ISSN: 0067-2904

Correlations of Osteonectin with other Biochemical parameters in Patients with Rheumatoid Arthritis

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Received: 5/7/2024 Accepted: 29/10/2024 Published: 30/11/2025

Abstract

Rheumatoid Arthritis (RA) is a long-term autoimmune disorder that causes ongoing inflammation in the joints, starting with smaller joints and gradually spreading to larger ones, with potential complications affecting other parts of the body. The chronic inflammation in the synovial membrane leads to the degradation of cartilage and bone. Osteonectin (SPARC), a protein involved in tissue remodelling, is found to be highly expressed in the cartilage and synovium of individuals with RA, indicating its potential role in the disease process. This research aimed to investigate serum Osteonectin (ON) concentrations as a potential marker of RA disease activity. The study included 58 patients with RA and 30 healthy individuals, divided into three groups: G1 (RA with mild disease activity, n=29), G2 (RA with moderate disease activity, n=29), and G3 (healthy controls, n=30). Clinical information, anthropometric parameters, duration of the disease, treatment type, and Clinical Disease Activity Index score (CDAIs), were recorded. Serum ON levels were measured using the ELISA technique on frozen samples. Statistical analysis involving ANOVA and Pearson's correlation was used. The results revealed that serum ON levels in G1 and G2 groups were higher than C group (49.29±10.27, 60.13±16.38 and 22.15±5.94) respectively. In G1, a strong negative correlation was found between serum ON levels and weight (r=-0.553, p=0.002). Additionally, positive correlations were noticed between serum ON levels and disease duration (r=0.513, *p*=0.004), triglycerides (r=0.428, *p*=0.021), and AST (r=-0.437, *p*=0.018). In contrast, G2 showed only a moderate negative correlation was observed between serum ON levels and AST (r=-0.437, *p*=0.018). The elevated levels of ON suggest that its involvement in RA is associated with clinical parameters. Also, ON may has a potential role in disease progression, lipid metabolism, and liver function.

Keywords: Osteonectin, Rheumatoid Arthritis, C - reactive protein, Rheumatoid Factor

علاقة الاوستيونيكتين مع عوامل كيموحيوية اخرى عند المرضى العراقين المصابين بالروماتزم الرثوي

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التهاب المفاصل الروماتويدي (RA) هو اضطراب مناعي ذاتي طويل الأمد يسبب التهابًا مستمرًا في المفاصل، بدءًا من المفاصل الأصغر حجمًا وانتشارًا تدريجيًا إلى المفاصل الأكبر حجمًا، مع مضاعفات محتملة تؤثر على أجزاء أخرى من الجسم. يؤدي الالتهاب المزمن في الغشاء الزليلي إلى تدهور الغضاريف والعظام. وجد أن أوستيونيكتين (SPARC)، وهو بروتين يشارك في إعادة تشكيل الأنسجة، يتم التعبير عنه بشكل كبير في الغضاريف والغشاء الزليلي للأفراد المصابين بالتهاب المفاصل الروماتويدي، مما يشير إلى دوره المحتمل في عملية المرض. يهدف هذا البحث إلى التحقيق في تراكيز أوستيونيكتين (ON) في المصل كعلامة محتملة لنشاط مرض التهاب المفاصل الروماتويدي. شملت الدراسة 58 مريضًا مصابًا بالتهاب المفاصل الروماتويدي و 30 فردًا سليمًا، مقسمين إلى ثلاث مجموعات: G1 (RA مع نشاط مرضي خفيف، n = 29)، و G2 (RA مع نشاط مرضي متوسط، n = 29)، و G3 (ضوابط صحية، n = 30). تم تسجيل المعلومات السريرية والمعايير الأنثروبومترية ومدة المرض ونوع العلاج ودرجة مؤشر نشاط المرض السريري (CDAIs). تم قياس مستويات ON في المصل باستخدام تقنية ELISA على عينات مجمدة. تم استخدام التحليل الإحصائي الذي يتضمن تحليل التباين وارتباط بيرسون. كشفت النتائج أن مستويات ON في المصل في المجموعتين G1 وG2 كانت أعلى من المجموعة C (49.29 ± 10.27 و60.13 ± 16.38 و22.15 ± 5.94) على التوالي. في G1، تم العثور على ارتباط سلبي قوي بين مستويات ON في المصل والوزن ($r = -0.553$، $p = 0.002$). بالإضافة إلى ذلك، لوحظت ارتباطات إيجابية بين مستويات ON في المصل ومدة المرض ($r = 0.513$، $p = 0.004$)، والدهون الثلاثية ($r = 0.428$، $p = 0.021$)، و AST ($r = -0.437$)، ($p = 0.018$). في المقابل، أظهرت G2 وجود ارتباط سلبي معتدل فقط بين مستويات ON في المصل و$r = -0.437$ AST)، ($p = 0.018$). تشير المستويات المرتفعة من ON إلى أن تورطه في التهاب المفاصل الروماتويدي مرتبط بالمعايير السريرية. كما قد يكون لـ ON دور محتمل في تطور المرض، واستقلاب الدهون، ووظائف الكبد.

