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Correlation between some hormones, interleukins and molecular parameters in rheumatoid arthritis patients with and without metabolic syndrome

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Abstract

Metabolic syndrome (MetS), characterized by an amalgamation of obesity, dyslipidemia, glucose intolerance, insulin resistance (IR), and hypertension, is a significant predictor of type 2 diabetes and cardiovascular disease (CVD). The prevalence of this condition among rheumatoid arthritis (RA) patients may elevate the risk of CVD. This study explored the relationship between MetS and RA using hormonal and immunological markers, in addition to some molecular analyses [energy homeostasis-associated (ENHO) gene expression]. It included 80 RA patients (40 with MetS and 40 without MetS) and 20 apparently healthy controls. The outcomes showed that MetS was more common in persons classified as overweight or obese, those with RA disease duration of 5-10 years, and older RA patients (>50 years). While RA mostly affected women, MetS showed a fairer division between sexes. In RA patients with MetS, both insulin and IL-23 showed significant positive correlations (p=0.011) as well as between adropin and interleukin (IL) 17 (p=0.024). These results highlight how metabolic and demographic factors affect the course of RA and underline the need of a thorough metabolic inflammatory therapy strategy.

Keywords: Rheumatoid arthritis, metabolic syndrome, interleukin (IL)-17, interleukin (IL)-23, adropin.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder marked by ongoing synovial and joints damage.[1] Although other joints may also be impacted, the primary symptom of RA is progressive, life-limiting joint pain and stiffness that mostly affects the hands, wrists, fingers, and feet. As result, the overall quality of life of those who are impacted by these symptoms may suffer greatly.[2] The etiology of RA remains not fully understood; its pathogenesis includes chronic inflammation of the synovial membrane, which leads to cartilage and bone loss. Cardiovascular disease (CVD) has been found to be the most prominent cause of death in RA patients.[3] Metabolic syndrome (MetS) is a cluster of cardiovascular disease risk factors, including hypertension, central obesity, hyperglycemia, and dyslipidemia.[4] Insulin resistance (IR) is thought to be the basic pathogenesis causing MetS. Increased levels of pro-inflammatory cytokines generated in RA, that cause IR, glucocorticoid treatment or any other kind of treatment and reduced level of

physical activity due of joint involvement and the consequent increase in body mass index (BMI), help to explain the likely accelerated disease process underlying MetS development in RA.[5] Moreover, old age, positive serology, and extra articular expression raise the risk of MetS development in RA patients.[6] Furthermore, MetS itself is in charge of releasing several adipokines and inflammatory cytokines that might aggravate the severity of disease and morbidity in RA in patients.[7]

Based on the diagnostic criteria and population ancestry, the general risk of developing MetS appears to be rather higher in RA patients than in healthy controls in several populations; however, this varies greatly. By contrast, studies carried out abroad, such as in Korea, showed a rather negative correlation between RA and MetS.[8] Comprehensive research studies on this topic in Latin American nations, including Mexico, is lacking. Therefore, more studies are needed to clarify the metabolic changes linked with MetS in RA and its major contribution to the beginning of CVD in RA patients in other geographical areas.[9] Sometimes the biochemical patterns of RA patients deviate from those of the general population. For RA patients, for example, low-density lipoprotein (LDL) has been linked to a great risk of CVD.[10] Furthermore, elevated BMI was reported to be protective against small joint damage during the first stage of RA. Early and chronic RA have different associations with MetS, and it is yet unknown how different disease features including disease duration, activity, and frequency of treatments contribute to this difference. Although there is much debate on what elements most influence RA-associated MetS, the diagnosis of MetS factors in RA patients presents a great possibility for preventive intervention.[11] Therefore, this study explored the relationship between MetS and RA using hormonal and immunological markers, in addition to some molecular analyses [energy homeostasis-associated (ENHO) gene expression].

