Original Article

The Possible Effect of Trimetazidine and Sitagliptin on Chronic Model of Arthritis in Male Albino Rats; Histomorphometric Study

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ABSTRACT

Background: Osteoarthritis is the most prevalent type of arthritis. It is an important cause of pain and disability in elder adults. Trimetazidine and sitagliptin have anti-inflammatory effects.

Material and Methods: Fifty adult Wister male albino rats divided into 4 groups. Group I: Five rats received a single dose of 1ml 0.9% saline intra-articular. Group II: Fifteen rats received a single dose of 1mg monosodium iodoacetate (MIA) diluted in 0.9% saline intra-articular and 1 ml of 1% gum acacia per gavage daily for 4 weeks. Group III: Fifteen rats received a single dose of 1mg MIA diluted in 0.9% saline intra-articular concomitant with oral administration of trimetazidine suspended in 1% gum acacia, in a dose of 10 mg/kg/day for 4 weeks. Group IV: Fifteen rats received a single dose of 1mg MIA diluted in 0.9% saline intra-articular concomitant with oral administration of sitagliptin suspended in 1% gum acacia, in a dose of 10 mg/kg/day for 4 weeks.

Results: Intra-articular injection of MIA induced arthritis. Trimetazidine and sitagliptin insignificantly increased the circulating levels of serum inflammatory cytokines; COMP, IL-1 β, and TNF α. While the circulating levels of TGF-β1 in the arthritis group was significantly reduced compared to the control group. Concomitant administration of trimetazidine with MIA showed normal organized chondrocytes and normal bone trabeculae. Concomitant administration of sitagliptin showed improvement of histological features, normal organized chondrocytes, normal bone trabeculae and decreased resorption cavities. Histomorphometric evaluation of the percent area of the articular cartilage thickness revealed a significant decrease in arthritis group and a significant rise in both sitagliptin and trimetazidine groups.

Conclusion: Sitagliptin and trimetazidine may have protective effect against arthritis.

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Key Words: Arthritis, cytokines, sitagliptin, trimetazidine.

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INTRODUCTION

Osteoarthritis (OA) is the most prevalent type of arthritis. OA is an important cause of pain and impairment in older adults[1]. With age, the prevalence of OA increases. In women aged more than 45 years, it is more common and is anticipated to rise due to an increase in the general population age[2]. Arthralgia, stiffness and loss of function are caused by osteoarthritis, which affects the hip, knee, hand, spine and other weight-bearing joints[3].

Tumor necrosis factor - alpha [TNF- α] is part of a series of cytokines expressed in systemic inflammation that stimulate acute phase reactions. TNFα controls the immune cells and stimulates the expression on the cell surface of molecules, resulting in adhesion[4].

TNF α secretion can be induced by endotoxins and various microbial products, immune complexes, physical damage, and various inflammatory stimuli[5].

Sitagliptin is one of the antidiabetic medications which inhibit dipeptidyl peptidase-IV (DPP-IV) enzyme that breaks down incretins; glucagon-like peptides-1 and glucose-dependent insulin-tropic polypeptides-1. The cell membranes mediating pro-inflammatory signals are expressed as CD26 by DPP-IV. This is how the anti-inflammatory effect of sitagliptin occurs[6].

Trimetazidine (TMZ) is an anti-angina medication that regulates the proper function of trans-membrane ion channels by controlling the production of intracellular ATP under ischemic conditions. TMZ prevents calcium accumulation in cardiac muscle, controls cellular acidosis and decreases free radical oxygen levels. TMZ can suppress neutrophil activation and this action can reduce tissue damage mediated by post-ischemic heart injury, a significant mechanism that explains the health effects and anti-inflammatory activity of this drug on ischemic heart disease[7]. This research was conducted to evaluate the possible anti-inflammatory effect of trimetazidine and sitagliptin on the joints in case of arthritis.

MATERIAL

Chemicals

Sitagliptin (Januvia 100 mg tablets, Merck & Co.), trimetazidine (35 mg tablets, Amrya Pharm. Ind., Cairo, Egypt), Monosodium iodoacetate (MIA), powder, Sigma)

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was purchased from Bristol-Myers Squibb. Januvia 100 mg tablet was dissolved in 10 ml solution of 0.5 carboxymethyl cellulose to give a suspension of 10 mg /ml[3]. Trimetazidine 35 mg tablet was crushed and suspended in 3.5 ml of 0.5% carboxymethyl cellulose to give a concentration of 10 mg/ml[8].

