Caspian Journal of Environmental Sciences
Online ISSN: 1735-3866
Print ISSN: 1735-3033

Possible effects of glucosamine on gait assessment and lipid peroxidation in ovariectomized rabbits

Mohammed M.K. Albadan[1]*, Shaymaa Abdullah Ahmed[2], Fahdil Hussam[3], Sarab W. Alwash[4], Saba Kadhim Naser[5], Ahmed Ayad Abdo Alqader[6], Alzahraa S. Abdulwahid[7], Zainab H. A.[8], Kuanysh Syman[9]

1. People Friendship University of Russia (RUDN University) Moscow, Miklukho-Malaya street 7, Russia
2. Department of Anaesthesia Techniques, Al-Noor University College, Nineveh, Iraq
3. Medical Technical College, Al-Farahidi University, Iraq
4 Medical Laboratory Techniques Department, Al-Mustaqbal University College, 51001 Hillah, Babylon, Iraq
5. Medical Laboratory Techniques Department, Mazaya University College, Iraq
6. National University of Science and Technology, Dhi Qar, Iraq
7. Al-Hadi University College, Baghdad,10011, Iraq
8. Department of Pharmacy, Al-Zahrawi University College, Karbala, Iraq
9. Department of Biological Sciences, Institute of Natural Sciences and Geography, Abai Kazakh National Pedagogical University, Almaty, Kazakhstan

** Corresponding author's E-mail: Mohammed.Albadan@yahoo.com*

ABSTRACT

In routine physiological procedures and/or pathological conditions, the living tissues produce free radicals, especially reactive oxygen species (ROS). It has been well documented that the primarily responsible mechanism for cell damage and destruction would be the lipid peroxidation conducted by ROS. It is approved that human articular chondrocytes actively lead to significant ROS production. DNA damage and telomere shortening have been known as the most important consequences of any increase in ROS production. Therefore, the current research was designed to investigate the effect of pre- and post- osteoarthritis administration of glucosamine on induced osteoarthritis in rabbits. In this experiment, 20 adult female New Zealand white rabbits with an average weight of 2.14 ± 0.45 kg were used. Visual inspection evaluated the animals to be free of any joints and muscular disorders. The animals were randomly divided into 4 groups (n = 5); Group A was ovariectomized without any treatments, while rabbits in Group B were ovariectomized, and after radiographic confirmation of OA, they were administered 75 mg kg^{-1} glucosamine. Rabbits in Group C were neither ovariectomized nor administered glucosamine, while rabbits in Group D were ovariectomized and administered glucosamine immediately after ovariectomy. Rabbits' gaits were scored before ovariectomy and at 4, 8, 12, 18, and 24 weeks post-ovariectomy (PO). Stifle joints radiographs and blood samples were obtained at 12, 18, and 24 weeks PO. Gait assessment score (GAS) was significantly ($p < 0.05$) lower in group A than in groups B, C, and D. Plasma concentration of TBARS was higher in groups A and B than in groups C and D, while plasma SOD decreased significantly ($p < 0.05$) between weeks 4 and 12 PO in all the groups. However, there were no significant differences in plasma concentrations of GSH, GPx, GST, tCHOL, TRIG, HDL, and LDL in all the groups. It was concluded that glucosamine inhibits lipid peroxidation; its prophylactic use has no significant advantage over its post-OA use.

Keywords: Induced osteoarthritis, Lipid peroxidation, Oxidative stress.
Article type: Research Article.

Caspian Journal of Environmental Sciences, Vol. 21 No. 2 pp. 403-409 Received: Aug. 08, 2022 Revised: Nov. 16, 2022 Accepted: Jan. 28, 2023
DOI: 10.22124/CJES.2023.6534

Publisher: University of Guilan,

INTRODUCTION

In normal physiological procedures and/or pathological conditions, the living tissues produce free radicals, especially reactive oxygen species (ROS). It has been well documented that the primarily responsible mechanism for cell damage and destruction would be the lipid peroxidation conducted by ROS. The unconfined production of free radicals has been considered the most pivotal factor in induced tissue destruction through various pathophysiological disorders (Gbotolorun & Salako 2022). The results of the previously published works showed an association between aging and reduction in mitochondrial activity. This reduction in mitochondrial activity plays a crucial role in the age-related cell damage induced by ROS (Durairajanayagam 2018; Gbotolorun & Salako 2022). It is approved that human articular chondrocytes actively lead to significant ROS production. DNA damage and telomere shortening have been known as the most important consequences of any increase in ROS production. This, in turn, led to a dramatic reduction in matrix regeneration, apoptosis, and chondrocyte senescence (Chen *et al.* 2008). Cartilage degradation is directly associated with increments in ROS and pro-inflammatory cytokines and matrix metalloproteinase (MMP) contents.

