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Evaluation of Serum Interleukin 35 and Interleukin 38 and Electrolyte Level in the Sera of Rheumatoid Arthritis and Osteoarthritis Iraqi Females

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ABSTRACT: ***Background:*** *Rheumatoid arthritis (RA), is a disease that happened because autoimmune and inflammatory effects, it is mean that the human immune system offence healthy cells in the body mistakenly, resulting in inflammation (swelling) in the impacted portions of the body. Osteoarthritis (OA) is treated as the most famous form of joint arthritis.* ***Objective:*** *It is a slowly developed, disabling joint problem that decrease quality of life (QOL) and affects 14% of adults ages 25 and older and nearly 34% of those ages 65 and older. Interleukin elevation levels have been linked to autoimmune and degenerative diseases, thus in the current study.* ***Methods:*** *We tried to evaluate the level of interleukins (IL-35 and IL-38) in the two diseases and found the relationship between immune system response and disease severity. Three groups (RA, OA and control) have been used in the study.* ***Results:*** *The comparison between the three groups has been done and the results show a high significant increase in the level of IL-35 and IL-38 in both patients groups (RA and OA) as compared with control ($p<0.001$). Furthermore, a highly significant ($p<0.001$) elevated Na level with a significant ($p<0.001$) decrease in K and Ca levels was found in the RA and OA patients compared with the control.* ***Conclusions:*** *The study shows that the rise in the levels of IL-35 and IL-38 declares the instinctive role of interleukins and the immune system in the regulation and severity of RA and OA diseases, the role of this parameter may be clear in the controlling and monitoring the progression of diseases.*

KEYWORDS: *Rheumatoid arthritis; Osteoarthritis; IL-35; IL-38; Autoimmune disease*

INTRODUCTION

Osteoarthritis is a kind of degenerative pathological injury that affects the joint in the first place and happens because of the collapse of cartilage in the joint and implied bone that impacts 1 in 7 adults in the U.S [1]. It is supposed to be considered the fourth driving reason for disability all around the world. The most famous symptoms are joint harm and stiffness [2]. Sometimes the symptoms proceed tardily over years of infection. Other symptoms may include swelling of joints, lowering the scale of motion, and, after that, the back is impacted, and numbness of the hands and legs [3]. Rheumatoid arthritis (RA), is an autoimmune and inflammatory disease, which means that the immune system attacks healthy cells in the body by mistake [4], causing inflammation (painful swelling) in the affected parts of the body. Mainly impacts the body joints and is correlated with significant scales of disability and decreased QOL [5]. The RA can break down a person's articular cartilage. In normal situations [6], articular (have to handle the joints of the body) cartilage coats the end of bones that work together to make the joints of the body. This prevents the bones from rubbing with each other. If the articular cartilage has been demolished by RA, the bones will rub against each other, which is a very harmful thing, RA can also affect other tissues throughout the body and cause problems in organs such as the lungs, heart, and eyes [7]. Electrolytes are substances that have a natural positive or negative electrical charge when dissolved in water [8]. An adult's body

is about 60% water, which means nearly every fluid and cell in the human body contains electrolytes [9]. They help the body regulate chemical reactions; maintain the balance between fluids inside and outside the cells, and more [10].

IL-35 is a unique cytokine that is reflected as a substantial immune modulatory. IL-35 attaches to IL-12 family of cytokine that contains IL-12, IL-23, IL-27, and IL-35 [11]. Those cytokines are hetero dimers that share subunits and their receptors even participating subunits. Whereas IL-12 and IL-23 are pro-inflammatory cytokines [12], the decrease of IL-35 is not obvious. All of the studies which have been conducted on mice proposed the impact of IL-35 by strengthening an anti-inflammatory investment by enhancing Tregs and Bregs and inhibiting Th17 [13].

Interleukin-38 is included in the IL-1 family and the IL-36 subfamily. It is substantial in the host defense and inflammation [14]. Mammalian cells produce IL-38 which: may bind the IL-1 receptors kind I. It is expressed in the skin basal epithelia, in proliferating B cells of the tonsil, spleen and other tissues, like: the thymus, placenta, fetal liver, intestine, heart, and urogenital system [15]. Tissue, which doesn't play a special role in immune response, IL-38 is expressed in down quantity similar to the other members of the IL-1 family. Whether IL-38 does a turn in carcinogenesis or growth of the cancer is: unclear; IL-38 may affect host immunity because it is a negative regulator functionally related to receptor antagonists and involved in human inflammation and autoimmunity [16].