Inflammatory cytokines: cartilage oligomeric matrix protein (COMP), interleukin -1 β (IL-1 β), transforming growth factor β1 (TGF- β1), tumour necrosis α (TNF α) and matrix metalloproteinase 3(MMP3) kits were obtained from Sigma.

Animals

Fifty adult Wister male albino rats with body weights from 150 - 200 gm were involved in the present research. In standard light and temperature conditions, the rats were kept in animal cages, with free access to water and food. Alexandria University's Ethical Guidance on Laboratory Animals and the National Institute for the Use and Care of Laboratory Animals (NHI Publications No80-23, updated 1978-1978) approved the present research[9]. Further the approval of Alexandria Faculty of Medicine Ethical Committee was obtained.

METHODS

Groups

Group I (control group)

Five rats received intra-articular 1ml 0.9% saline solution in the left knee.

Group II (arthritis group)

Fifteen rats received single injection of 1 mg of MIA (to induce osteoarthritis) diluted in 0.9% saline in the left knee and 1 ml of 1% gum acacia per oral gavage daily for 4 weeks[10].

Group III (Trimetazidine group)

Fifteen rats received single injection of 1 mg of MIA diluted in 0.9% saline in the left knee concomitant with oral administration of TMZ suspended in 1% gum acacia, in a dose of 10 mg/kg/day for 4 weeks[11].

Group IV (Sitagliptin group)

Fifteen rats received single injection of 1 mg of MIA diluted in 0.9% saline in the left knee concomitant with oral administration of sitagliptin suspended in 1% gum acacia, in a dose of 10 mg/kg/day for 4 weeks[3].

Biochemical studies

At the end of the study (4 weeks), the rats were anaesthetized and sacrificed. Blood was collected from the aorta to analyze serum inflammatory cytokines; COMP, IL-1 β, TGF- β1, TNF α and MMP3.

No mortality was reported during the study period.

Histological studies

The distal end femur and proximal end tibia with a joint space between them were removed using a bone cutter after sacrificing the animals on day 28, and any traces of muscle tissue were cleaned up. The bones were fixed in 10% formal aldehyde, then put in molds and inserted into paraffin to form paraffin blocks for histo-morphometric parameters. The specimens were longitudinally sectioned (thickness 3-5 μm) and prepared for Haematoxylin and Eosin (H & E)[12] and Gomori's trichrome staining[13]. Digital images from H&E stained sections were obtained by digital camera connected to microscope (Olympus BX41). The image magnifications were (100X) and (400 X).

Histomorphometric studies

Using the computer system image analyzer, the data was obtained (Leica Qwin 500, Leica, Cambridge, England). For each slide, the morphometric analysis used 3 histological sections, with a total of 9 sections per animal. The test was performed on Gomori trichrome stained slides. The software was adjusted to convert the measurement units (pixels) of software to micrometer. It was used to calculate the percentage area of articular cartilage. The area was calculated using lower magnification for ten separate randomly selected microscopic fields for each group[3].

Statistical Analysis

Results have been expressed as mean ± standard deviation. The one-way analysis of variance with Dunnett's post hoc test was used to analyze all experimental data. Values of $p \leq 0.05$ were considered statistically significant[14].

RESULTS

Biochemical results

(Table 1, Bar Charts 1-5) show the mean level and the standard deviation of different biochemical parameters of the different research groups.

In group II (arthritis group), the levels of COMP, IL-1 β, TNF α, and MMP3 were significantly increased in comparison with the control group while the TGF- β1 was significantly reduced compared to the control group.

The levels of COMP, TGF-β1, TNF a, and MMP3 were significantly increased in group III (Trimetazidine group) compared to the control group, while the increase in IL-1 β was insignificant.

In group IV (sitagliptin group), the levels of COMP, TGF- β1, TNF α, and IL-1 β were significantly increased compared to the control group while the increase in MMP3 was insignificant.

Histological results

A- Haematoxylin and Eosin stain

Microscopic examination of H&E stained sections of the distal end femur and the proximal end tibia of the

control group showed normal bone trabeculae and normal appearance of the epiphyseal plate of hyaline cartilage with well-organized chondrocytes and homogenously stained cartilage matrix (Figure 1). On the contrary, sections of the arthritis group showed disrupted thin bone trabeculae, epiphyseal plates with disorganized zones of chondrocytes and decreased eosinophilia of the matrix (Figures 2-4).

Microscopic examination of H&E stained sections of the distal end femur and the proximal end tibia of the trimetazidine group showed normal organized chondrocytes and normal bone trabeculae (Figure 5). Sections of the sitagliptin group illustrated improvement of the histological features in the form of normal organized chondrocytes, normal bone trabeculae and decreased resorption cavities (Figure 6).