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1. Introduction

Rheumatoid arthritis (RA) is a type of disorder that affects the muscles and joints, characterized by chronic inflammation of the joints, leading to weakness and potential long-term damage. RA is a symmetrical, persistent, inflammatory autoimmune disease that initially affects small joints before progressing to larger joints and eventually impacting the skin, coronary heart, eyes, kidneys and lungs. Joints typically lose their cartilage, which weakens tendons and ligaments [1-4]. The worldwide occurrence of the sickness is imagined around 1–2%, with a large variant among distinct populations [5]. The ailment affects females 2 to 3 instances more often than males and happens at any age, and the peak of occurrence is within the 6th decade. The pathophysiology of RA involves chronic irritation of the synovial membrane, which can damage both articular cartilage and articular bone [6]. Patients with RA are characterized by the presence of various circulating vehicle antibodies in their blood. In clinical exercise, the most common diagnostic tests include Rheumatoid Factor (RF), C- Reactive Protein (CRP), erythrocyte sedimentation rate (ESR), and anti-cyclic citrullinated peptide (anti-CCP), which are widely recognized by rheumatologists and recommended through the European League of Arthritis and Rheumatism (EULAR) [7, 8]. The handiest therapeutic method calls for early prognosis and a most effective non-pharmacological and pharmacological treatment, related to periodic evaluation of healing efficacy and protection. The primary goal of therapy is to achieve remission and minimize side effects [9]. Pharmacological agents that help maintain joint features can be categorized as traditional synthetic Disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs and centred synthetic DMARDs, which are included in a new class of nonbiologic DMARDs utilizing the American College of Rheumatology (ACR) [6, 10]. Inadequate symptom manipulation in RA sufferers calls for using nonsteroidal anti-inflammatory tablets (NSAIDs) and steroids glucocorticoids (GCs) as adjunctive therapy in reducing inflammation [11]. Osteonectin (ON), also known as acidic and cysteine-rich secreted protein (SPARC), is

a multifaceted matricellular protein concerned with both regular and pathological tissue transformation. SPARC is a multifunctional regulator of smooth tissue cells, exhibiting various biological effects, including the regulation of proliferation, migration, and synthesis of smooth tissue cellular-matrix proteins and binding to collagens without delay regulating their meeting. It is tremendously expressed in normal tissues in bones, teeth, eyes, and at sites of wound restoration and tissue reworking [12-14]. The SPARC expression degree within the floor and centre layer of articular cartilage in RA patients is drastically multiplied, and the level of synovial fluid and synoviocytes is increased [15, 16]. The study aims to evaluate serum ON levels, as well as, the possibility of using ON as a predictive marker for RA activity.

2. Materials and Methods

2.1. Study subjects

The current study involved 58 women with RA who attended Al-Yarmouk Teaching Hospital between October 2022 and March 2023, as well as 30 healthy women as a control. All patients had given their signed informed consent to take part.

2.2. Questionnaire and clinical data

A convenient sampling technique was employed to include 58 females with RA in this study, matched by age with 30 healthful controls. Individuals with RA had been recognized using a representative rheumatologist in keeping with ACR / EULAR standards in 2010 [17]. The following data were analysed: age, weight, height, BMI, period of disease, period of treatment, own family records, fever, and Clinical Disease Activity Index (CDAI) measurement.