Subjects and Methods

Subject and sampling

The current study included 80 RA patients with age range (20-70 years), and 20 apparently healthy controls. The patients were divided into two groups; the first group included 40 RA patients with MetS, and the second group involved 40 RA patients without MetS.

Blood samples were collected from all patients and controls during their attendance to Al-Immamain Al-Kadimain Hospital. This study was extended from January, 2024 to June, 2024. Venous blood samples (10 ml) were taken from each study subjects via vein puncture, and then distributed into two tubes: A whole blood sample (5ml) was transferred to an EDTA tube for molecular examinations. Another whole blood sample (0.5 ml) was subsequently transferred to a 1.5 ml triazole tube for RNA extraction. A third whole blood sample (5 ml) was placed into a gel tube and let it to coagulation and then centrifuged at 1000 xg for 10 minutes to get serum for hormones and immunological tests.

Calculation of Body Mass Index (BMI)

BMI (kg/m^2) was measured by the following equation: weight (Kg) / height^2 (M).[12]

Weight status	Values of BMI (kg/m^2)
Underweight	<18
Normal	18-24.9
Overweight	25-29.9
Obesity	30-39.9

Hormonal Assay

Insulin hormone in serum was quantitatively assessed using sandwich enzyme linked immunoassay (ELISA) Kits (provided by DGR/USA), according to the manufacturer's instructions. Serum adropin was quantitatively measured using commercial sandwich ELISA kits (Sun Long Biotech Company, China), according to the manufacturer's instructions.

Immunological Assays

In order to assess interleukin (IL)-17 and IL-23 antibodies in human serum, commercial ELISA kits were used (Innova and Sun Long Biotech

Company, China), according to the manufacturer's instructions. A plate reader was used to measure the absorbance at a wavelength of 450 nm.

Molecular Assays

-Ribonucleic acid (RNA) Analysis

For extraction and assessment of RNA from blood samples, the TransZol up plus RNA kit reagent (Alpha AND Company, Canada), was used according to the manufacturer's instructions. In order to determine the quality of the sample for the quantitative reverse transcription polymerase chain reaction (qRT-PCR) analysis that followed, the concentration and purity of the extracted RNA were assessed using a spectrophotometer (Nanodrop Spectrophotometer 2000c, Thermo Fisher Scientific, USA). To assess RNA purity, the tasters were examined at two wavelengths (260 and 280 nm), with RNA concentrations ranging from 84 to 126 ng/µl. The quality of the RNA sample was indicated by an A260/A280 ratio of around 2.0.

Complementary DNA (cDNA) was produced from total RNA using reverse transcription. Commercial kits (Easy Script® one-step super mix kit), was used for cDNA synthesis and genomic DNA (gDNA) elimination, following the manufacturer's instructions. For the reverse transcription, 4 µl of total RNA was placed in a 20 µl reaction volume, and exposed to 25 °C for 10 minutes under heat conditions. For quantitative PCR, GSP and an oligo (dT) 18 primer were incubated at 42°C for 15 minutes. After five seconds of incubation at 85°C, the enzymes were rendered inactive. RT-qPCR primer design: The ENHO gene's expression levels were evaluated using the qRT-PCR technique, which was renowned for its sensitivity in measuring steady-state mRNA levels. A qRT-PCR SYBR Green test was used to confirm the target gene's expression. As shown in Table 1, primer sequences for the ENHO gene were taken into consideration, synthesized by Alpha DNA Ltd. (Canada), lyophilized, and kept at -20°C as specified in Table 1.

To perform the qRT–PCR, the QIAGEN Rotor gene Q Real-time PCR System (Germany) was used. The threshold cycle (Ct) was measured and the ENHO and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) gene expression levels and fold changes were assessed by using commercial kits (TransStart® top green qPCR super mix kit). The cycling regimen was formulated grounded on the thermal profile outlined in Table 2.