B-Gomori's Trichrome stain

Microscopic examination of Gomori's Trichrome stained sections of the distal end femur and the proximal end tibia of the of control group showed highly organized chondrocytes embedded in an abundant bluish matrix at the articular cartilage (Figure 7). The matrix of the articular cartilage in the arthritis group had a weak staining affinity and appeared faint basophilic (Figure 8).

Microscopic examination of Gomori's Trichrome stained sections of the distal end femur and the proximal end tibia of the trimetazidine and sitagliptin groups showed the matrix of articular cartilage with a less reduced staining affinity in comparison with control group (Figures 9,10).

Morphometric results

Histomorphometric assessment of the percentage area of articular cartilage thickness (Bar Charts 6, Table 2) showed a substantial decrease in the arthritis group compared with control animals ($p < 0.05$). However, relative to the control group, these morphometric parameters were significantly increased ($p<0.05$) in both the sitagliptin and trimetazidine groups.

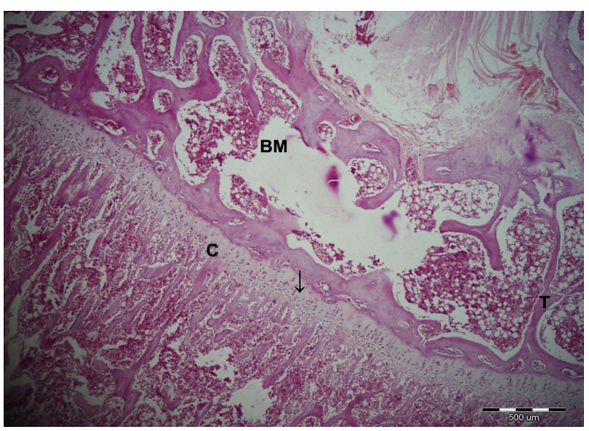


Fig. 1: A photomicrograph of the distal end of femur of the control rat showing normal histological appearance of epiphyseal plate of hyaline cartilage. Normal organized chondrocytes (C) and the cartilage matrix (↓) appears homogenously stained.BM: bone marrow,T: trabeculae. (H&E stain, Mic.Mag X 100)

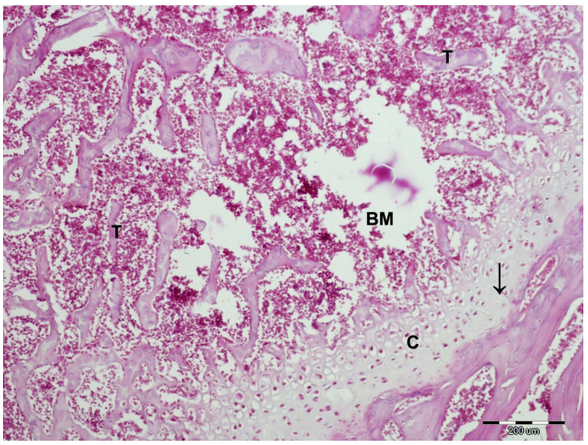


Fig. 2: A photomicrograph of distal end femur and proximal end tibia of the arthritis group showing the articular side of the epiphyseal plates with disorganized zones of chondrocytes (C). The bone trabeculae (T) appeared disrupted, decreased eosinophilia of the matrix (↓). BM: bone marrow. (H&E stain, Mic.Mag X 100)

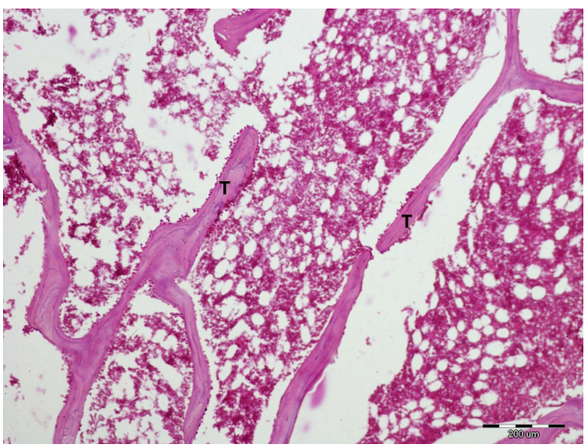


Fig. 3: A photomicrograph of distal end femur of the arthritis group showing the articular side of the epiphyseal plates demonstrating thinning of bone trabeculae (T). (H&E stain, Mic.Mag X 100)