MATERIALS AND METHODS

Sample Collection

In this study, 80 female patients were involved and divided into two groups (40 females with RA and 40 females with OA), the participated patients ages ranged between (31-52) years. This study was carried out in the medical city of Baghdad Iraq, conducted during the time from January 2022 to March 2022. After a clinical assessment by the consulting doctors and following patient approval. They provided blood samples, and information about their medical history and way of life was taken into consideration. They were compared with 40 healthy controls of females with the same ages of patients.

The blood samples were collected and placed at room temperature for coagulation for 15 min. Then, the blood samples were centrifuged at 5000 x g and the separated serum samples were frozen at -20 °C for using it in the biochemical analysis.

Biochemical Parameters Analyses:

Serum (Na, K and Ca) levels were assessed by the colorimetric method utilizing the company kits by (LABKIT, CHINA)(5), the IL-38 and IL-35 were assessed by (ELISA) method, the ELISA kit supplied by (Sun Long Biotech, China).

Statistical Analysis

Statistical analysis of the data has been accomplished by using SPSS statistics. The descriptive statistics for each parameter consisted of the mean and the standard deviation (SD). The T-test was utilized to match the chemical variables between patients and control groups at the level of probability ($P \leq 0.05$) [17].

RESULTS AND DISCUSSION

The results of age and BMI for both patients (RA and OA) and control are listed in Table 1, by using the mean ± (SD).

Table 1. ANOVA 1-way results for age and BMI

Parameter	Control	RA	OA	*p*-value
Age (year)	40.43±8.96	44.25±8.24	43.85±7.84	0.106[a], 0.164[b], 0.975[c]
BMI (kg/m^2)	28.23±3.60	29.63±4.31	29.86±4.15	0.266[a], 0.169[b], 0.965[c]

[a] Control vs RA, [b] control vs OA and [c] RA vs OA

[*] significant at $P<0.05$

There are non-significant increase (P>0.05) in age among the three groups control (43±8.96), RA (44.25±8.24) and OA (43.85±7.84) as well as BMI among the three groups control (28.23±3.60), RA (29.63±4.31) and OA (29.86±4.15).

The age and BMI have been targeted to be the same in all studied flocks to exclude the impact of age and BMI on the studied kits and parameters, without overlaps. The results of electrolyte levels (Na, K and Ca) for the three groups are listed in Table 2.

Table 2. ANOVA 1 way results for (Na, K and Ca) for all studied groups

Parameter	Control	RA	OA	*p*-value
K	5.10±0.56	4.75±0.83	4.52±1.58	$0.001^{a,b**}$, 0.320^{c}
Na	148.33±12.07	166.06±8.22	169.49±14.43	$0.001^{a,b**}$, 0.414^{c}
Ca	10.18±0.56	9.01±0.51	8.65±1.07	$0.001^{a,b**}$, 0.09^{c}

[a] Control vs RA, [b] control vs OA and [c] RA vs OA

[*] significant at P<0.05

[**] significant at P<0.01

There are high significant differences (>0.001) between RA and OA patients as compared with control in K among the three groups controls (5.1±0.56), RA (4.75±0.83) and OA (4.52±1.58), as shown in Figure 1.

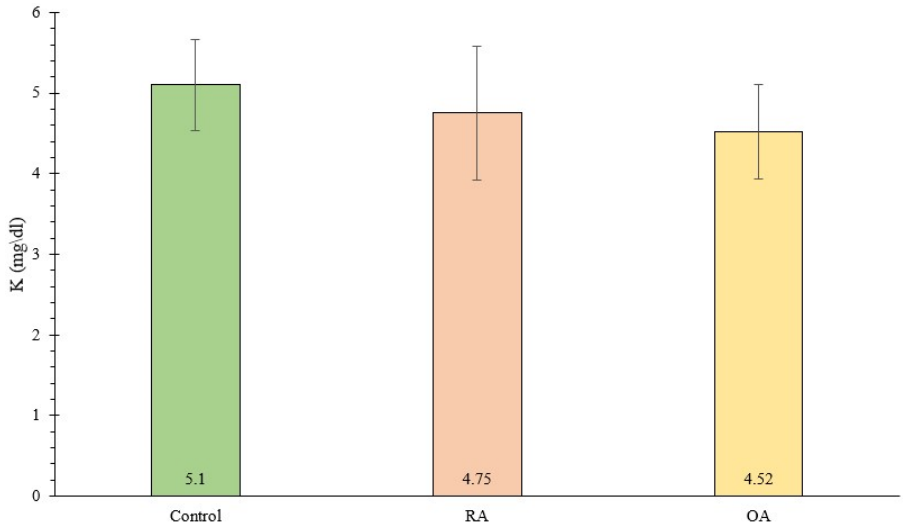

Figure 1. The means ± SD of K in control, RA and OA

This result is in agreement with another study that found a decrease in the level of potassium among RA and OA patients [18].