The disease activity was measured using the following equation:

CDAI= Swollen 28-joint Count + Tender 28-joint Count + Patient Global disease Activity + Evaluator's Global disease Activity, tender joint number and swollen joint number [18].

2.3. Collecting samples

Samples were collected from women, and all 88 patients and controls who met the inclusion criteria were enrolled and divided into groups according to disease activity. Group 1 with mild disease activity (n=29), group 2 with moderate disease activity (n=29), and Group 3 control (n=30). Patients were excluded if they had overlapping inflammatory conditions with RA, such as seronegative arthritis or connective tissue diseases (like SLE), malignancy, cardiovascular disease, thyroid disease, and liver or renal diseases.

2.4. Samples handling

Approximately 5 ml of blood was drawn from each patient with RA and healthy controls in the morning and after fasting for 12 hours. The samples were divided into two portions; the first portion was located in gel tubes and centrifuged at 3000 ×g for 10 minutes. After that, the serum was placed in a small tube (Eppendorf tube) and saved frozen at -20 ºC until being used to estimate the biochemical parameters. The ON levels were measured using an ELISA kit (MyBioSource), with optical density absorbance read at 450 nm using a microplate reader. Hemolyzed serum samples were excluded. The second portion was dispensed in an EDTA tube; which was used for measuring ESR.

2.5. Biochemical Parameters

Fasting blood sugar (FBS), glycated hemoglobin (HbA1c), lipids profile (total cholesterol TCh, triglyceride TG, high-density lipoprotein HDL, low-density lipoprotein LDL, and very low-density lipoprotein VLDL), liver profile (ALT/GPT, AST/GOT, and ALP), renal profile

(urea, creatinine, and uric acid), were all measured using colorimetric methods except liver profile were determined using UV Spectrophotometric detection.

2.6. Statistical analysis

Statistical analysis records evaluation changed into accomplished the use of SPSS statistical software version 28.0. Analysis of variance (ANOVA) is used to determine whether there are any statistically tremendous variations among the approaches. Statistics had been provided as mean ± Stander Deviation. Pearson's correlation (r- -coefficient) becomes used between ON, C-RP, RF, disease activity and other parameters. A *p*-value of ≤0.05 is considered statistically significant.

3. Results

Our study included 88 participants divided into 3 groups: the mild disease group (n=29), the moderate group (n=29) and the control group (n=30). The general anthropometric, clinical and biochemical features of the participants are represented in Table 1. Statistical analysis using ANOVA and post hoc test revealed that there is a significant difference in age between the control and mild groups as well as control and moderate groups at ($P < 0.001$). However, there were no significant differences in weight and height among the control, mild and moderate groups. The BMI was significantly higher in the mild group and moderate group compared to the control group at ($P < 0.001$).

The Disease Activity Score 28 (DAS 28) demonstrated a highly significant difference ($P < 0.001$) when comparing both patient groups (mild and moderate) to the healthy group, with a similar significance noticed in comparison mild group to the moderate group.
Additionally, when comparing the mild and moderate groups to the control group; RF, CRP and ESR were considerably significantly higher ($P < 0.001$) in both patient groups.

The mild and moderate groups exhibited significantly higher fasting blood sugar (FBS) and HbA1C than the control group ($P < 0.001$). There were also significant increases ($P< 0.01$) in serum cholesterol, TG, LDL and VLDL in patients' groups compared to healthy individuals. Conversely, serum HDL levels showed a significant decrease ($P <0.01$) in both mild and moderate groups compared to the control group.

Serum levels of ALT and AST showed a high significant difference ($P<0.01$) when comparing mild and moderate groups with the control group, as well as when comparing the mild group to the moderate group.

Additionally, serum ALP, creatinine, and uric acid levels were significantly higher in both patient groups ($P <0.01$) compared to the control group. Similar significant increases were noticed in blood urea and serum ON in comparison between patients and control groups, as well as between both patients' groups.

