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RESEARCH ARTICLE

Relation of Resistin, Visfatin, and Carotid Intima-Media Thickness to Metabolic Syndrome and Insulin Resistance in Egyptian Rheumatoid Arthritis Patients

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ABSTRACT

Introduction: Adipocytokines are hormones secreted by adipose tissue, playing a significant role in the pathogenesis of the immune response in rheumatoid arthritis (RA).

Objective: We investigated the changes in resistin, visfatin, and carotid intima-media thickness (CIMT) in rheumatoid arthritis patients and their relationship with metabolic syndrome and insulin resistance.

Research design and methodology: We studied 140 subjects: 70 with RA, 41 patients with metabolic syndrome (MetS) (group A), 29 without MetS (group B), and 70 controls (group C). We compared the five parameters of metabolic syndrome, level of both visfatin and resistin in serum, CIMT, and Homeostatic Model Assessment of Insulin Resistance (HOMA IR) among the three groups.

Results: There was an increase in means of systolic blood pressure (SBP) ($P< 0.03$), waist circumference (WC) ($P<0.001$), triglycerides (TG) ($P<0.001$), fasting blood glucose (FBG) ($P<0.02$), visfatin ($P<0.001$), CIMT ($P<0.001$) and (HOMA IR) ($P < 0.001$) in cases than controls. In patients of group A, the CIMT mean was higher than in group B ($P<0.001$). Visfatin mean was higher in group B than in group A ($P<0.001$). There was an add-on effect of MetS on RA. Regardless of MetS, WC was higher in cases of RA than in controls ($P<0.001$), and patients in group A showed higher FBG level ($P<0.006$). Resistin showed a positive correlation with the WC ($B=0.101$, $P<0.008$) while CIMT showed a positive correlation with both WC ($B=0.000$, $p=0.017$) and diastolic blood pressure (DBP) ($B=0.001$, $P<0.003$). Patients of RA with insulin resistance (IR) were more in group A than group B (36.6% vs 6.9%, respectively) ($P<0.0001$). Means of TG and FBG were higher in cases of RA with IR than those without ($P < 0.007$, 0.0001, respectively).

Conclusions: Resistin, visfatin, and CIMT can be used as markers of both immune and metabolic activity in cases of RA.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease of joints with autoimmune characteristics that has a predilection for synovial joints. Apart from its musculoskeletal effects, RA is also associated with an excess cardiovascular disease (CVD) risk, including accelerated atherosclerosis [1]. The excess cardiovascular risk is partly due to the systemic inflammation in RA, which contributes to endothelial dysfunction, insulin resistance, and dyslipidemia. Metabolic syndrome (MetS), a cluster of disorders that increase the risk of heart disease, stroke, and type 2 diabetes, is prevalent in RA patients. The components of MetS: abdominal obesity, hypertension, hyperglycaemia, and dyslipidemia are all individually prevalent in RA patients, further increasing their cardiovascular risk [2].

Adipokines, bioactive peptides secreted by adipose tissue, play significant roles in the pathophysiology of RA and MetS. Among them, resistin and visfatin have been of interest with their pro-inflammatory effects and their potential involvement in insulin resistance [3]. Resistin has been postulated to be the link between obesity, insulin resistance, and inflammation, while visfatin, also known as nicotinamide phosphoribosyl transferase (NAMPT), has been implicated in immune cell function and inflammation. Carotid intima-media thickness (CIMT) is a non-invasive ultrasound indicator of subclinical atherosclerosis and a predictor of future cardiovascular events [4].

Literature Review

Rheumatoid arthritis (RA) is a generalized autoimmune disease in which chronic, low-grade to high-grade inflammation reaches far beyond the synovium to incorporate vascular and adipose tissues [5]. Carotid intima-media thickness (CIMT), a non-invasive ultrasonographic measure of subclinical atherosclerosis, has consistently been found to be greater in RA than in control individuals and to reflect the chronic inflammatory and metabolic burden of these patients [6].

The association between inflammation, dyslipidemia, and insulin resistance (IR) in RA underlies a common "immuno-metabolic" phenotype, and CIMT has been extensively used as an early marker and prognostic surrogate of future CV events[7]. In Egyptian cohorts in particular, RA patients are more likely to have MetS than matched controls, showing population-level vulnerability and requiring context-dependent prevention [8].