Statistical Analysis

The statistical analysis for this study was done employing the Statistical Package for the Social Sciences (SPSS), software version 26 (IBM, SPSS, Chicago, Illinois, USA), and Microsoft excel 2010 program. The mean of the investigated parameters was compared between the two groups using t-Test. The Chi-Square test was applied to compare between percentages. Differences among groups were analyzed using one-way analysis of variance (ANOVA) analysis of variance. In addition, Microsoft excel 2010 program was employed to draw chart figures. The Results of all hypothesis tests with *p*-values <0.05 (two-side) were considered statistically significant.[13,14]

Table 1. The study designed primers.

Primer	Sequence (5'→3' direction)	primer size bp	Product size bp	Tm C^{o}
ENHO gene expression				
Forward	CCCAGGACCTAAGTCCACCT	20	142	62
Reverse	CTCCTATTGGAGCCAAGCTG	20		

Table 2. The thermal profile of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and energy homeostasis-associated (ENHO) gene expression.

Step	Temperature (°C)	Time (sec.)	Cycles
Enzyme activation	94	30	1
Denaturation	94	10	40
Annealing	58	15	
Extension	72	20	
Dissociation	55 ºC-95 ºC		1

Results

Distribution of the RA patients according to their descriptive and clinical data

-Distribution of the RA patients according to age

The distribution of patients' groups according to their ages is shown in Figure 1. They were divided into three age groups: < 35, 35-50, and >50 years; in < 35 y group. RA patients without MetS showed higher percent (32.5%) compared with those with MetS (5%). In the second group 35-50 y, the percentages of the two groups were close as they were 42.5% for RA patients with MetS and 45.5% for RA patients without MetS. In the age group >50y, the percentage of RA patients with MetS (52.5%) with was more than the percentage of RA patients without MetS (22%).

-Distribution of the RA patients according to sex

Figure 2, displays the distribution of patient's groups according to sex. Only a significant difference was recorded between RA patients without MetS, where the females were significantly higher (65%) than males (35%) (p=0.0027); while the percentages were close between males and females in the group of RA patients with MetS, 42.5% for males and 57.5% for females.

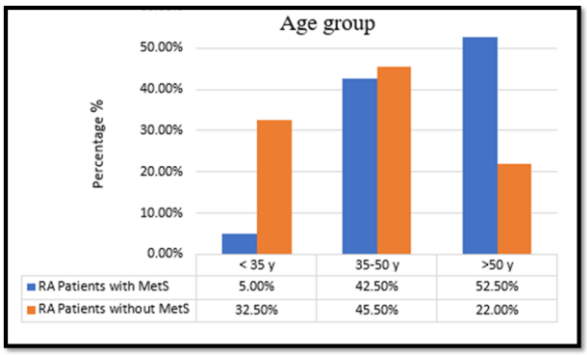

Figure 1. Distribution of the rheumatoid arthritis (RA) patients according to age. The bar graph shows percentage distribution of RA patients by the presence or absence of MetS among three separate age groups: <35, 35 -50, and >50 years. There were higher RA patient frequencies without MetS among those below 35 years, but highest percentage RA patient frequencies with MetS were among those above 50 years. The 35 to 50-year age category showed equal percent distributions among both categories.

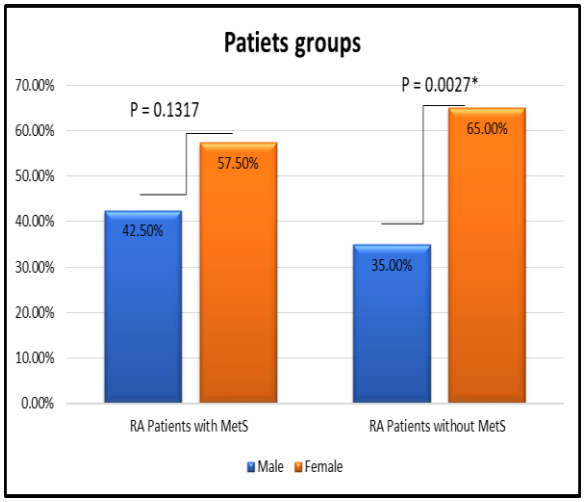

Figure 2. Distribution of the rheumatoid arthritis (RA) patients according to sex. This figure compares the sex distribution of RA patients with and without MetS. Among RA patients without MetS, females were significantly more prevalent than males. In contrast, RA patients with MetS showed a relatively balanced distribution between sexes, with no significant difference.