Therefore, oxidative stress is directly linked with osteoarthritis (OA) and promotes cartilage damage, leading to an inflammatory response (Kyung *et al.* 2021). The most prevalent type of arthritis is known as osteoarthritis, which affects more than 70% of the over 50 years old human population. It accounted for 70% of hospital visits for dogs' and cats' knee, hip, elbow, and wrist joint disorders (Li *et al.* 2022). The imbalance between synthesis and degradation of chondrocytes' extracellular cartilage matrix led to severe damage to the articular cartilage. It is well documented that Interleukin-1 (IL-1), a pro-inflammatory cytokine secreted by macrophages, monocytes, and synovial cells, is responsible for developing AO (TenBroek *et al.* 2016).It is approved that glucosamine is a pivotal component of glycosaminoglycans. It has been known that glucosamine may induce proteoglycan synthesis and prevent catabolic enzyme activity such as metalloproteases (Bruyère *et al.* 2016). Despite the purported claim that glucosamine is chondroprotective, there appears to be controversy on the benefits of its prophylactic use. Therefore, the current study was designed to investigate the effect of pre- and post- osteoarthritis administrations of glucosamine on induced osteoarthritis in rabbits.

MATERIALS AND METHODS

Animals

Twenty adult female New Zealand white rabbits weighing an average of 2.14 0.45 kg were used in this experiment. Visual examination revealed the absence of joint and muscle abnormalities in the animals.

Ethics

The Research and Ethical Committee of the College of Veterinary Medicine in Kerbala, Iraq, approved and permitted this work.

Osteoarthritis induction

Experimental OA was induced using ovariectomy. The rabbits were pre-medicated with an intramuscular injection of 2% xylazine hydrochloride (XYL-M2®, VMD, Belgium) at the rate of 3.0 mg kg^{-1} described previously (Dadashpour Davachi *et al.* 2022). Afterward, anaesthesia was induced and maintained with an intramuscular injection of 5% Ketamine hydrochloride (Rotexmedica®, Trittau, Germany) at 50 mg kg^{-1}. The rabbits were placed on dorsal recumbency, with the hind limb restrained in extension. Five mL of 2% Lignocaine were infiltrated sub-dermally along the *linea alba*.

A skin incision measuring about 3 cm was made along the ventral midline. After meticulously dissecting the subcutaneous tissue, the *linea alba* was identified, and a stab incision was made on it. A pair of my-scissors were then used to lengthen the incision to acquire access to the abdominal cavity. The ovary was exteriorized by gripping the ovarian fat pad with tissue forceps, and the pedicle between the uterine horn and the ovary was ligated and removed. The remaining tissue was returned to the abdominal cavity. The *linea alba* and the muscle layer were closed using a simple continuous suture pattern with a size 2/0 chromic catgut; the subcutaneous layer was closed using a subcuticular suture pattern with a size 2/0 chromic catgut, and the skin was closed using a simple interrupted suture pattern with size 0 polyester.

Experimental Design

All 20 rabbits were randomly assigned into four groups (n = 5) as follows: (i) Group A comprised five rabbits that were ovariectomized but not treated with oral glucosamine; (ii) Group B comprised five rabbits that were ovariectomized and treated daily with 75 mg kg^{-1} of oral glucosamine for twelve weeks following radiographic confirmation of OA; (iii) Group C consisted of five rabbits that were neither ovariectomized nor treated with oral glucosamine; and (iv) Group D comprised five ovariectomized rabbits dosed daily with 75 mg kg^{-1} of glucosamine orally for 12 weeks post-ovariectomy (PO), followed by radiographic confirmation of OA at 12 weeks.