Two adipokines, resistin and visfatin (nicotinamide phosphoribosyl transferase, NAMPT), are invariably involved with metabolic homeostasis and innate immunity. In RA, elevated resistin has been linked to disease activity and severity in several reports [9]. Visfatin, produced by adipocytes and immune cells, is upregulated in RA and is pro-inflammatory [10].

Various reports from Middle Eastern populations are attributing increased CIMT to composite metabolic burden, substantiating the pathophysiological concept of "immuno-metabolic" atherogenesis [11].

High MetS prevalence and high central adiposity (high waist circumference) within Egyptian female RA groups suggest that early, holistic CV prevention must be integrated into routine rheumatology management [12].

While resistin and visfatin are not yet clinical targets, they could serve as metabolic and cardiovascular biomarkers in RA with metabolic risk, extreme inflammatory burden, or rising CIMT [13].

Aim of work:

Our research aimed at evaluating a possible association of some adipocytokines (namely, resistin and visfatin) with metabolic syndrome (MetS) and inflammation, and discussed the relation of MetS to carotid intima-media thickness (CIMT) as a marker of cardiovascular (CV) risk in RA rheumatoid arthritis (RA) patients.

Patient and methods:

INCLUSION CRITERIA:

Our study enrolled 70 patients with RA who were chosen according to the 1987 American College of Rheumatology (ACR) classification criteria for RA [14]. They attended the outpatient clinic of the internal medicine department, rheumatology and clinical immunology division, of Cairo University School of Medicine from January to December 2019. We also enrolled 70 age and sex-matched “apparently” healthy control subjects.

EXCLUSION CRITERIA:

We excluded patients with other autoimmune diseases, including spondyloarthropathies, connective tissue diseases such as systemic lupus and systemic sclerosis, dermatomyositis, mixed connective tissue disease, crystal-induced arthropathies like gout and pseudogout, degenerative joint disease, e.g., osteoarthritis, patients with primary or secondary vasculitis, and sarcoidosis.

Insulin resistance was then estimated using the homeostatic model assessment index for peripheral tissue insulin resistance (HOMA-IR), which is calculated according to Wallace et al. [15], as follows: Fasting plasma insulin (FPI) x Fasting plasma glucose (FPG) (mg/dl)/405. MetS was diagnosed according to the NCEP/ATP III criteria modified in 2005 by the NHLBI. The criteria for clinical diagnosis of MetS are described by Alberti et al. and necessitate three or more of the 5 parameters of metabolic syndrome [16] which are:

1. Glucose: Elevated fasting glucose ≥100mg/dL (5.6 mmol/L) (or drug treatment of elevated glucose)
2. HDL cholesterol: Reduced HDL-C <40 mg/dL (1.0 mmol/L) in males; and <50 mg/dL (1.3 mmol/L) in females (or drug treatment for reduced HDL-C).
3. Triglycerides: Elevated triglycerides ≥150 mg/dL (1.7 mmol/L) (or drug treatment for elevated triglycerides).
4. Obesity: Elevated waist circumference: for men ≥102cm, for women≥88cm)
5. Hypertension: Elevated blood pressure: Systolic ≥130 and/or diastolic ≥85 mm Hg (or

antihypertensive drug treatment in a patient with a history of hypertension)

All cases and controls in the study were subject to full history taking, including joints affected, onset, course, duration of the disease, morning stiffness, as well as medications taken, such as antihypertensive drugs, antihyperlipidemic drugs, anti-inflammatory drugs, Disease Modifying Anti-Rheumatic Drugs (DMARDS), and other medications. Family history was taken, stressing previous cardiovascular events and family history of rheumatic diseases. Blood pressure was measured in mmHg. Waist circumference (WC) was measured in cm. A full musculoskeletal examination was applied. Investigations included measuring serum levels of fasting insulin, fasting glucose, fasting triglycerides, HDL, HOMA IR, and calculated MetS criteria. Two adipocytokines (resistin and visfatin) were selected and measured using the enzyme-linked immunosorbent assay (ELISA) and compared between patients and controls [17]. We used ELISA kits from AssayPro (USA) (for resistin), catalogue number ER1001-1/ER1001-7, analytical sensitivity 74 pg./mL, intra-assay CV $\leq 5.6\%$, and inter-assay CV $\leq 11.2\%$ *and* , Glory Science (for visfatin) (China), catalogue number 11560, analytical sensitivity $\gg 1\mu g/L$, intra-assay CV [<9%], inter-assay CV [<15%]. CIMT was measured bilaterally on a SONODEPOT PHILIPS HDI 5000 ultrasound using a [7–12 MHz] linear probe. Six measurements per subject were averaged (at the common carotid arterial bulb, approximately 1 cm proximal to it, and 1 cm distal to it (at the origin of the internal carotid artery) on both sides.

