The Physiological Role of the Hormone Adropin And Its Relationship to Oxidative Stress In Patients With Degenerative Arthritis

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ABSTRACT

This study examined adropin, oxidative stress, and antioxidants in osteoarthritis patients and a control group, as well as the relationship between adropin and these factors. To achieve this goal, we collected 150 samples from 30–65-year-old men and women. Osteoarthritis affected 92 people. Patients were classified by disease severity: mild, moderate, or severe. The control group of 58 people is used for comparison. Quantified were adropin, glutathione (GSH), uric acid (UA), and MDA. Results show significant Adropin reduction ($p \leq 0.0001$) in osteoarthritis patients (282 ± 158.6 ng/L) compared to the control group (433.5 ± 119.7 ng/L). Adropin significantly reduced severe osteoarthritis (111±24.8 ng/L) compared to moderate (336.3±99.1 ng/L) and mild (410.3±108.4 ng/L) instances compared to the control group ($p \leq 0.0001$). Adropin and GSH are positively correlated in severe ($r=0.446$, $p=0.004$) and moderate ($r=0.519$, $p=0.0013$) cases. Adropin is negatively correlated with MDA in mild ($r=-0.493$, $p=0.031$) and severe ($r=-0.542$, $p=0.001$) instances. Adropin negatively correlates with uric acid in moderate ($r=-0.525$, $p=0.012$) and severe ($r=-0.467$, $p=0.002$) cases. This study supports the use of adropin to diagnose and track osteoarthritis. We also find a link between adropin and oxidative stress, suggesting it contributes to disease progression.

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1. Introduction

Osteoarthritis is the second most common rheumatic disease after rheumatoid arthritis, affecting approximately 78 million adults worldwide by 2040 [1, 2]. Also, it is characterized by the loss of cartilage and the occurrence of pain when moving, finally leading to obstruction of movement [3, 4]. Although the causes of the disease are still unknown, some factors cause the disease, such as cytokine release and inflammatory factors in the synovial joint, as other risk factors, such as mechanical stress, changes in levels of vital compounds, metabolic disorder, and obesity and genetic factors that appear It has a role to play in the occurrence and development of the disease [5,6-7]. Females are more infected and have more severe illnesses, and the incidence increases after menopause [8]. Adropin was discovered by scientist Kumar in 2008 while studying the expressed gene that affects obesity in mice [9]. Adropin is also a peptide hormone whose molecular weight ranges from 45-59 kDa [10]. It is encoded by the Enho gene, which is expressed in the liver and increases 6-fold in the brain, indicating that it contains neuropeptide properties [11]. Adropin participates in energy balance and control of fat and glucose metabolism [12]. The concentration of adropin is inversely related to age; as we noted, its levels in men are higher than in women [13]. Oxidative stress is an imbalance that produces more reactive oxygen species (ROS) and reduces the body's natural antioxidant defenses [14]. ROS are active molecules or radicals generated during incomplete reduction of an oxygen molecule or during additional ROS reactions [15]. and these, in turn. It plays an important role in the human organism, such as destroying pathogens or regulating cellular signals [16]. Excessive production of ROS leads to damage to macromolecules such as lipids, proteins, and DNA [17]. Also, oxidative stress and high levels of ROS play an important role in the development of OA [18]. Glutathione (GSH) is a vital factor that protects the mitochondria from the resulting oxidative stress from a physiological and pathological perspective [19]. Malonaldehyde (MDA) is a biomarker used to measure the level of fat oxidation [20]. As for the antioxidant uric acid, it is a product of the metabolism of purines in humans and mammals and is excreted in the urine. Uric acid is one of the important antioxidants as it reduces the reaction of free radicals and works to eliminate free oxygen species [21]. Our study aimed to estimate the serum levels of adropin, oxidative stress, and antioxidants in patients and control and correlate adropin with the variables studied in patients.