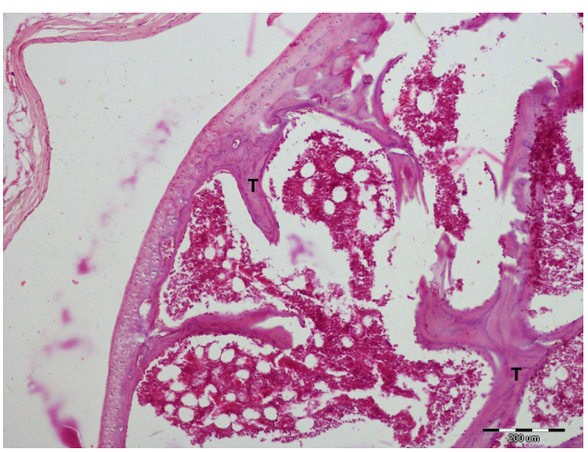


Fig. 4: A photomicrograph of distal end femur and articular cartilage of the arthritis group showing the articular side of the epiphyseal plates with degenerative changes and thinning of bone trabeculae (T). (H&E stain, Mic.Mag X 100)

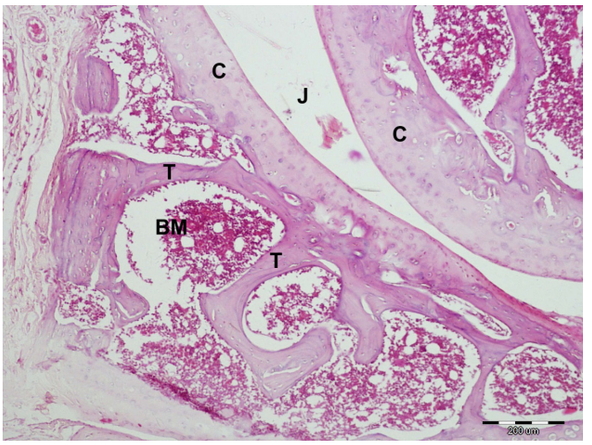


Fig. 5: A photomicrograph of distal end femur and articular cartilage of the trimetazidine group showing the presence of joint cavity (J), normal organized chondrocytes (C) and normal bone trabeculae (T). BM: bone marrow. (H&E stain, Mic.Mag X 100)

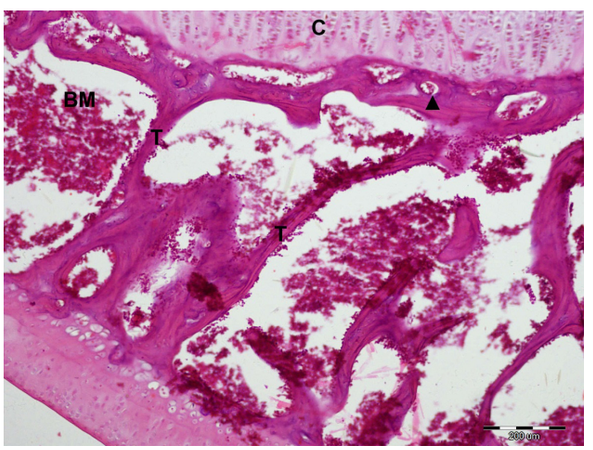


Fig. 6: A photomicrograph of distal end femur and articular cartilage of the sitagliptin group showing slight improvement of the histological features, of the chondrocytes (C) and bone trabeculae (T) and decreased resorption cavities (▲). BM: bone marrow. (H&E stain, Mic.Mag X 100)

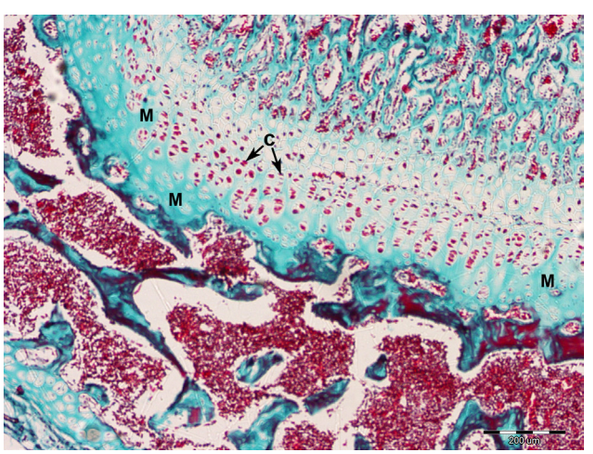


Fig. 7: Photomicrograph of the control group showing highly organized chondrocytes (C) embedded in anabundant bluish extracellular matrix (M) at the articular cartilage. (Gomori'sTrichrome stain, Mic.Mag X 100)