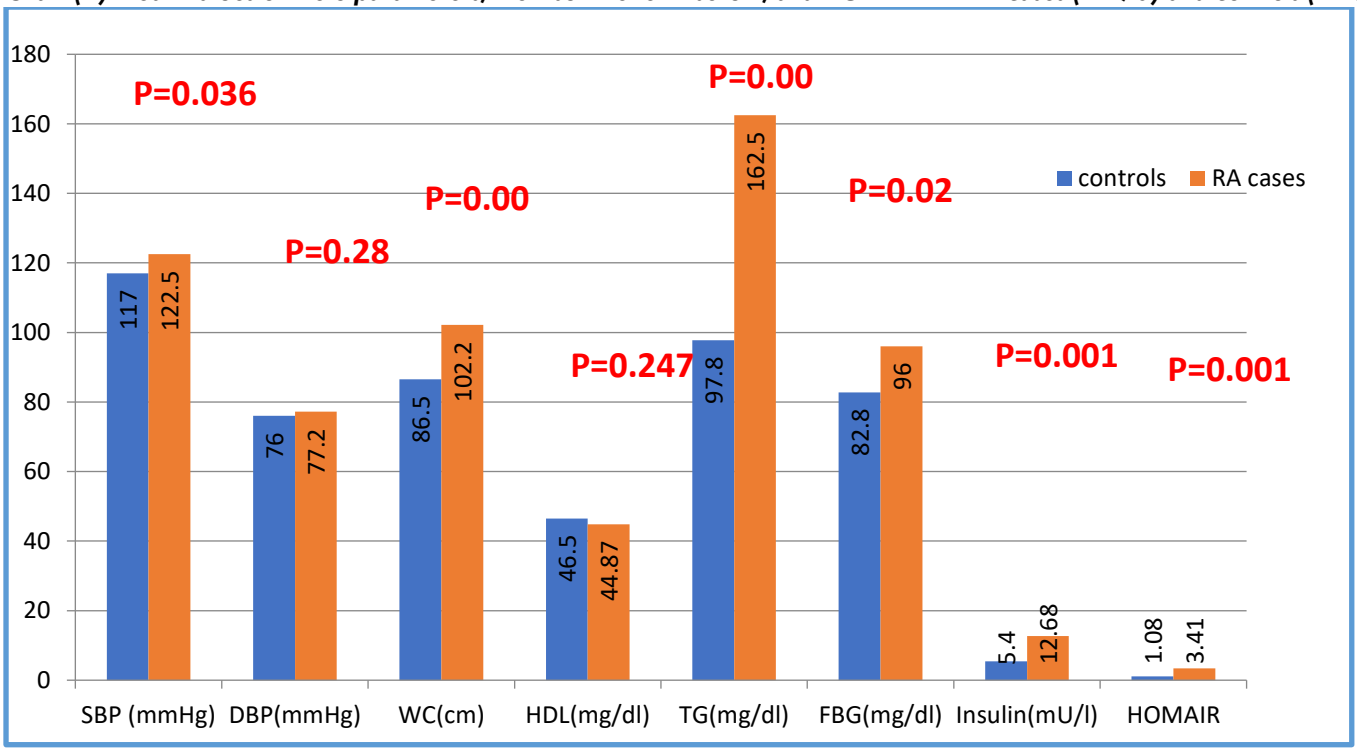
Results

Data were statistically described in terms of mean, standard deviation (± SD), median, and range, or frequencies (number of cases) and percentages when appropriate. A comparison of numerical variables between the study groups was made using the Student t-test for independent samples when comparing two groups of normally distributed data and the Mann-Whitney U test for independent samples when comparing non-normal data. A Chi-square ($\chi 2$) test was performed to compare categorical data. The exact test was used instead when the expected frequency was less than 5. Correlation between different variables was done using Spearman's equation. Multivariate linear regression analysis was used to test for the preferential effect of the independent variable(s) on resistin, visfatin, and CIMT thickness. P values less than 0.05 were considered statistically significant. All statistical calculations were done using the computer program SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA), release 15 for Microsoft Windows (2006).