-Distribution of the RA patients according to BMI

According to BMI categories, the study population was distributed in three categories: normal, overweight, and obese. RA patients with MetS showed that the highest significant percentage (62.5%) of patients was in the overweight category. While the comparison within-RA patients without MetS group, showed that the highest significant percentage of patients was in overweight category (45%) and in obese category (45%), as shown in Figure 3.

-Distribution of the RA patients according to duration of disease

Figure 4, shows the distribution of the patients according to duration of disease. Patients were divided into three groups: <5, 5-10, and >10 years. The results of statistical analysis revealed significant differences within-RA patients groups with and without MetS, where the highest percentage (72.5% and 70%, respectively) were in the 5-10 years group.

Correlation between some hormones, interleukins and molecular parameters in RA patients with MetS

The correlation between hormones, interleukins and molecular parameters in the study groups (RA with MetS) are shown in Table 3. In RA patients with MetS, the correlation and reversion analysis revealed that insulin had a significant positive correlation with IL-23 (p=0.011); adropin had a significant positive correlation with IL-17 (p=0.024).

This study explored the multifaceted interplay between the two hormones (insulin and adropin), pro-inflammatory cytokines (IL-17 and IL-23), and molecular markers (ENHO and glycerol-3-phosphate dehydrogenase (GPDH)) in RA patients with and without MetS. The aim was to understand the mechanistic associations between immune response mechanisms, metabolic control, and molecular processes in RA with a focus on interaction among these factors and how they contribute towards pathology of disease. One of the most significant findings of the current study was that there were no significant correlations between the levels of adropin or insulin and molecular parameters, such as ENHO and GPDH.

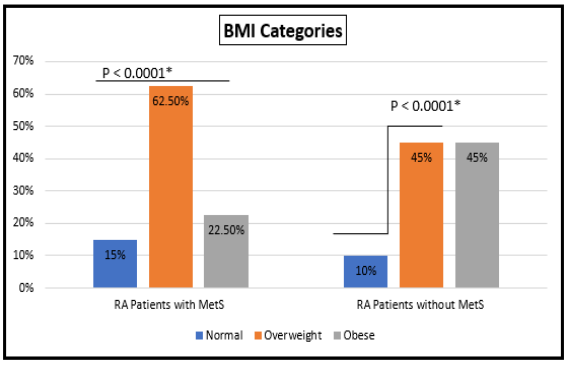

Figure 3. Distribution of the rheumatoid arthritis (RA) patients according to body mass index (BMI). The figure shows the percentage of RA patients with and without MetS according to BMI, categorized into normal, overweight, and obese BMI groups. A significantly higher proportion of patients with MetS were in the overweight category, while RA patients without MetS showed an even distribution between overweight and obese categories.

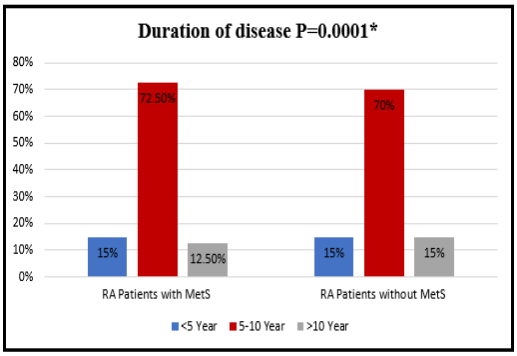

Figure 4. Distribution of the rheumatoid arthritis (RA) patients according to duration of disease. This figure presents the distribution of RA patients with and without MetS based on disease duration: <5, 5–10, and >10 years. The majority of patients in both groups were within the 5–10 years category, indicating a possible association between intermediate disease duration and increased MetS prevalence.