Table 1: The demographic data and clinical characteristics of the studied groups distributed according to disease activity

Parameter (mean ±SD)	G 1 (n=29)	G 2 (n=29)	G 3 (n=30)	*p*-value
Age (year)	55.00±11.26**a	52.41±8.52**b	42.13±12.85	<0.01
Weight (Kg)	77.90±8.10	80.66±11.96	74.70±9.33	0.76
Height (m)	1.64±0.07	1.64±0.06	1.68±0.10	0.74
BMI (Kg/m^2)	28.98±3.34**b	29.72±4.13**a	26.20±2.25	<0.01
DAS 28	4.21±0.27**b	3.68±0.33**a,c	1.38±0.27	<0.01
RF (IU/mL)	9.12±1.84**b	8.10±1.24**a,c	2.25±0.85	<0.01
C-RP (mg/L)	20.71±4.19**b,c	18.42±2.84**a,c	5.36±1.72	<0.01
ESR (mm/hr)	25.90±5.24**b	23.03±3.55**a,c	6.37±2.44	<0.01
FBS (mg/dl)	124.07±4.85**b	114.86±3.90**a,c	103.60±6.71	<0.01
HbA1C (%)	8.10±0.47**b	7.73±0.27**a,c	7.35±0.56	<0.01
Cholesterol (mg/dl)	219.55±14.57**b	211.00±11.59**a,*c	165.90±12.81	<0.01
Triglyceride (mg/dl)	187.10±9.67**b	182.62±9.25**a	83.17±9.85	<0.01
HDL (mg/dl)	50.76±4.87**b	54.90±4.25*a,**c	58.27±4.60	<0.01
LDL (mg/dl)	101.24±6.07**b	99.86±6.54**a	74.20±6.90	<0.01
VLDL (mg/dl)	59.17±7.27**b	56.07±6.03**a	41.53±8.34	<0.01
ALT/GPT (U/L)	32.86±5.87**b	29.03±3.47**a,c	25.60±3.77	<0.01
AST/GOT (U/L)	38.14±6.18**b	34.69±5.95**a,c	27.33±3.56	<0.01
ALP (U/L)	113.62±7.93**b	110.34±7.62**a	59.70±4.93	<0.01
Urea (mg/dl)	49.21±4.21**b	46.72±2.71**a,c	30.10±2.42	<0.01
Creatinine (mg/dl)	1.48±0.08**b	1.46±0.08**a	0.82±0.08	<0.01
Uric Acid (mg/dl)	8.51±0.93**b	8.26±0.90**a	6.57±1.13	<0.01
ON (ng/mL)	49.29±10.27**b	60.13±16.38**a,c	22.15±5.94	<0.01

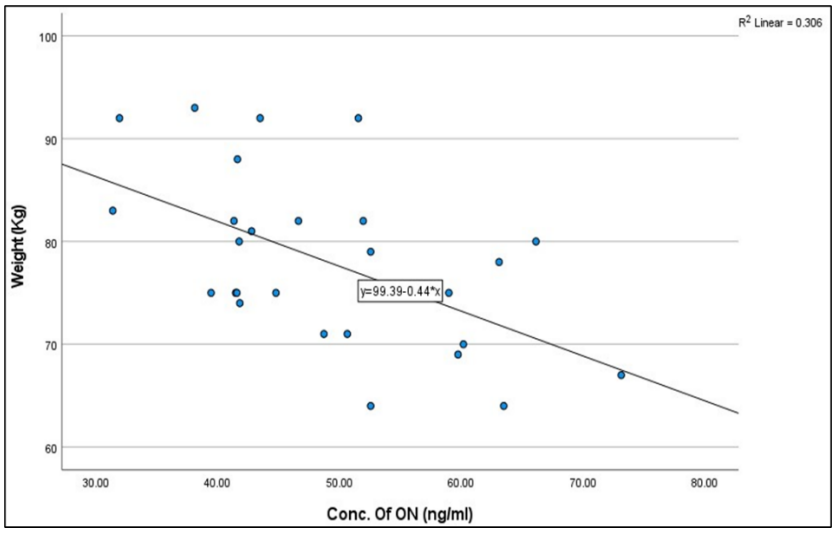
The results were expressed as mean ± SD (mean± standard deviation), a): refer to the significant difference between G1 and G3. b): refer to the significant difference between G2 and G3. c): refer to the significant difference between G1 and G2.
****The difference is highly significant at $p \leq 0.01$. *The difference is significant at $p < 0.05$.**