All our RA patients were females (70 patients: 100%) with a mean age of 44.6 +/- 11.7 years. Control subjects were also females (70: 100%) with a mean age of 42.8+/- 11.7 years.

Of all our 70 patients, 14 had erosions (20%), and 27 patients suffered from extra-articular manifestations (38.6%) (namely, lung fibrosis, tenosynovitis, skin nodules, vasculitis, and muscle wasting).

Chart (1) Mean values of MetS parameters, the insulin level in serum, and HOMA-IR in RA cases (N=70) and controls (N=70):



***SBP** systolic blood pressure, **DBP** diastolic blood pressure, **WC** waist circumference, **HDL** High-density lipoproteins, **TG** triglycerides, **FBG** fasting blood glucose

Chart (1) showed a significant difference between SBP, WC, TG, FBG, fasting insulin, and HOMA-IR values in both cases and controls.

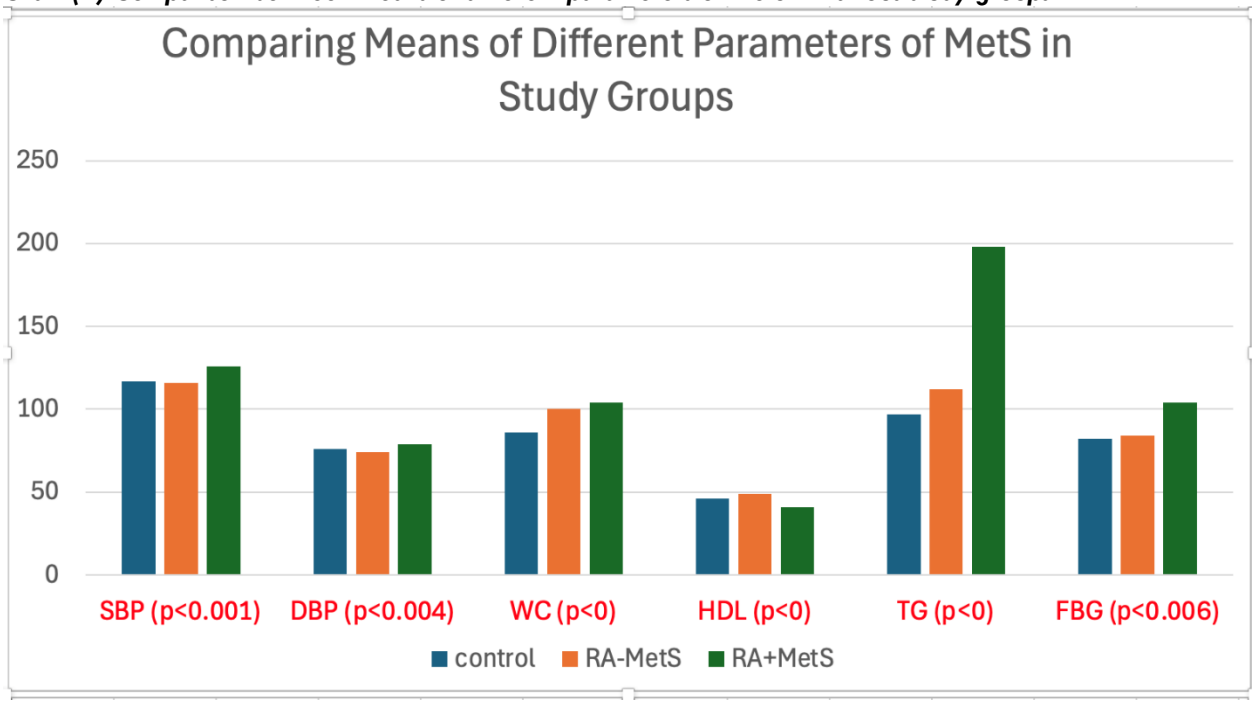
Mean serum levels of resistin and visfatin in RA patients were 15.9 ± 3.9 ng/ml and 9.86 ± 9.7 ug/l versus 15.2 ±2.3 ng/ml and 4.3±0.5ug/l in controls with P values of 0.21 and <0.001, respectively.