Radiographic Protocol

In a non-weight bearing extended caudo-cranial position, rabbits' anteroposterior radiographs of the femorotibial joints were obtained. The animals were sedated with an intramuscular injection of 5 mg kg^{-1} xylazine hydrochloride (XYL-M2®, VMD, Belgium). The sedative-treated animals were positioned in sternal recumbency with both hind legs extended caudally. A vertical X-ray beam was centered over the femorotibial joints and collimated from the mid-femur to the mid-tibia to produce radiographs. To evaluate the progression of the induced osteoarthritis, the radiographs were taken at 12, 18, and 24 weeks post ovariectomy. Femoro-tibial medial joint space width was graded as normal (grade 0), reduced (grade 1), or absent (grade 2). Osteophytes of the medial femoral condyle were graded independently based on their presence and size (0 = nonexistent, 1 = little, 2 = moderate, and 3 = severe). The medial fabella osteophytes were evaluated as either absent or present (grade 0 or grade 1 respectively).

Gait assessment evaluation

Gait assessment was subjectively evaluated for each rabbit. The assessments were conducted at 0, 4, 8, 12, 18, and 24 weeks PO. Scores ranging from 1- 4 were assigned to criteria such as the ability to bear weight on the legs, pain perception from the knees, and responses to walking and climbing.

Blood collection

About 5 mL of blood was collected from the jugular vein of each rabbit into a lithium heparin bottle. Blood samples were obtained at 12, 18, and 24 weeks PO for the determination of plasma concentrations of thiobarbituric acid reactive substance (TBARS), glutathione peroxidase (GPx), glutathione (GSH), glutathione –s- transferase (GST), superoxide dismutase (SOD), total cholesterol (tCHOL), total triglycerides (TRIG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL).

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Radiographic scores were compared using the Wilcoxon Rank sum test. Gait assessments were compared between the different groups using Mann's Whitney test. Plasma concentrations of TBARS, GSH, GST, GPx, SOD, tCHOL, TRIG, HDL, and LDL were analyzed using analysis of variance (ANOVA) for repeated measures. Values were significant at $p < 0.05$. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 17.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

The recorded data showed that three out of the five rabbits in group A (OA without glucosamine administration) were observed with difficulty walking and stiffness of the hind limbs 4 weeks after ovariectomy. The results revealed that the signs lasted for about three weeks, followed by improved gait and walking. In addition, the rabbits were observed with decreased appetite 4 weeks PO which lasted for five days. There were no observable changes in the gait and appetite of rabbits in groups B (OA + post-OA administration of glucosamine), C (No OA and No glucosamine administration) and D (OA + pre-OA administration of glucosamine) throughout the study

Gait assessment score significantly decreased in group A rabbits 4 weeks PO and then increased gradually up to 12 weeks PO where it then appeared to stabilize up to 24 weeks PO. The gait assessment score was significantly ($p < 0.05$) lower in group A than in groups B, C and D.

There were no significant differences in the gait assessment scores between rabbits in groups B, C, and D. Radiographic signs of OA were detected 12 weeks PO and were characterized by joint space narrowing and medial femoral condyle osteophyte formation. The radiographic score was significantly ($p < 0.05$) higher among rabbits

in group A than those in groups B, C, and D at 12 and 18 weeks PO (Table 1). However, there were no significant differences in the radiographic scores of rabbits in groups A, B, and D by week 24 PO. Although there was no significant difference in the radiographic scores between rabbits in groups B and D by 12 weeks PO, the radiographic scores were slightly higher in group A than in group B. Plasma concentration of TBARS was significantly ($p < 0.05$) higher in rabbits in groups A and B than in groups C and D. In groups A and B, the plasma concentration of TBARS increased up to 18 weeks PO and then decreased gradually. However, the plasma concentration of TBARS decreased in group C up to 18 weeks PO and, afterward, increased gradually. Plasma concentration of superoxide dismutase was significantly ($p < 0.05$) higher in groups A and D than in groups B and C at 4 weeks PO.