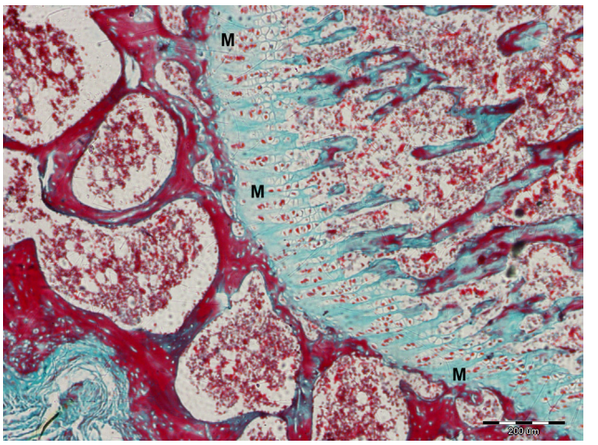


Fig. 8: Photomicrograph of arthritis group showing extracellular matrix (M) of articular cartilage having a weak staining affinity and appeared faint basophilic. (Gomori'sTrichrome stain, Mic.Mag X 100)

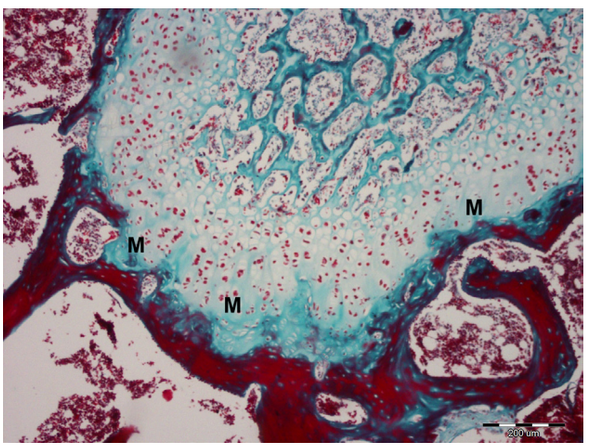


Fig. 9: Photomicrograph of trimetazidine group showing the matrix (M) of articular cartilage with a less reduced staining affinity in comparison with control group. (Gomori'sTrichrome stain, Mic.Mag X 100)

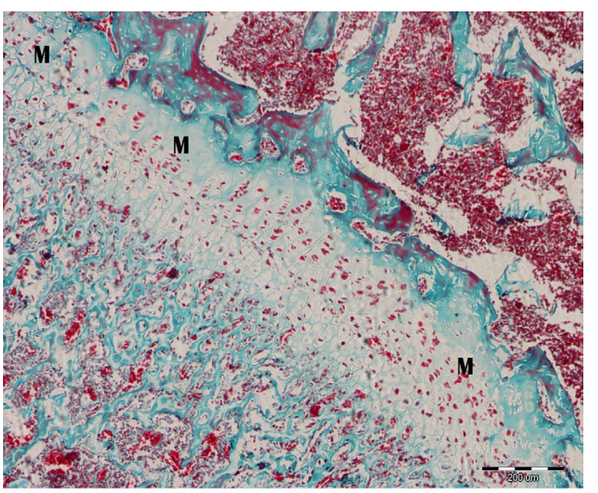


Fig. 10: Photomicrograph of sitagliptin group showing the matrix (M) of articular cartilage with a less reduced staining affinity in comparison with control group. (Gomori'sTrichrome stain, Mic.Mag X 100)

Table 1: Shows the mean level and the standard deviation of different biochemical parameters among different study groups

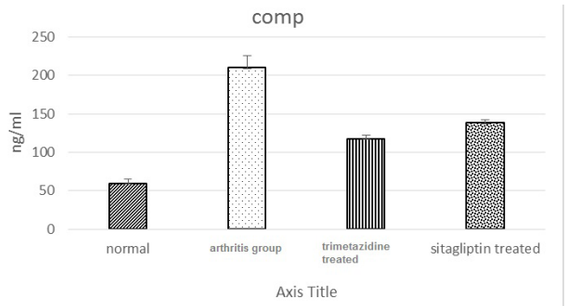
Group	COMP (ng/ml)	IL-1 β (pg/ml)	TGF- β1 (ng/ml)	TNF α (pg/ml)	MMP3 (ng/ml)
Group I	64(±1.21)	68 (±0.1)	150(±1)	63(±1.1)	3(±0.1)
Group II	212(±1.3)	160(±0.21)	98(±1)	152(±1.1)	10(±0.11)
Group III	125(±1.1)	80(±0.21)	170(±1)	98(±1.2)	4.8(±0.11)
Group IV	150(±1.2)	100(±0.1)	230 (±1)	120(±1.11)	3.2(±0.01)