Table 3. Correlation between hormones, interleukins and molecular parameters in rheumatoid arthritis (RA) patients with MetS.

Study population	Parameters		Insulin	Adropin	IL-17	IL-23	ENHO	GPDH
RA patients with Mets	Insulin	Pearson Cor.	1					
		p value	-					
	Adropin	Pearson Cor.	-0.139	1				
		p value	NS					
	IL-17	Pearson Cor.	0.003	0.357	1			
		p value	NS	0.024				
	IL-23	Pearson Cor.	0.396	0.034	-0.042	1		
		p value	0.011	NS	NS			
	ENHO	Pearson Cor.	-0.043	-0.146	-0.035	-0.042	1	
		p value	NS	NS	NS	NS		
	GPDH	Pearson Cor.	0.158	-0.155	-0.187	0.080	-0.133	1
		p value	NS	NS	NS	NS	NS	

p > 0.05 is not significant (NS).

Correlation between some hormones, interleukins and molecular parameters in RA patients without MetS

The correlation between hormones, interleukins and molecular parameters in the study group (RA without MetS) is clarified in Tables 4. In RA patients group without MetS, the correlation and regression analysis revealed that IL-23 had a significant negative correlation with insulin (*p*=0.029); GPDH showed a significant negative correlation with ENHO (*p*=0.045).

Table 4. Correlation between hormones, interleukins and molecular parameters in rheumatoid arthritis (RA) patients without MetS.

Study population	Parameters		Insulin	Adropin	IL-17	IL-23	ENHO	GPDH
RA patients without Mets	Insulin	Pearson Cor.	1					
		p value						
	Adropin	Pearson Cor.	0.126	1				
		p value	NS					
	IL-17	Pearson Cor.	-0.087	-0.089	1			
		p value	NS	NS				
	IL-23	Pearson Cor.	-0.346	-0.075	0.048	1		
		p value	0.029	NS	NS			
	ENHO	Pearson Cor.	0.064	-0.067	0.084	-0.265	1	
		p value	NS	NS	NS	NS		
	GPDH	Pearson Cor.	-0.132	0.211	0.071	-0.183-	-0.319	1
		p value	.415S	NS	NS	NS	0.045	

p > 0.05 is not significant (NS).

Discussion

The <30 years age group, showed a striking contrast between RA patients with and without MetS. This suggested that MetS is significantly less prevalent among younger individuals with RA. Several biological and lifestyle-related factors may explain this finding. MetS is known to develop gradually over time as a result of long-term exposure to risk factors such as obesity, sedentary behavior, poor diet, chronic inflammation, and age-related changes in the metabolism.[15] Individuals under 35 are generally

less exposed to these cumulative risk factors, which may protect them from developing MetS at this early stage of life.[16]

On the other hand, the close percentages observed in the 35-50 age group in the RA patients with and without MetS suggested that factors beyond age might contribute to the development of MetS in RA patients. The use of disease-modifying anti-rheumatic drugs (DMARDs) and glucocorticoids, both known to influence metabolic parameters, could be influencing the observed patterns.[17]

The prevalence of RA with MetS in the age category (>50 years) with higher percentage may indicate that age is a significant factor in the development of MetS among RA patients, with older individuals showing a higher predisposition. This is in agreement with an earlier study by Metelskaya, 2012.[18] Furthermore, RA itself has been related with an improved risk of MetS due to chronic inflammation and immune system dysregulation, which may become more pronounced with age.[19] Literature indicating that age alone is the primary determinant of MetS prevalence in RA patients. Other confounding factors, such as lifestyle choices, medication use (e.g., corticosteroids), and genetic predisposition, could equally play significant roles.[20]