In all the groups, the plasma concentration of superoxide dismutase decreased significantly ($p < 0.05$) between the values at 4 and 12 weeks PO. All the groups showed plasma concentration of glutathione decreased up to 24 weeks PO. At the same time, there was no significant difference in glutathione concentration in all the groups. Also, the plasma concentration of glutathione peroxidase increased gradually up to 24 weeks PO in all the groups. At the same time, there was no significant difference in glutathione peroxidase concentration in all the groups.

The plasma concentration of glutathione-s-transferase was significantly ($p < 0.05$) higher in groups A and B than in groups C and D at 18 and 24 weeks PO, respectively. Similarly, the plasma concentration of glutathione-s-transferase increased significantly ($p < 0.05$) from 12 to 18 weeks PO.

Total plasma cholesterol concentration tended to increase in all the groups up to 12 weeks PO except for rabbits in group B. In general, there was no significant difference in the total plasma cholesterol concentration except in the group D, where the value was significantly ($p < 0.05$) higher at 12 weeks PO. The total plasma triglycerides tended to increase in group A, while it decreased in other groups. In general, there was no significant difference in the total plasma triglyceride concentration in all the groups. Plasma concentration of high-density lipoprotein was significantly ($p < 0.05$) higher in group A than in the other groups at 4 weeks PO. In general, there was no significant difference in the plasma concentration of high-density lipoprotein in all the groups except at 24 weeks PO, where it was significantly ($p < 0.05$) higher in group B than in other groups. Plasma low-density lipoprotein was higher in groups A and D than in groups B and C which tended to increase in groups A and B, while decreased in groups B and C.

DISCUSSION

The current study finding showed no significant differences in the gait assessment and radiographic scores when glucosamine was administered before the onset of OA and when it was administered after the onset of OA. However, oral glucosamine improved gait assessment scores and reduced radiographic scores following experimental OA in rabbits. In addition, the plasma concentration of TBARS was elevated in rabbits with experimental OA, while the plasma concentration of superoxide dismutase was decreased. Also, OA or treatment with glucosamine did not exhibit any significant effect on the plasma lipid profile. The early stages of OA are challenging to diagnose with radiography. Radiographic changes include joint effusion, joint space narrowing, osteophytes, and subchondral sclerosis at the later stages of OA (Krawetz *et al.* 2022). In this study, the significant radiographic changes observed were joint space narrowing, mainly affecting the medial compartment and mild osteophyte formation at the medial condylar aspect of the joint. The medial compartment appeared to be more affected than the lateral compartment because of the more severe joint space narrowing involving the medial compartment. Plasma concentration of TBARS increased gradually in the rabbits except for the control rabbits up to six weeks after commencement of treatment, suggesting that there is increased lipid peroxidation following ovariectomy in the rabbits and might explain the possible antioxidant role of both exogenous and endogenous estrogen. A previous human population study has also reported a significant increase in oxidative response in postmenopausal women (Ma *et al.* 2018).

The lower plasma concentration of TBARS in rabbits treated prophylactically with glucosamine probably suggests the antioxidant role of glucosamine. *In vitro* studies have shown that glucosamine inhibits cartilage catabolism and prevents IL-1β-induced increase in nitric oxide synthesis (Cason et al. 2014; Fenton *et al.* 2002). The prophylactic administration of glucosamine might have reduced the severity of lipid peroxidation, suggesting that prophylactic use of glucosamine might be advantageous in patients at high risk of developing osteoarthritis. The enzyme superoxide dismutase (SOD) catalyzes the dismutation of superoxide (O_2) radicals into oxygen or hydrogen peroxide. It is a crucial antioxidant defense in almost every live cell. Decreased expression of SOD has

been linked to an increase in the concentration of reactive oxygen species and the onset of osteoarthritis. In this study, the plasma concentration of SOD dropped four weeks after ovariectomy, indicating a probable reduction in the plasma concentration of this antioxidant in the blood. This is supported by the increased plasma level of TBARS at this period and suggests that increased lipid peroxidation occasioned by the absence of estrogen due to ovariectomy results in cartilage damage and increased lipid peroxidation. Glutathione is an essential antioxidant in plants and animals. It prevents damage to important cellular components caused by reactive oxygen species. Glutathione reduces disulfide bonds from within cytoplasmic proteins to cysteine by serving as an electron donor (Pompella *et al.* 2003; Kim *et al.* 2017).

