault VA, Lennox R, Flatt PR. Sitagliptin, a dipeptidyl peptidase-4 inhibitor, improves recognition memory, oxidative stress and hippocampal neurogenesis and upregulates key genes involved in cognitive decline. Diabetes Obes Metab 2015;17:403-13.
29. Coskun ZM, Koyuturk M, Karabulut S, Bolkent S. CB-1R and GLP-1R gene expressions and oxidative stress in the liver of diabetic rats treated with sitagliptin. Pharmacol Rep 2017;69:822-9.
30. Zhu S, Gu Y, Wang W, Bai J, Ge G, Zhang W, *et al.* Sitagliptin ameliorates advanced glycation end-product (AGE)-induced degradation of extracellular matrix in human primary chondrocytes. Am J Transl Res 2019;11:2775-83.
31. Wang Z, Xu M, Bai J, Ge G, Guo X, Yu B, *et al.* Vildagliptin reduced extracellular matrix degradation in human primary chondrocytes. Eur J Pharmacol 2019;844:49-55.
32. Reinhold D, Bank U, Täger M, Ansorge S, Wrenger S, Thielitz A, *et al.* DP IV/CD26, APN/CD13 and related enzymes as regulators of T cell immunity: Implications for experimental encephalomyelitis and multiple sclerosis. Front Biosci 2008;13:2356-63.
33. Preller V, Gerber A, Wrenger S, Togni M, Marguet D, Tadje J, *et al.* TGF-beta1-mediated control of central nervous system inflammation and autoimmunity through the inhibitory receptor CD26. J Immunol 2007;178:4632-40.