As shown in Table 2; a considerable negative impact correlation was noticed between serum ON and weight in G1 group (r=-0.553, *P*=0.002) and a positive impact correlation between serum ON and duration of disease (r=0.513, *P*=0.004) and Triglycerides (r=0.428, P=0.021) (Figure 1), as quite well with AST (r=-0.437, *P*=0.018) in G2 group (Figure 2).

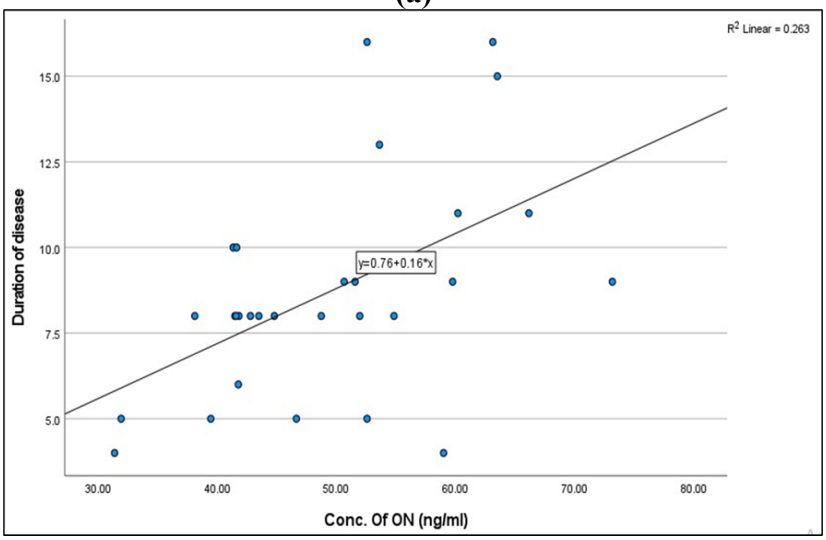
Table 2: Correlation of ON in (G1 and G2) groups with other parameters

Parameter	Serum ON with mild disease			Serum ON with moderate disease		
	r	*P*	Sig.	r	*P*	Sig.
Duration of Disease	0.513	0.004	HS	0.204	0.288	NS
Weight (Kg)	-0.553	0.002	HS	0.002	0.991	NS
Height (m)	-0.282	0.138	NS	-0.079	0.685	NS
BMI (Kg/m^2)	-0.289	0.129	NS	0.040	0.836	NS
FBS (mg/dl)	-0.206	0.284	NS	-0.186	0.334	NS
HbA1c (%)	0.197	0.305	NS	0.182	0.345	NS
Cholesterol (mg/dl)	0.326	0.084	NS	-0.105	0.588	NS
Triglycerides(mg/dl)	0.428	0.021	S	0.082	0.674	NS
HDL (mg/dl)	0.215	0.263	NS	-0.033	0.867	NS
LDL (mg/dl)	0.268	0.160	NS	0.027	0.891	NS
VLDL(mg/dl)	0.186	0.334	NS	0.211	0.273	NS
DAS 28	-0.352	0.061	NS	-0.234	0.221	NS
RF(IU/mL)	-0.223	0.245	NS	0.111	0.568	NS
CRP (mg/L)	-0.223	0.246	NS	0.111	0.565	NS
ESR (mm/hr)	-0.223	0.246	NS	0.111	0.565	NS
ALT (U/L)	0.197	0.306	NS	-0.116	0.548	NS
AST(U/L)	-0.082	0.671	NS	-0.437	0.018	S
ALP(U/L)	-0.056	0.774	NS	-0.011	0.953	NS
Urea (mg/dl)	-0.201	0.295	NS	0.110	0.571	NS
Creatinine (mg/dl)	0.155	0.421	NS	-0.022	0.909	NS
Uric acid (mg/dl)	-0.036	0.853	NS	-0.254	0.184	NS

HS: $P < 0.01$, S: $P < 0.05$, NS: $P > 0.05$.