2. Materials and Methods:

The current study was conducted from August 10 to December 2023.

2.1. Population Study:

The study included (150), where the number of patients was (92), of both sexes, where the number of women was (65), the men (27), whose ages ranged from (30-63) years, and (58) samples were chosen as a control group also from both sexes, where The number of women (38) and men (20) were aged (30-65). These samples were collected from the outpatient clinics of the joint unit at Ibn Sina Teaching Hospital in Mosul, Iraq. Patients with degenerative arthritis were divided according to the severity of the disease into three groups: mild, moderate, and severe, after being diagnosed by a specialist physician through clinical examination and x-rays. Patients with a medical history of other diseases, for example, cancer, kidney disease, and thyroid disease were excluded. And heart disease. After the doctor diagnoses the patient.

2.2. Sample Collection:

Blood is drawn using a clean, sterile needle of approximately (5 ml). It is placed in a clean gel tube and left for ten minutes at room temperature. Then, it is separated in a centrifuge at a speed of 3000 x g for five minutes. The serum is then separated and stored. -20°C until measurements are taken

2.3. Various Parameters Estimation:

2.3.1. Estimation of adoption:

Adropin was measured using an ELISA kit from BT LAB, and it containsCat.NO.E3231Hu of Chinese origin (bt-laboratory). The principle of ELISA involves using an enzyme system to detect the specific binding of the antigen and its corresponding antibody. The intensity of the concentration is directly proportional to the amount of antigen in the sample assayed at 450 nm.

2.3.2. Estimation of Glutathione (GSH):

Glutathione was estimated in serum using a modified method [22]. The principle of the method is based on reducing the thiol group of glutathione with a mannan solution containing 5,5-Dithio – bis (2-nitrobenzoic acid). As a result of the reduction, a colored substance is produced, and the absorbance intensity is measured. At a wavelength of (412 nm) in µmol/L.

2.3.3. Estimation of Malonaldehyde (MDA):

Malonaldehyde was estimated in blood serum using a modified method [23]. The principle of the method is based on the reaction in acidic media between malondialdehyde and thiobarbituric acid (TBA). It is a colored product, and the absorbance intensity is measured at a wavelength of (532nm) in µmol/L.

2.3.4. Estimation of Uric acid (UA):

Uric acid was estimated using a kit from BIOLABO Company, which is an enzymatic method where the uricase oxidizes uric acid to allantoin, carbon dioxide, and hydrogen peroxide, where the latter reacts with 4-aminophenazone and 4,2- dichlorophenolsulfonate in the presence of the peroxidase enzyme and appears. A red color resulted from the quinone imine compound, and the absorbance was measured at a wavelength of (520nm) in mmol/L [24].

2.4. Statistical analysis:

Statistical analysis was done using (SPSS) program version 25. The results are expressed as mean ± standard deviation (SD); an independent T-test was used to compare the two groups. ANOVA test employed the differentiation between the three groups. Also, Pearson's correlation coefficient was used to explore the relationship between the osteopontin level and the variables studied. P-values of 0.05 were considered statistically significant [25].

3. Result and Discussion:

3.1. Level of adropin in patients with osteoarthritis

The result in Table (1) and Figure (a1) showed a very high significant decrease($p \leq 0.0001$) in the level of the hormone adropin in OA patients (282±158.6 ng/L) when compared to healthy people (433.5±119.7 ng/L). Our study found that there is a decrease in adropin levels in the blood serum of OA patients compared with controls [26]. This decrease may be due to a relationship between adropin in serum and various disorders associated with low-grade chronic inflammation and the downstream of pro-inflammatory cytokines, such as diabetes and arteriosclerosis [27].