Mean CIMT was 0.07 ±0.01 and 0.06 ±0.00 cm for RA patients and controls, respectively, with a P-value of <0.001

Rheumatoid Arthritis and Metabolic Syndrome:
Rheumatoid arthritis cases were subdivided into 41 cases with MetS (MetS+) (58.6%) and 29 cases without MetS (MetS-) (41.4%).

The relation between Rheumatoid Arthritis Disease Duration and Metabolic Syndrome:
RA/MetS+ cases had a mean disease duration of 6.48±3.9 years, significantly lower than RA/MetS- cases, 9.52±6.34 years (P<0.028). This may indicate that cases of RA that develop MetS tend to get it quickly, or they may have developed it before they showed the symptoms of RA.

Chart (2) Comparison between means of different parameters of MetS in various study groups



*__SBP__ systolic blood pressure, __DBP__ diastolic blood pressure, __WC__ waist circumference, __HDL__ High-density lipoproteins, __TG__ triglycerides, __FBG__ fasting blood glucose, __RA__ rheumatoid arthritis, __MetS__ metabolic syndrome

Chart (2) showed a significant statistical difference between controls, RA/MetS- and RA/MetS+ regarding all MetS parameters.

Chart (3) Comparison between mean values of resistin, visfatin, and CIMT in RA / MetS+ (N=29), RA/MetS- (N =41), and controls (N=70):