(a)



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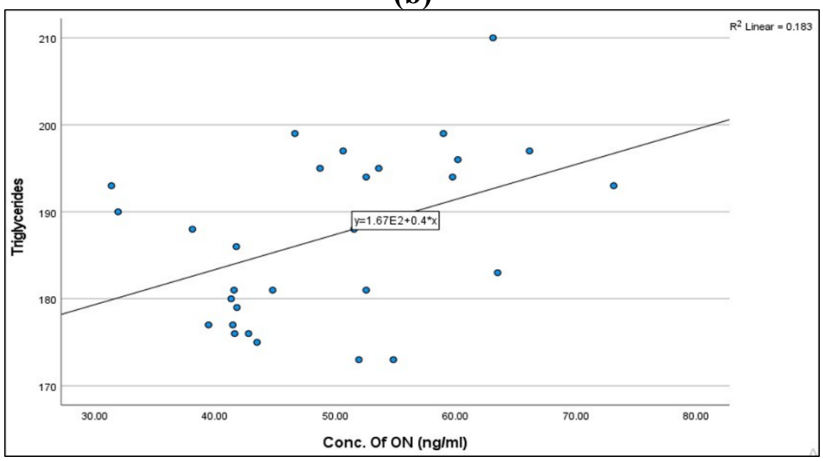

(c)

Figure 1: The positive significant Pearson correlation of ON with (a) Duration of Disease (b) Triglycerides (c) negative significant Pearson correlation of ON with Weight in the G1 group

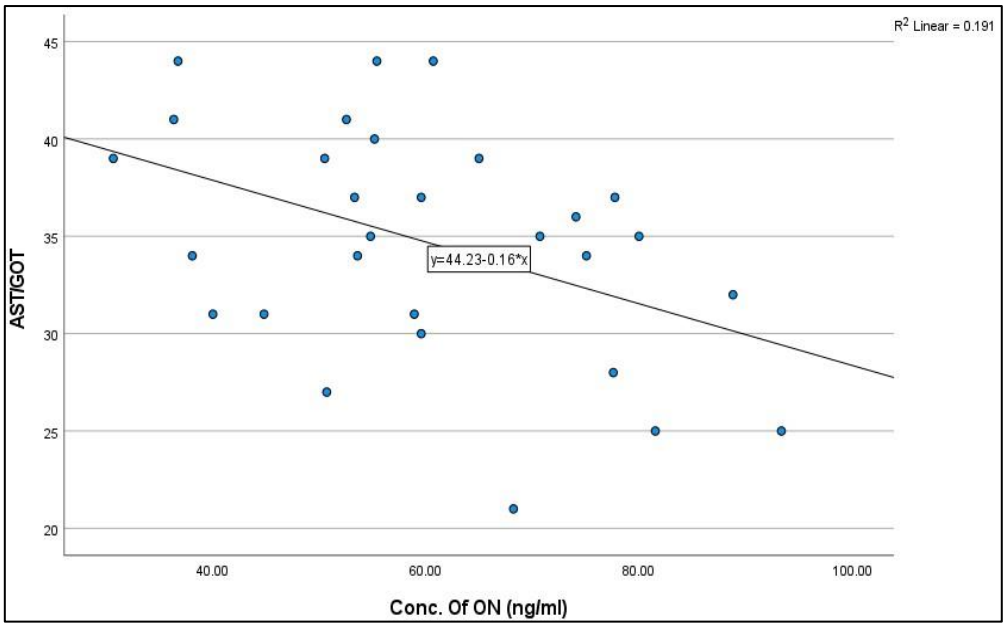

Figure 2: The negative significant Pearson correlation of ON with AST in the G2 group

4. Discussion

Consistent with our findings, patients with RA exhibited higher serum ON levels than healthful controls. Several studies have shown a connection between ON and several autoimmune diseases, such as RA. The synthesis of ON is increased in the synovial cells of RA and OA joints, and the degrees of ON in synovial fluids of individuals with RA were significantly elevated [19, 20].