Table 1: Level of adropin in patients with osteoarthritis

Variables	(Mean±SD)		P-value
	Control, n=58	Patients, n=92	
Adropin (ng/L)	433.5 ± 119.7	***282 ± 158.6	0.0001
*** Significant at (p ≤0.0001); n= number; ng= nanogram; L= liter; SD= standard deviation			

3.2. Level of Antioxidant and Oxidative Stress Variables in OA Patients

The results in Table (2) and Figure (1b) showed that patients had a highly significant decrease (p≤0.0001) in antioxidants, including glutathione, in OA patients (14.4±5.6 µmol/L) compared to healthy people (7.8±5.7 µmol/L), among the types of non-enzymatic antioxidants, including, for example, the compound glutathione, which comes from an endogenous source and consists of three amino acids: glycine, glutamic acid, and cysteine [28]. The level of antioxidants in biological fluids and cartilage decreases with inflammatory changes, and this applies to our study, where we observed a lower level of GSH in OA patients compared to healthy controls [29]. And antioxidants, deduced in Table (2) and Figure (1c), uric acid showed a highly significant increase (p≤0.0001) in OA patients (264±57.2 mmol/L) compared to healthy people, (329.3±68.8). mmol/L). The increased concentration of uric acid in the synovial fluid is a catalyst for cartilage damage [30]. The deposition of uric acid in the form of crystals leads to the stimulation of oxidative stress within the cartilage cells, the effect, and the production of cytokines, including, for example, the main 1L-1β, which participates in the mechanisms behind the progression of OA [31]. Table (2) and Figure (1d), The oxidizing factor malondialdehyde showed a highly significant increase (p≤0.0001) in OA (2.3±1.3µmol/L) compared to healthy people. This is consistent with our study in OA. We observed high values of MDA, which affects the degradation and oxidation of collagen in cartilage [32].

Table 2: Level of Antioxidant and Oxidative Stress Variables in OA Patients

Variables	Control, n=58	Patients, n=92	P-value
	(Mean±SD)		
GSH (µmol/L)	14.4 ± 5.6	***7.8 ± 5.7	0.0001
Uric acid (mmol/L)	264 ± 57.2	***329.3 ± 68.8	0.0001
MDA (µmol/L)	2.3 ± 1.3	***5.4 ± 3.2	0.0001
*** significant at (p ≤0.0001); n= number; SD= standard deviation; µmol=Micromole; mmol= millimol; L=Liter; GSH=Glutathione; MDA=Malonaldehyde			