Due to a compromised immune system, RA patients have a lower ability to store or absorb K than others, according to studies. This may exacerbate some inflammatory symptoms of RA [19]. Studies support the concept that a low potassium concentration in the blood of RA patients is a defining feature of inflammation and is connected with the disease's longest course.

For OA patients, researchers found that changes in potassium and sodium ion concentrations are connected with aberrant potassium ion transit between the three spaces: cellular, extracellular, and intracellular. The decrease in potassium content shown by us could be because of intervertebral disc dehydration, that is general in degenerative diseases. According to the results, the outflow of potassium from the intra cellular empty, together with the input of calcium, increases the release of reactive oxygen species (ROS), initiates and then develops inflammation, and degrades mitochondria [20].

The Na-level among the three groups control (148.33±12.07), RA (166.06±8.22) and OA (169.49±14.43), as shown in Figure 2.

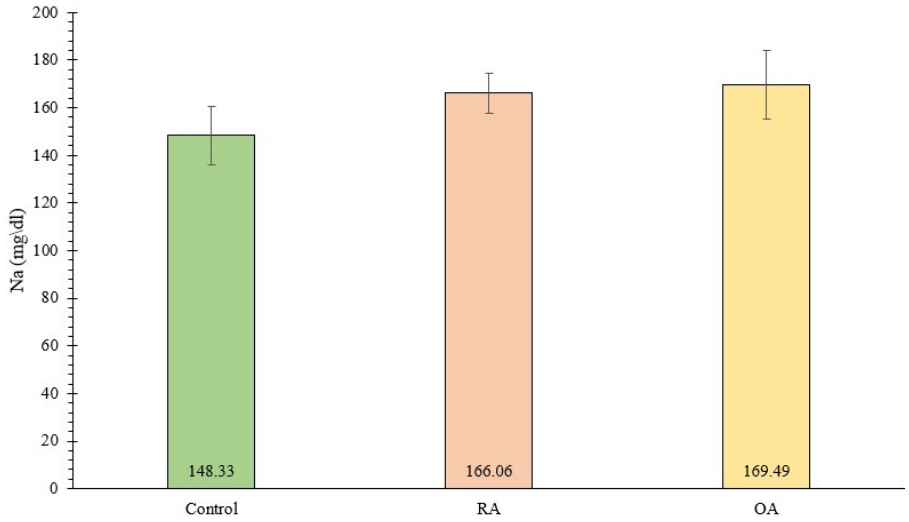

Figure 2. The means ±SD of Na in control, RA and OA

This result is in agreement with earlier researchers who found an elevation level of Na in RA and OA patients as compared to control.

Sodium levels have been linked to increased joint inflammation [21], food is connected with early RA activity and a good predominance of pro-inflammatory hormones. A high input of sodium chloride salt myth effects the development of autoimmune diseases. High sodium was seen in active T helper 17 (Th17) differentiation and activation [22], that is substantial in the pathos physiology of RA. A link between a high-salt diet and the development of RA has previously been proposed. For OA patients, an increased level of sodium is joined with the severity of disorder and harm, and an increased sodium level is one of the risk factors of OA. Furthermore, the symptoms of the disease are associated with the imbalance seen in electrolytes [23].

Ca level among the three groups controls (10.18±0.56), RA (9.01±0.51) and OA (8.65±1.07), as shown in Figure 3.