COMP: Cartilage oligomeric matrix protein, IL-1 β: Interleukin -1 β, TGF- β1: Transforming growth factor β1, TNF α: Tumour necrosis α, MMP3: Matrix metalloproteinase 3

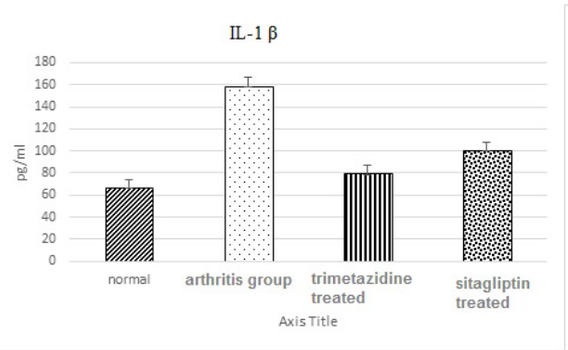
Table 2: Comparison between the study groups regarding the percent area of the thickness of articular cartilage (in µm)

Percent of area	Group I	Group II	Group III	Group IV
Range	45.8-90.1	15.7-20.2	25.3-88.9	25.3-73.2
Mean	75.6	19.1	69.0	59.7
S.D.	±13.1	±4.2	±16.9	±17.5
ANOVA			19.1	
P			0.0022*	
P1			0.0036*	
P2			0.021*	
P3			0.038*	

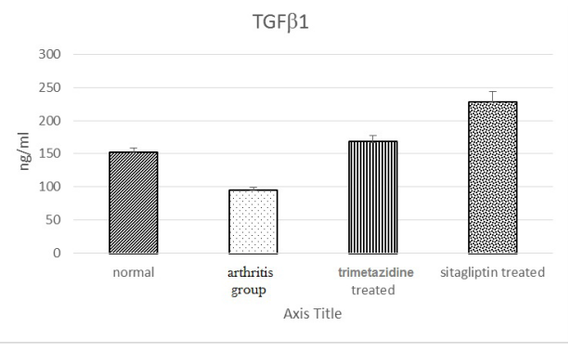
P is significant if < 0.05
P1 comparison between arthritis and control
P2 comparison between sitagliptin and control
P3 comparison between trimetazidine and control



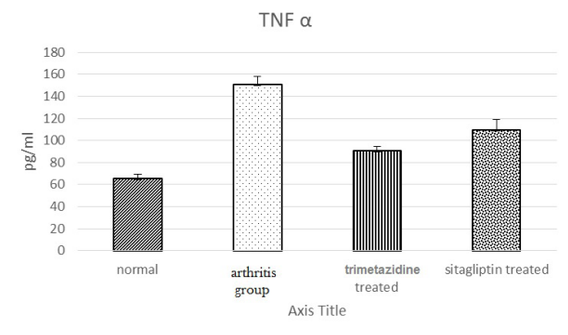
Bar Chart 1: Bar chart showing the mean of inflammatory cytokine COMP among the study groups.



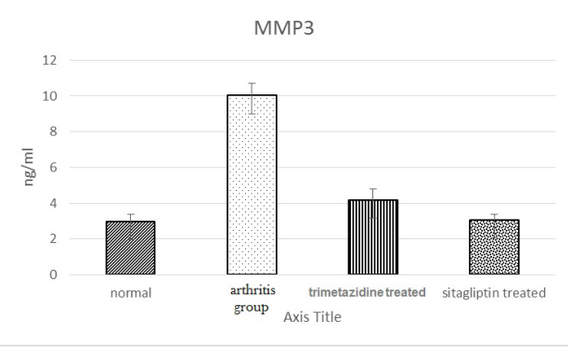
Bar Chart 2: Bar chart showing the mean of inflammatory cytokine IL-1 β among the study groups.



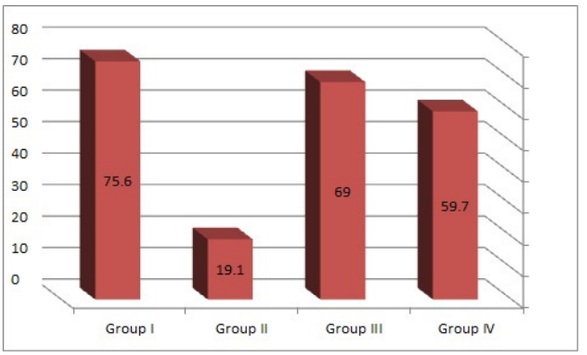
Bar Chart 3: Bar chart showing the mean of inflammatory cytokine TGF β1 among the study groups.