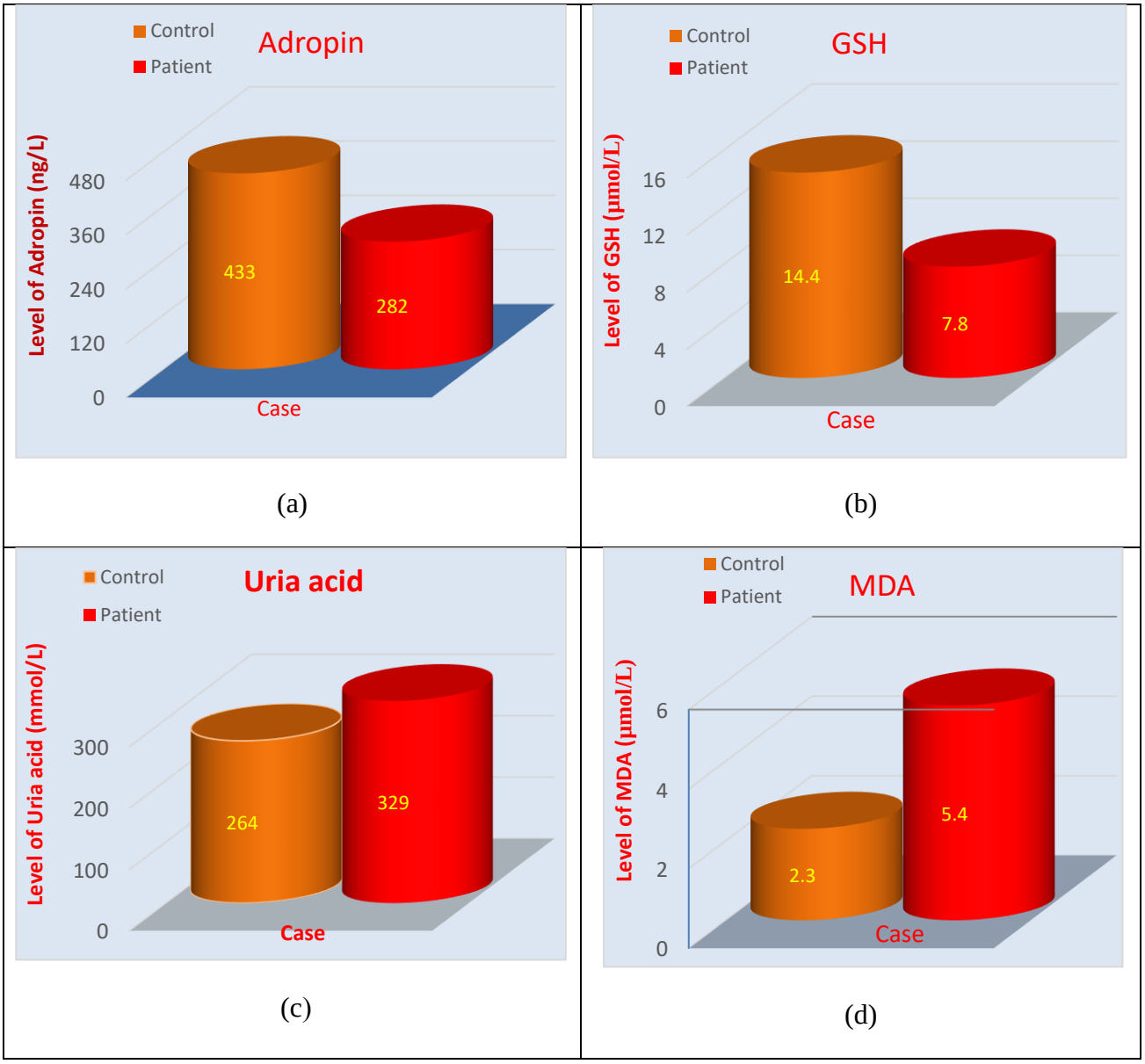

Figure 1: (a) The Adropin level in OA patients compared to control, (b) the GSH level in OA patients compared to control, (c) the uric acid level in OA patients compared to control, (d) the MDA level in OA patients compared to control. GSH= Glutathione; MDA= Malonaldehyde