Oxidized glutathione is reduced by the enzyme glutathione reductase, while glutathione-s-transferase in the cytosol, microsomes, and mitochondria is involved in the conjugation and reduction of glutathione. All of these form part of the body's antioxidant system, which protects cellular structures from damage by reactive oxygen species. In this study, the plasma concentration of glutathione decreased, while that of glutathione peroxidase and glutathione-s-transferase were elevated by the progression of osteoarthritis. This implies the depletion of the antioxidant systems of the blood and confirms the role of reactive oxygen species in the pathogenesis of OA (Panahi *et al.* 2016, Carlson *et al.* 2019). The absence of any significant difference in the plasma levels of the antioxidant between rabbits treated prophylactically with glucosamine and those in which glucosamine treatment commenced after OA could suggest that prophylactic glucosamine may not be a beneficial advantage over glucosamine administration following OA. This assertion is further supported by the lack of significant differences in the gait assessment and radiographic scores of the rabbits.

It has been shown that changes in blood lipoprotein fractions during inflammatory and non-inflammatory arthropathies are proportional to the disease's degree of inflammation (Lepetsos 2016). Experimental research revealed that during inflammation, the liver consumes amino acids primarily for the creation of inflammatory mediators rather than for the development of enzymes essential for lipid metabolism, resulting in a decrease in lipoprotein formation (Gundogdu *et al.* 2020). Since the inflammatory component of OA is limited, it is anticipated that the lipid profile changes associated with OA will be fewer than those of rheumatoid arthritis. In postmenopausal women, a positive link between HDL cholesterol and TBARS has been documented (Apak *et al.* 2016). In this study, the HDL cholesterol decreased by elevating TBARS. This might result from the inverse association between HDL cholesterol and insulin resistance.

In rheumatoid arthritis patients, abnormal lipoprotein patterns were characterized by low levels of serum tCHOL, LDL, VLDL, and TRIG, but in OA patients, altered lipid levels were characterized by an upraise in tCHOL concentration (Abella *et al.* 2014). In addition, dogs with hip OA had elevated blood lipid levels, hypofibrinolysis, and enhanced platelet aggregation (Visser *et al.* 2015). This has been connected with the patient's decreased physical activity. In this Investigation, the plasma cholesterol levels increased as the rabbits' OA advanced. This may result from the ovariectomy-induced reduction of estrogen and its effect on cartilage degradation. One of the objectives of this study was to evaluate the usefulness of the alterations in lipid peroxidation, antioxidant systems, and plasma lipid as metabolomic and lipidomic biomarkers to monitor the efficacy of drugs for the management of osteoarthritis. The National Institute of Health, USA defines a biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Mobasheri *et al.* 2017).

The inconsistent results in the measured parameters between rabbits treated before OA and those treated after OA make it difficult to recommend any of the parameters as helpful biomarkers to monitor the drug's efficacy. These inconsistencies might be due to the parameters determined from the blood, where it is expected that the alterations in the plasma concentration of the substances might also reflect changes in other parts of the body apart from the joint. Thus, evaluation of the levels of these substances in the synovial fluid could probably give a better and more consistent result. Due to the results of the current study, the proposed model of induced osteoarthritis used in the current work would be a suitable model for studying postmenopausal OA in women. However, the biological alterations recorded in this study may not be the same as for all natural forms of OA. The effect of glucosamine on osteoarthritis reported here could be due to their anti-inflammatory effects on the regulation of the activity of IL-6 and MMP-3, reduction of lipid peroxidation, and consequent inhibition of the formation of reactive oxygen species. All in all, the limited time in the current experiment had not allowed for sufficient duration to complete the OA process. The findings of the current study are encouraging and further support the previous evidence on the ameliorative role of glucosamine on the progression of OA.

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Bibliographic information of this paper for citing:

Albadan, M, M, K, Ahmed, S, A, Hussam, F, Alwash, S, W, Naser, S, K, Alqader, A, A, A, Abdulwahid, A, S, H.A., Z, Syman, K 2023, Possible effects of glucosamine on gait assessment and lipid peroxidation in ovariectomized rabbits. Caspian Journal of Environmental Sciences, 21: 403-409.