Bar Chart 4: Bar chart showing the mean of inflammatory cytokine TNF α among the study groups.



Bar Chart 5: Bar chart showing the mean of inflammatory cytokine MMP3 among the study groups.



Bar Chart 6: Bar chart showing comparison between the study groups regarding the percent area of the thickness of articular cartilage (in μm).

DISCUSSION

The pathology of OA was studied in an animal model that simulates the structural changes associated with OA. Intra-articular rat injection of MIA, a glycolysis suppressor, induces articular cartilage loss close to that seen in human OA[13]. In the present study, a single injection of 1 mg MIA diluted in 0.9% saline in the left knee was done to induce OA.

Anti-inflammatory cytokines are a set of immune-regulatory factors that regulate the pro-inflammatory effects. Cytokines function to control the human immune system response by joining to particular cytokine suppressors and certain cytokine receptors. Their physiological participation in inflammation and pathological activity in systemic inflammatory states is being increasingly recognized[15].

In the present study, in group II (arthritis group), the levels of COMP, IL-1 β, TNF α, and MMP3 were significantly increased compared to control group while the TGF- β1 was significantly reduced in comparison with control group.

Mechanical damage causes local inflammation, inducing the extracellular matrix to be deposited. This inflammatory process leads to the development of many anti-inflammatory and pro-inflammatory factors caused by complex interactions between various cell types[16]. As arthritis is an inflammatory process affecting the joints, this could explain the increased inflammatory cytokines in the present study.

The levels of COMP, TGF-β1, TNF α, and MMP3 in the present study were significantly increased in group III (Trimetazidine group) as compared to control group, meanwhile the increase in IL-1 β was insignificant.

It was found that there was a beneficial impact on the inflammatory profile and endothelial function in a clinical practice study of Trimetazidine[17]. In this research, inflammatory cytokines are increasing because these cytokines take time to become normal.

In group IV (sitagliptin group), the levels of COMP, TGF- β1, TNF α, and IL-1 β were significantly increased in comparison with control group while the increase in MMP3 was insignificant.

In a Sitagliptin research has shown that serum inflammatory markers such as low density lipoproteins (LDL), C- reactive protein (CRP), and TNF α have significantly reduced serum inflammatory markers. On the other hand, sitagliptin increased the inflammatory cytokine levels of IL-10[18]. Receptor affinity may explain the unique rise in some cytokines and the decrease in others.

The present findings are congruent with previous studies showing that the IL-8 / IL-8R pathway can play a key role in the pathogenesis of psoriasis[19,20]. But their rule in pathogenesis of OA is not clearly studied.

Trimetazidine is used commonly to treat coronary artery disease as a cellular mitochondrial anti-ischemic agent[19].

The main role of TMZ is to suppress the enzyme thiolase, which results in an increase in mitochondrial metabolism and a decline in myocardial fatty acid absorption and oxidation with the consequent activation of the oxidation of glucose[21].

Microscopic examination of the H&E stained sections of the distal end femur and the proximal end tibia of the trimetazidine group revealed normal structured chondrocytes and normal bone trabeculae. This could be explained by the antioxidant and anti-inflammatory effects of TMZ and is also due to the effect of inflammatory cytokines observed in the biochemical part of the study.

TMZ studies have revealed that it can act as an antioxidant, increase endothelial function, decrease the infiltration of ischemic neutrophils and inhibit the necrosis and apoptosis cycle[20].

Other studies have also shown that trimetazidine decreases the damage to the cell membrane caused by reactive oxygen species (ROS) and protects the tissue from free radicals[22].

ROS and NO-mediated nitric oxide damage are promoted by the release of pro-inflammatory mediators such as CRP, TNF-alpha, IL-1, and IL-8 from macrophages. Researches on coronary intervention revealed that TMZ has been shown to suppress the elevation of inflammatory markers such as CRP, TNF-alpha and NO levels[23].

DPP-IV inhibitors are a relatively new generation of oral antidiabetic medicinal products, with sitagliptin, the first medicinal product, approved in 2006 on the basis of test results demonstrating efficacy in HbA1c regulation[24].