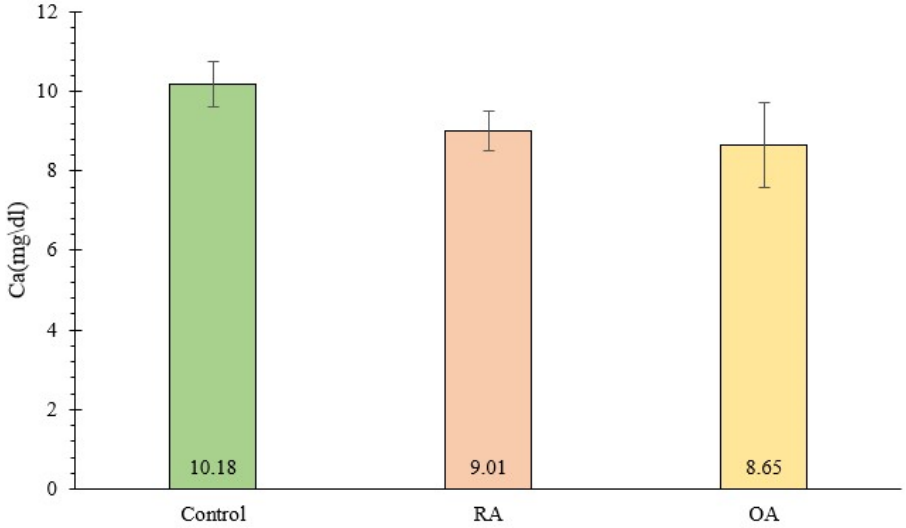

Figure 3. The means and SD of Ca in control, RA and OA

This result is in agreement with earlier researchers who found a decreased level of Ca in RA and OA patients as compared to the control [24]. The decreased calcium concentrations in RA and OA patients were owing to unsuitable calcium reabsorption from the intestines or the impact of glucocorticoid drugs, that induced osteoporosis and loss of the bone in RA and OA patients. In addition to glucocorticoid treatment, calcium reabsorption in the intestines and kidney tubules is blocked because of mechanisms which rely on Vitamin D [25]. The Ca plays an important role in

increasing bone density and has preventive turns in disorders impacting the bone. The results observed that a lowering in calcium is connected with a raise in the severity of the disorder and the show of symptoms for the infected [26].

The results of LI-35 and IL-38 for the three groups (control, RA and OA are listed in Table 3.

Table 3. ANOVA test result for (LI-35 and IL-38) in (p/ml) for all studied groups

Parameter	Control	RA	OA	*p*-value
IL-35	53.1±27.2	454.8±212.6	101.0±31.2	0.001[a,c] 0.024[b]
IL-38	2.8±0.83	6.9±2.9	4.64±1.36	0.001[a, b,c]

[a] Control vs RA, [b] control vs OA and [c] RA vs OA

A high significant difference ($p<0.01$) between RA and OA patients as compared with control in IL-35 among the three groups controls (53.1±27.2), RA (454.8±212.6) and OA (101.0±31.2), as shown in Figure 4.

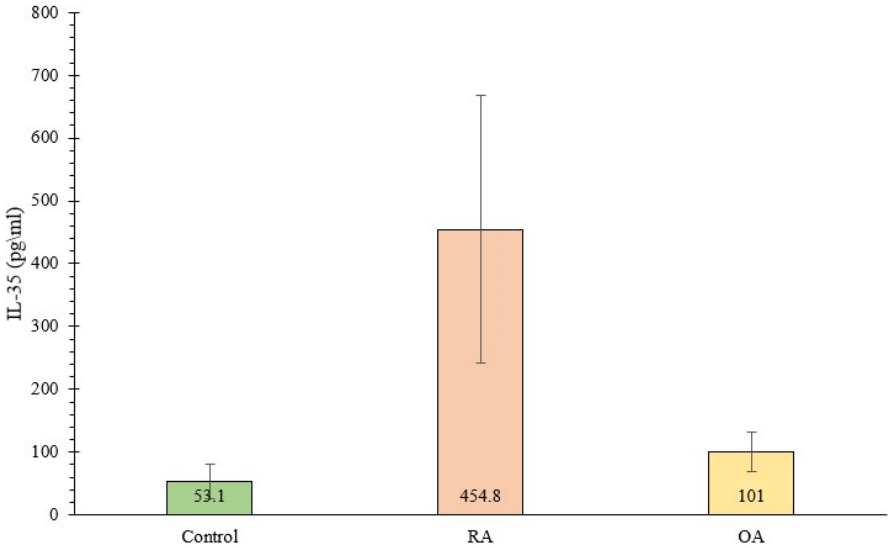

Figure 4. The means ±SD of IL-35 in control, RA and OA

This result is in line with earlier results that found an elevation in the level of IL-35 in the RA and OA patients as compared with the control [27].

Endogenous IL-35 raise myth participate in the negative feedback immune response activated by inflammatory stimuli [28], that myth void a too much inflammatory response and works a preventive role in RA patients. Depending on present and past research, the IL-35 myth has an immune regulatory turn in the inflammatory medium of RA and OA [29].