3.3. Effect of the disease severity of osteoarthritis on the level of antioxidant and oxidative stress

The results in Table (3) and Figure (2 a) showed that there was no significant difference (p≤0.08) in the level of adropin in healthy people (433.5±119.6 ng/L) compared to mild case patients (410.3±108.4 ng/L). Also, they showed a high significant decrease (p≤0.001) in healthy people compared to the moderate case (336.3±99.1 ng/L). In contrast, it showed a very high significant decrease (p≤0.0001) in healthy people compared to the severe case (111±24.8 ng/L). Finally, in adropin it showed a very high significant decrease (p≤ 0.0001) in the moderate case compared to the severe case. Through this work, adropin could distinguish between patients and controls with a specificity of 90% and a sensitivity of 80%. These results were consistent with Gundogdu, who indicated for the first time that adropin levels decreased with OA compared to healthy people. The severity of the disease can also be determined according to the KL classification, as they indicated a decrease in adropin levels in parallel with an increase in the severity of the disease [33]. The results in Table (3) and Figure (2b) showed that there was no significant difference (p≤0.07) in the level of GSH in healthy people (14.4±5.59 µmol/L) compared to mild patients (12.1±5.4) µmol/L) and also showed a significant decrease (p≤0.001) in healthy people compared to the moderate case (8.6±4.1 µmol/L). In contrast, it showed a very high significant decrease (p≤0.0001) in healthy people compared to the severe case (2.7±1.2 µmol/L). Finally, GSH showed a very high significant decrease (p≤0.0001) in the moderate case compared to the severe case. The results in Table (3) and Figure (2 c) showed that there was no significant difference (p≤0.07) in the level of MDA in healthy people (2.3±1.3 µmol/L) compared to the mild case (2.9±1.5 µmol/L). Also, they showed a significant increase (p≤0.001) in healthy people compared to the moderate case (3.9±1.1 µmol/L), while it showed a significant increase (p≤0.0001). In healthy people, compared to the severe case (8.9±1.9 µmol/L). Finally, in MDA, the results showed a very high significant increase (p≤0.0001) in the moderate case compared to the severe case. This study may agree with [32]. The results in Table (3) and Figure (2 d), showed that there was no significant difference (p≤0.06) in the level of uric acid in healthy people (264±57.2 mmol/L) compared to mild case (288.6±59.8 mmol/L), and also showed a high significant increase in (p≤ 0.001) in healthy people compared to the moderate case (321.5±66.1 mmol/L). In contrast, it showed a very high significant increase (p≤0.0001) in healthy people compared to the severe case (377.4±47.2 mmol/L). Finally, in uric acid it showed a high significant increase (p ≤0.001) in the moderate case

compared to the severe case. As the severity of the disease progresses, the possibility of local chondrocyte death generates UA, which serves as a danger signal to activate the inflammatory responses of neighboring cells to enhance the pathological processes of OA, which may explain why higher SUUA levels were associated with synovitis. This explanation is consistent with what was stated in our study [34].

Table 3: Effect of the disease severity of osteoarthritis on the level of antioxidant and oxidative stress

Case / Variables	Control N=58 A	Mild N=36 B	Moderat N=22 C	Sever N=34 D	p-value			
					A vs b	A vs c	A vs d	C vs d
Adropin (ng/L)	433.5±119.6	410.3±108.4	336.3±99.1	111±24.8	0.08	0.001	0.0001	0.0001
GSH (µmol/L)	14.4 ± 5.59	12.1±5.4	8.6±4.1	2.7±1.2	0.07	0.001	0.0001	0.0001
MDA (µmol/L)	2.3 ± 1.3	2.9±1.5	3.9±1.1	8.9±1.9	0.08	0.001	0.0001	0.0001
Uric acid (mmol/L)	264 ± 57.2	288.6±59.8	321.5±66.1	377.4±47.2	0.06	0.001	0.0001	0.001
GSH= Glutathione; MDA=Malonaldehyde ; ng= nanogram ; mmol= millimol; µmol= micromole ;L=liter ; u= unit								