The mechanism of action of the DPP-IV inhibitor is to block the trans-membrane DPP-IV glycoprotein present in the intestinal epithelia and other body tissues, including fibroblasts, T cells, and macrophages, including joint fluids and immune cells[25].

The anti-inflammatory effects of DPP-IV inhibitors explains its function in rheumatoid arthritis (RA),

characterized by inflammation, stiffness and weakness of the joints[26].

In the present work, microscopic examination of H&E stained sections of the distal end femur and the proximal end tibia of the sitagliptin group showed improvement of histological features in the form of normal organized chondrocytes, normal bone trabeculae and decreased resorption cavities.

Similarly, another study exploring the association between DPP-IV inhibitors and the risk of autoimmune disorders showed a lower risk of autoimmune disorders in type 2 diabetic patients[27]. This explains the anti-inflammatory effects observed in the joints of sitagliptin group in the present study.

In accordance with the present study, Kathe *et al*[25] observed that the risk of rheumatoid arthritis in patients with DPP-IV inhibitors was not significantly associated with the risk of rheumatoid arthritis compared to other second-line anti-diabetic therapies. However, evidence from case studies indicates that DPP-IV inhibitors could be associated with increased pain in the joints[28], the presence of multiple co-morbidities may explain this.

In the histomorphometric examination of the present work, treatment with oral trimetazidine and sitagliptin significantly increased the articular cartilage thickness towards normal which expresses their osteo-protective properties in MIA induced arthritis in rats.

CONCLUSION

These findings illustrate that oral trimetazidine and sitagliptin significantly reduce arthritis and inflammatory cytokines suggesting a chondroprotective effect.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

التأثير المحتمل لتريميتازيدين وسيتاجليبتين على نموزج الالتهاب المفصلي المزمن في ذكور الجرذان البيضاء. دراسة هيستومورفومترية

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الخلفية: هشاشة العظام هي أكثر أنواع التهاب المفاصل انتشارًا. إنه سبب مهم للألم والعجز لدى كبار السن. ترايميتازيدين وسيتاجليبتين لهما تأثيرات مضادة للالتهابات.

المواد والطرق: خمسون من الجرذان البالغةالذكور البيضاء البيضاء قسمت إلى ٤ مجموعات. المجموعةالاولي : تلقي خمسة جرذان جرعة واحدة من ١ مل ٠,٩٪ محلول ملحي داخل المفصل. المجموعه الثانية : تلقت خمسة عشر جرذا جرعة واحدة من ١ ملغ يودواسيتات أحادي الصوديوم (MIA) مخفف في ٠,٩٪ محلول ملحي داخل المفصل و ١ مل من ١٪ صمغ يومياً لمدة ٤ أسابيع. المجموعة الثالثة٣: تلقى خمسة عشر جرذًا جرعةواحدة من ١ ملغ MIA مخففة في ٠,٩٪ محلول ملحي داخل المفصل مع تناول من تريميتازيدين معلق في ١٪ عن طريق الفم بجرعة ١٠ مجم / كجم / يوم لمدة ٤ أسابيع. المجموعة الرابعة: خمسة عشر جرذا تلقت جرعة واحدة من MIA مخففة بنسبة ٠,٩٪ محلول ملحي داخل المفصل مع تناول سيتاجليبتين معلق في ١ ٪ ، بجرعة ١٠ مجم / كجم عن طريق الفم لمدة ٤ أسابيع.

النتائج: زاد الحقن داخل المفصل لالتهاب ب MIA المفاصل تريميتازيدين وسيتاغليبتين بشكل ضئيل من المستويات المتداولة من لسيتوكينات الالتهابية في الدم. COMP و IL-١ β و TNF α. بينما المستويات المتداولة لـ TGF-β١ انخفضت مجموعة التهاب المفاصل بشكل ملحوظ مقارنة بالمجموعة الضابطة. ما يصاحب ذلك من تناول تريميتازيدين كما أظهر MIA خلايا غضروفية منظمة طبيعية وترابيق عظمي طبيعي. أظهرت تناول السيتاجليبنين تحسن السمات النسيجية ، الخلايا الغضروفية المنظمة الطبيعية ، الترابيق العظمي الطبيعي وانخفاض التجاويف. أظهر التقييم النسيجي للنسبة المئوية لسماكة الغضروف المفصلي انخفاضًا ملحوظًا في مجموعة التهاب المفاصل وارتفاع كبير في كل من مجموعات السيتاجليبتين والترايميتازيدين.

الخلاصة: قد يكون للسيتاجليبتين والترايميتازيدين تأثير وقائي ضد التهاب المفاصل.