In the group of RA patients with MetS, the proportion of females and males was close, with no significant difference. According to Cai *et al*., 2022,[21] the pooled occurrence of MetS in RA patients is around 32%, with no significant gender difference in MetS prevalence among RA patients. The possible explanation is that RA patients with MetS might represent a subgroup with additional risk factors, such as malignancy, which has a different sex distribution. Several malignancies, particularly lung cancer and hematologic malignancies are more common in males and can be associated with RA.[22] Additionally, chronic inflammation in RA has been linked to increased cancer risk due to persistent immune activation, cytokine-mediated DNA damage, and oxidative stress.[23]

In RA patients without MetS, higher prevalence of females (65%) aligns with the well-established epidemiological pattern of RA, which predominantly affects females more than males. Previous studies suggested that hormonal, genetic, and immunological factors contribute to this disparity.[24] Also, Oliver & Silman, 2009[25] mentioned that estrogen and other sex hormones are thought to play a role in modulating immune responses, potentially increasing susceptibility to RA in women. Furthermore, X-chromosome-linked immune regulatory genes may also contribute to the higher prevalence in females with RA.[26]

Regarding to BMI, the present outcomes are in agreement with the findings of Giraud *et al.,* 2021,[27] who stated that the highest prevalence of the RA disease was in the overweight group. One possible explanation for these findings is that overweight individuals with RA may experience metabolic dysregulation due to chronic inflammation, IR, and altered lipid metabolism, which collectively contribute to the development of MetS.[28] Additionally, cytokines such as tumor necrosis factor (TNF)-α and IL-6, which are elevated in RA, were implicated in both obesity-related metabolic disturbances and RA pathophysiology.[29]

The result revealed that the long term inflammation in RA, especially in those with disease duration of 5-10 years, has an important role in the development of MetS. This could be attributed to the chronic up-regulation of pro-inflammatory cytokines that is involved in IR and dyslipidemia.[30] Also, prolonged exposure to glucocorticoids and DMARDs exacerbates metabolic derangements, contributing to a high prevalence of MetS in this group.[31] One potential cause of increased MetS rate in this group could be due to the combination of disease active and drug side effects. In addition, reduced physical activity secondary to pain and fatigue may further deteriorate metabolic health at this point.[32] However, some studies have shown a larger prevalence of the reverse with disease duration above 10 years, suggesting that collective inflammation and long-term side effects of treatment may have an extra obvious impact on metabolic health over time.[33]

In patients suffering from both RA and MetS, it appears that the molecular markers under investigation are not directly influenced by

metabolic peptides or insulin levels. While earlier research by Yolbaş, *et al*., 2018,[34] hinted at possible connections between metabolic health and molecular signaling in various diseases, the current findings suggest that such links in RA might be more complex and dependent on the specific physiological context.

Interestingly, in the group of RA with MetS, the study found a statistically significant positive correlation between insulin levels and IL-23 concentrations. This suggests that elevated insulin potentially reflecting underlying IR may be associated with increased expression of IL-23. Since IL-23 is a cytokine central to the Th17 immune pathway and is known to drive autoimmune inflammation in RA,[35] this link is notable. Varra *et al*., 2024[29] also pointed to a meaningful association between systemic inflammation and IR, possibly mediated by the up-regulation of inflammatory cytokines such as IL-23. These findings could have therapeutic implications. Targeting IR through interventions like dietary adjustments, physical activity, or insulin-sensitizing medications (e.g., metformin) may not only improve metabolic profiles but also reduce inflammatory markers and possibly decrease IL-23 levels, thereby influencing the course of RA.[36]