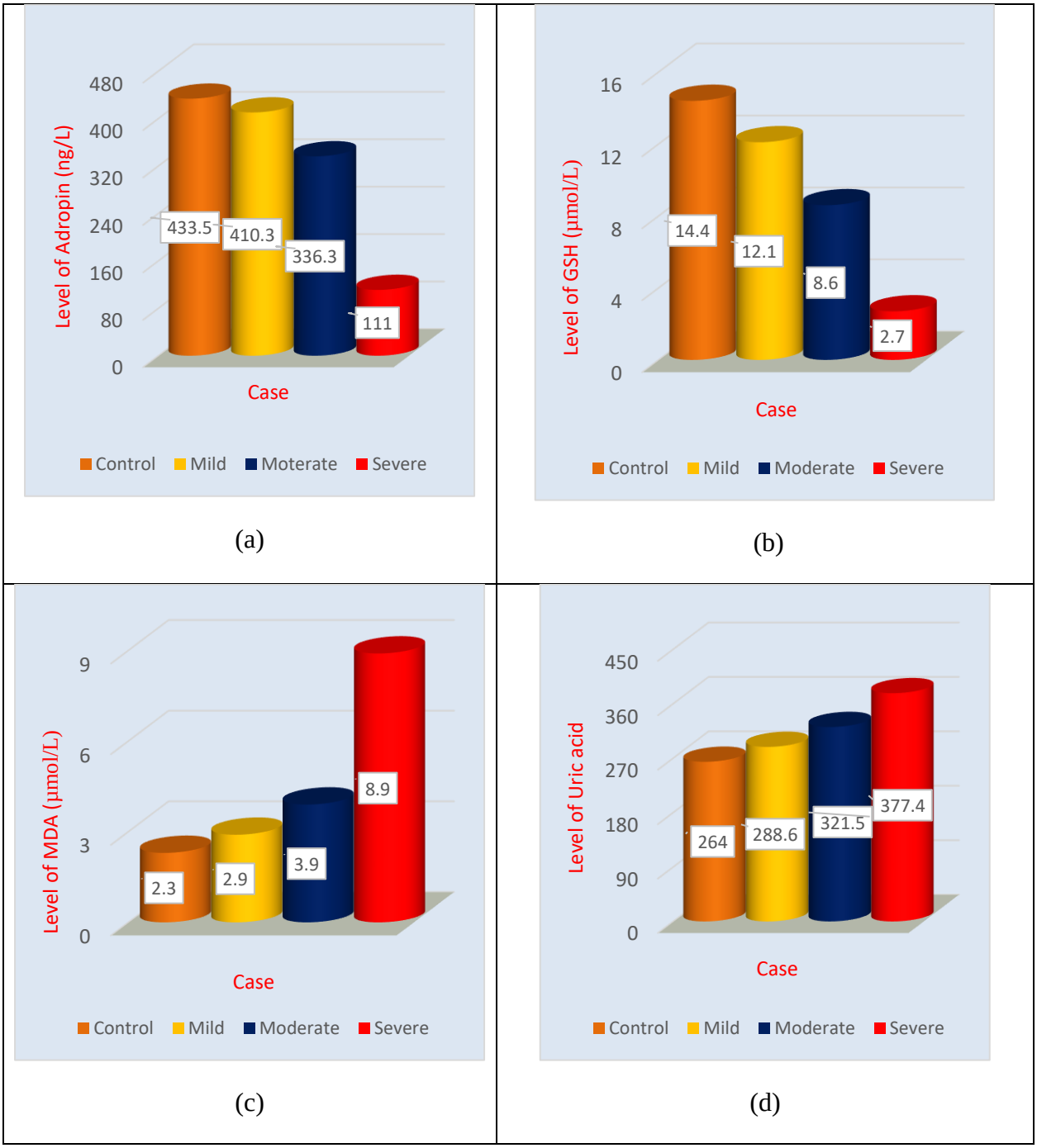

Figure 2: (a) Effect of the Disease Severity of osteoarthritis on the Adropin, (b) Effect of the Disease Severity of osteoarthritis on the GSH, (c) Effect of the Disease Severity of osteoarthritis on the MDA, (d) Effect of the Disease Severity of osteoarthritis on the Uric acid. GSH= Glutathione; MDA= Malonaldehyde

3.4. Correlation of adropin biochemical variables study in osteoarthritis.

The results, as shown in Table (4), showed that the relationship of adropin with the studied variables, GSH, MDA, Uric acid, showed a significant difference relationship with each of the MDA (r=-0.493; p≤0.031), Uric acid (r=-0.525; p≤0.012) in the moderate case and the relationship was negative, and showed a significant difference relationship with GSH (r=0.522; p≤0.01), in the moderate case and it was positive. On the contrary, it showed a highly significant relationship with both MDA (r=-0.542; p≤0.001) and Uric acid (r=-0.467; p≤0.002); in the severe case, the relationship was negative and showed a highly significant relationship with GSH (r=0.446; p≤0.004). In the severe case, the result was positive. While there is no relationship for adropin in the mild case, which reflects the effect of adropin as the severity of the disease progresses.