IL-35 has participated in a diversity of immune-related diseases, containing biliary cirrhosis, Crohn's disorders, OA and RA [30]. The turn of IL-35 in the pathogenesis of RA and OA is tied to immunological dysfunction and the pathogenic mechanism. IL-35 improves Treg proliferation while preventing Th17 cell differentiation [31].

Immune cells going inside the joint, containing Tregs and Th17 cells, and are general for synovial inflammation and joint degeneration. As a result, IL-35 has an important turn in the pathogenic mechanism of arthritis by balancing Tregs and Th17 cells [31].

There are high significant difference ($p <0.01$) between RA and OA patients as compared with control in IL-38 among the three groups controls (2.8±0.83), RA (6.9±2.9) and OA (4.64±1.36), as shown in Figure 5.

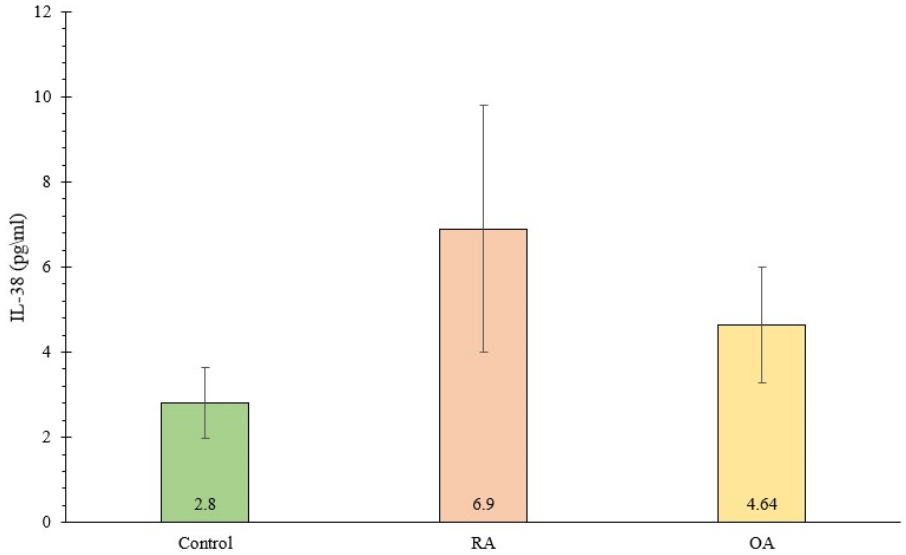

Figure 5. The means ±SD of IL-38 in control, RA and OA

This result is in agreement with earlier results that found a rise in the concentration of IL-38 in the RA and OA patients as compared with the control [32].

IL-38 restricts cytokine production in macrophages via antagonizing JNK phosphorylation and AP-1 activation. These 2 signaling pathways have been connected to the pathogenesis of RA and joined to a variety of pro inflammatory signaling cascades. As a result, the results said that IL-38 has a turn in decreasing the severity of RA [33].

For OA, IL-38 can work as an anti-inflammatory cytokine by preventing inflammatory signaling pathways, decreasing inflammatory mediators and stop harming inflammatory responses. The raised IL-38 expression myth shows a negative feedback method inhibiting excessive immunopathological responses and blocking robust inflammation in OA patients [34]. In addition, IL-38 may have a protective job in lowering the development of OA. several of the aforementioned inflammatory diseases [35].

CONCLUSION

The rise in the levels of IL-35 and IL-38 declares the instinctive role of interleukins and the immune system in the regulation and severity of RA and OA diseases, the role of this parameter may be clear in controlling and monitoring the progression of disease. The increase in the level of Na and decrease in the level of K and Ca declare that the imbalance in the body and, consequently, the effect on the cells due to the existing inflammation, also explains the increase in Na and the decrease in K, the reasons for the high rate of inflammation and the severity of the disease. Low calcium also indicates a clear lack of bone strength and density, which is one of the most important causes associated with joint diseases. In the end, the ILS parameter is still new and needs more studies and more numbers of volunteers to confirm the relationship between the immune system and the two diseases.

SUPPLEMENTARY MATERIAL

None.

AUTHOR CONTRIBUTIONS

Montadher Ali: Validation, visualization, and investigation. Mustafa Taha: Methodology. Montadher Ali and Nisred K. Klichkhanov: Writing-review and editing.

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None.

DATA AVAILABILITY STATEMENT

None.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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