Another point of interest is the observed association between adropin levels and IL-17 concentrations. Adropin, a peptide hormone that plays a role in energy regulation, showed a positive correlation with IL-17 levels in patients with RA and MetS. IL-17 demonstrates pro-inflammatory properties, T helper 17 (Th-17) cells secrete cytokines encoded by particular cytokine genes,[37] and this could further underscore the intertwined nature of metabolic and immune pathways in disease progression. Zi *et al*., 2023[38] postulated that adropin may modulate immune cell metabolism, with effects on Th17 cell differentiation and production of cytokines. Additionally, systemic inflammatory syndrome widely observed in RA may modulate adropin metabolism, giving rise to an increase in concentration of adropin, as described by Memi & Yazgan, 2021,[39] in their induced models of chronic inflammation. The relationship highlights a possible link between regulation of metabolism and immune system activation. Consenting with Rooban *et al*., 2024,[40] hypothesis, modulation of adropin concentration or it signaling pathway may provide a new modus operandi to treat both metabolic derangements as well as Th17-mediated inflammatory processes in RA, thereby giving way to more integrative disease management.

Regarding to RA patients without MetS group, there was no significant associations between insulin or adropin and the ENHO, GPDH nor between IL-17 and IL-23 with adropin, ENHO, or GPDH. However, two notable negative correlations were identified between the insulin peptide hormones with IL-23, offering valuable insight into disease mechanisms in this patient subgroup. The current study concurs with previous research among patients with RA with MetS, where a strong relationship between IL-23 and insulin was noted,[41] These findings add credence to the fact that IR plays a pivotal role in systemic inflammation by promoting pro-inflammatory cytokine production, including IL-23. In RA patients with normal metabolic health, preservation of sensitivity to insulin may result in reduced inflammatory pathway activity, with particular noteworthy observation in this case being the decrease in IL-23/Th17 pathway activity. The observation ties with IL-23's well-documented role in inducing Th17 differentiation and maintaining ongoing inflammation in RA. Additionally, low insulin levels may also mean a more favorable state of metabolism, possibly curtailing IL-23-induced immune responses.

Conversely, Zhao *et al.,* 2023,[42] provided a different perspective, based on the contention that an absence of evidence in these populations towards metabolic dysregulations, including IR, explains these differences in findings. To this point, evidence by Galle-Treger *et al.,* 2022,[43] showed dysmetabolic dysfunctions, including autophagy disruption, caused an overproduction of IL-23, with this serving as a reminder of how critical metabolic well-being is in shaping inflammatory responses. Clinically, these results highlighted the imperative of maintaining metabolic homeostasis. Although evidence presently suggests reducing pro-inflammatory activity by

controlling IR may possibly improve treatment in patients with RA, the interacting dynamics between metabolic state and IL-23-mediated immunity are complex and require more study.[42]

The inverse relationship between ENHO and GPDH levels in RA patients without MetS, suggests that increased ENHO expression is associated with decreased GPDH levels in these patients, potentially indicating a regulatory interplay between oxidative metabolism and neutrophil activity within the inflammatory environment of RA. These current results agreed with those of Lovren *et al.,* 2010,[44] who reported that ENHO contributes to metabolic homeostasis and exhibits anti-inflammatory properties, supporting the notion that elevated ENHO levels may reflect an adaptive response aimed at mitigating inflammation and oxidative stress in RA. Although that GPDH is considered housekeeping gene assumed to be stably expressed across most cell types and tissues. However, in practical research contexts particularly under pathological conditions such as chronic inflammation, cancer, or autoimmune diseases RA, thus the expression of GAPDH may not remain stable under all conditions. In conclusion, the study results highlighted how metabolic and demographic factors affect the course of RA and underline the need of a thorough metabolic inflammatory therapy strategy.

Author Contributions

MQA; proposed and designed the study and supervised the research process. AAH; examined the patients, collected samples and performed the laboratory work. MQA, AAH; interpreted the laboratory test results and analyzed the data and participated in writing and reviewing the paper and prepared the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of the College of Science, University of Baghdad (Ref.: CSEC/1123/0071, dated November 2023).

Informed consent

An informed consent was obtained from each subject before being included in the study.

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