Table 4: Correlation of Adropin biochemical variables study in osteoarthritis

Biochemical Variable	Adropin, pearson correlation (r),p °		
	Mild	Moderate	Severe
GSH (µmol/L)	0.164 ; 0.338	*0.519 ; 0.013	**0.446 ; 0.004
MDA (µmol/L)	-0.29 ; 0.865	*-0.493 ; 0.031	**-0.542 ; 0.001
Uric acid (mmol/L)	-0.22 ; 0.897	*-0.525 ; 0.012	**-0.467 ; 0.002
*correlation is significant at the 0.05level; **correlation is significant at the 0.001 level; GSH= Glutathione; MDA=Malonaldehyde; ng= nanogram; mmol= millimol; µmol= micromole; L=liter U= unit.			

4. Conclusions

According to the obtained results, adropin can be considered one of the biochemical indicators for OA patients, as the results indicated a significant difference (p≤0.0001) between the levels of adropin in patients compared to healthy people. In addition to the relationship of adropin with vital indicators of oxidation and antioxidants such as GSH, Uric acid, and MDA, any defect throughout the body can be inferred.

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الدور الفسيولوجي لهرمون الادروبين وعلاقته بالاجهاد التاكسدي لدى مرضى المصابين بالتهاب المفاصل التنكسي

مصطفى عامر طه و زهراء محمد علي احمد حمودات

قسم الكيمياء كلية العلوم جامعة الموصل

المستخلص

يعد التهاب المفاصل التنكسي ثاني اكثر الامراض الروماتيزمية شيوعا بعد التهاب المفاصل الرثوي. هدفت الدراسة الى تقدير مستويات الادروبين والاجهاد التاكسدي ومضادات الاكسدة في مصل المرضى والاصحاء, وعلاقة الادروبين مع المتغيرات المدروسة في المرضى. اجريت الدراسة على 150 شخصا من كلا الجنسين (30-65) سنة. اثنان وتسعون منهم كانوا مرضى بالتهاب المفاصل التنكسي . وتم تقسيم هؤلاء المرضى حسب شدة المرض , الى خفيف, متوسط وشديد. ويمثل باقي البالغين مجموعة مراقبة, بما في ذلك 58 شخصا بالغ تم اختيارهم للمقارنة. تم قياس هرمون الادروبين ومضادات الاكسدة كلوتاثايون وحامض اليوريك وأكسدة المالونالديهايد. تشيرالنتائج الى انخفاض مستوى الادروبين بدرجة كبيرة ($p\leq0.001$) في المرضى OA (282±158.6 ng/L) مقارنة مع مجموعة السيطرة (433.5±119.7 ng/L). الادروبين انخفاض كبير للغاية ($p\leq0.0001$) في الحالة الشديد من OA (111±24.8 ng/ L) اكثر من المتوسط (336.3±99.1 ng/L) والخفيف (410.3±108.4 ng/L), عند مقارنة مع مجموعة السيطرة . هناك علاقة موجبة معنوية بين الادروبين مع GSH في كل من الحالات الشديدة (r=0.446, p=0.004) والمتوسطة (r=0.519, p=0.0013) .في المقابل هناك علاقة سالبة بين الادروبين مع MDA في كل من الحالات المتوسطة (r=-0.493, p=0.031) والشديدة (r=-0.542, p=0.001). وايضا هناك علاقة سالبة معنوية بين الادروبين وحامض اليوريك في الحالات المتوسطة (r=-0.525, p=0.012) والشديدة (r=-0.467, p=0.002) . نستنتج من هذه الدراسة امكانية استخدام هرمون الادروبين في تشخيص ومراقبة تطور التهاب المفاصل التنكسي . كما نلاحظ وجود علاقة الادروبين بالاجهاد التأكسدي مما يدل على ان الاجهاد التأكسدي يساهم في تطور المرض.