All participants in this study were females, which aligns with the known higher prevalence of RA in women. These findings are consistent with Brewer, D'Agata, et al., 2023 who reported that RA is more common in women than in men [16]. Patients in groups G1 and G2 were significantly older than those in the control group (G3), likely due to RA being more prevalent in older adults. This observation agrees with Serhal, Lwin, et al., 2020 who found that the elderly have more prevalence of RA [21]. Additionally, patients in groups G1 and G2 have higher BMI than controls, indicating greater body fat mass. This may be a result of chronic inflammation associated with RA or steroid-induced side effects. This agrees with Qiu, Wu, et al., 2021 who found that RA is characterized by chronic inflammation, which can interfere with metabolism and lead to fat storage [22]. Moreover, our results agree with Letarouilly, Flipo, et al., 2021 who demonstrated that steroids can cause weight gain and fat redistribution, leading to greater fat accumulation in certain areas [23]. Patients in G1 and G2 had significantly ($P< 0.01$) higher levels of DAS 28, RF, C-RP, ESR, and FBS than controls, indicating more active disease and systemic inflammation. These results agree with Dissanayake et al., 2021 who found that patients presumed to have RA exhibited much higher levels of DAS 28, RF, C-RP, ESR, and FBS compared to the control group [24].

Patients in Groups 1 and 2 exhibited higher levels of HbA1C, cholesterol, triglycerides, LDL, vLDL, ALT/GPT, AST/GOT, ALP, urea, and uric acid than controls. This suggests potential metabolic disturbances associated with RA or steroid treatment, like impaired glucose metabolism, dyslipidemia, and liver enzyme elevation. These results are consistent with Boissier, Biton, et al., 2020 who noted that chronic inflammation related to RA can disrupt metabolism and organ function and steroids are known to have side effects like impaired glucose metabolism and dyslipidemia [25]. G1 and G2 groups had slightly higher creatinine levels than controls, although these remained within the normal range, indicating no significant impairment in kidney function. This result agrees with Khadim and Al-Fartusie,

2021 who suggested that although RA patients might have slightly reduced kidney function, it is not yet significantly impaired [26].

Strong negative correlation between serum ON with weight (r=-0.553, P=0.002) in G1, which illustrates the association of weight increment with the decreasing ON levels. The negative correlation in Rheumatoid arthritis patients could be due to steroid-induced weight gain or metabolic changes affecting ON production [27].
Positive correlations between serum ON with Duration of Disease (r = 0.513, P = 0.004) were noticed in G1. Higher disease duration seems to be associated with increased ON levels, which might reflect chronic inflammation or disease progression [28].
Positive correlations between serum ON with Triglycerides (r = 0.428, P = 0.021). This association indicates a potential link between elevated triglycerides and higher ON levels that may illustrate the involvement of lipid metabolism in ON regulation [29].
A moderate negative correlation was observed between serum ON with AST (r=-0.437, P=0.018), suggesting an inverse relationship between ON and an enzyme marker for liver function (AST). The negative correlation in both groups, though stronger in G1, hints at a possible influence of liver function on ON levels [30].
In the G2 group, none of the parameters showed a statistically significant association with ON. Since steroids were not a factor in G2, the underlying links between ON and other parameters may have been obscured, explaining the lack of statistically significant correlations in that group [31]. To a lesser extent than G1, only AST demonstrates a negative association with serum ON (r=-0.437, p=0.018). Further research is needed to validate the negative correlation with AST, which suggests a possible connection between liver function and the modulation of ON in RA [32].

Conclusion

This study offers new insights into the potential function of ON in RA and its correlation with other clinical variables. The results indicate that RA patients have higher serum ON levels compared to healthy controls, which may be associated with inflammation or disease activity. Additionally, metabolic alterations may be at play due to the robust negative association between ON and weight in G1. Furthermore, ON appears to be involved in disease development, lipid metabolism, and liver function, as it is positively correlated with illness duration, triglycerides, and AST in G1. Curiously, other than AST, no significant connections were found in G2. This suggests that disease activity may be obscuring other interactions. Further investigation into the processes underlying the relationships between ON, RA, and disease activity is warranted in light of these findings, which highlight the intricate relationship between the three.

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