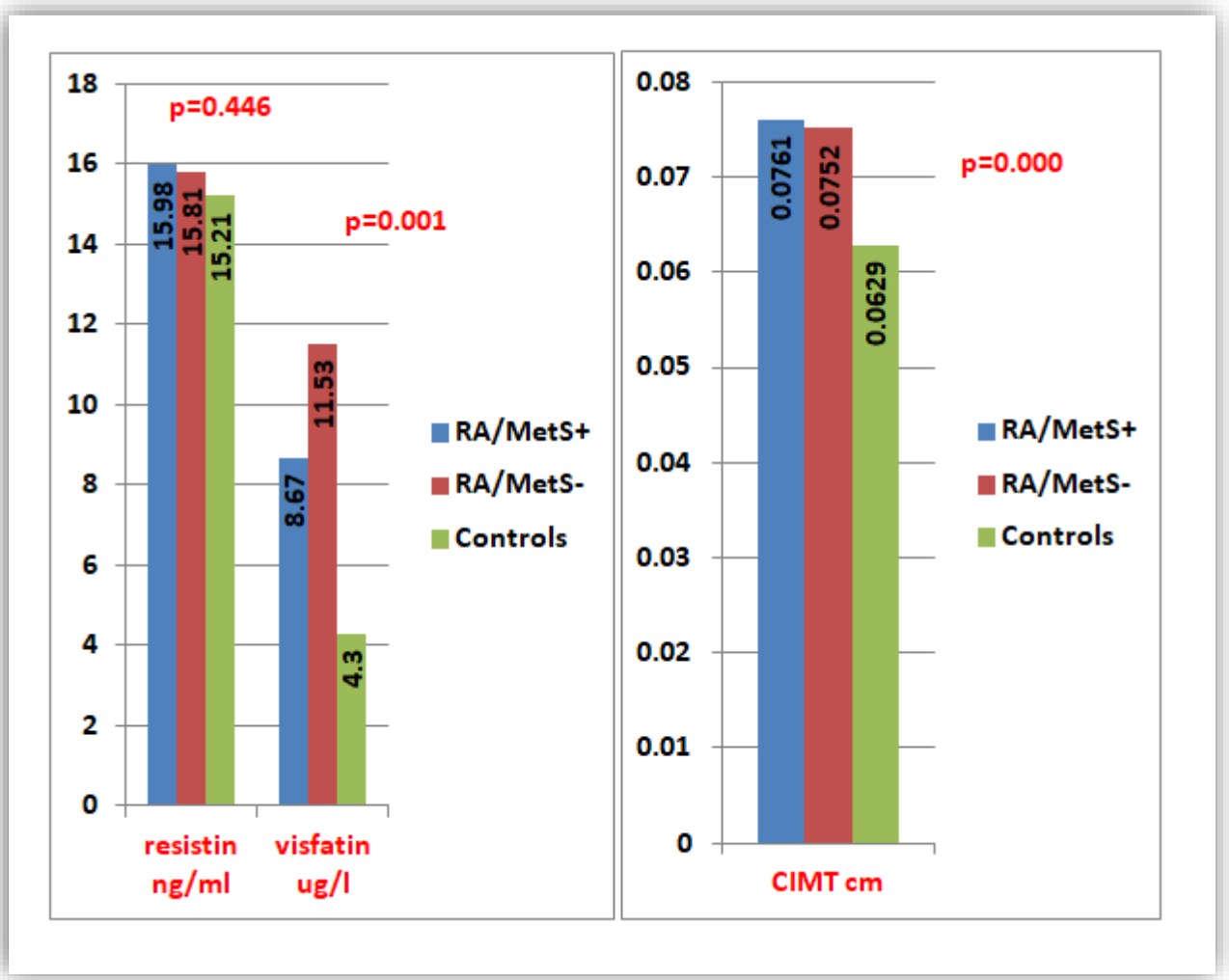


Chart (3) showed that resistin and CIMT were higher in RA/MetS+>RA/MetS->controls, while serum levels of visfatin were higher in RA/MetS-> RA/MetS+>controls with p values of 0.446, <0.0001, and <0.001, respectively.

Insulin resistance:
Seventeen out of 70 RA patients have IR, further subdivided into 15 out of 41 with RA/MetS+ (36.6%), and 2 out of 29 (6.9%) with RA/MetS-, versus 4/70 (5.7%) controls with P value<0.0001

Table (1) Spearman's correlation between different research parameters in our study:

Research Parameters		Visfatin	Resisitin	Thickness
IR	Correlation Coefficient(r)	-0.096	0.017	0.028
	p value	0.428	0.887	0.817
Met S	Correlation Coefficient(r)	-0.045	0.116	0.068
	p value	0.710	0.338	0.575

Table 1 showed a negative correlation between visfatin and both IR and MetS, and a positive correlation between both resistin and CIMT and both IR and MetS, although insignificant.

Age of studied subjects significantly correlated with each of resistin, visfatin, and CIMT, with p-value <0.0001,0.004,0.0001 with CI (95%) of 0.1-0.27,0.09-0.45,0.001-0.001, respectively.

Discussion

It is now well-established that visceral and subcutaneous adipose tissues produce a specific group of adipokines to mediate inflammation [18]. Resistin and visfatin are

among the recent adipocytokines; resistin was introduced in 2000 [19,20,21], while visfatin appeared in 2004 [22]. Therefore, we used them in the current study as inflammatory markers in cases of RA.

Patients with MetS have their CV outcomes increase by 2-fold, and all-cause mortality increases by 1.5-fold [23]. In addition, IR significantly increases the risk of CV disease. There are links between IR and the associated dyslipidemia, hypertension, hypercoagulability, and atherosclerosis. Some of these links are related to genes that independently impact lipid metabolism, blood pressure regulation, coagulation, and arterial wall status. In addition, abnormal fatty acid metabolism has a significant impact on the development of IR. Thus, the association between IR and dyslipidemia emerges from increased free fatty acids (FFA) release from or defective uptake of FFAs into adipocytes. Moreover, fatty acids are related to endothelial dysfunction and, hence, CV risks [24].

Our study examined resistin and visfatin as markers of inflammation, and CIMT as a measure of CV risk. We not only compare cases of RA to control healthy subjects but also add RA/MetS and RA/IR co-morbidity.

Our study stands out as one of the few to categorize RA cases into those with and without MetS. Unlike some studies that rely on BMI or waist-hip ratio [25,26], we adhered to the NCEP/ATP III criteria modified in 2005 under NHLBI [27], using waist circumference as our primary measure of obesity.

Our study found a significant positive correlation between age and markers of inflammation, as well as CIMT as a marker for CV risk. These findings, consistent with Wagenknecht et al.'s extensive population study [28], could have important clinical implications.

Age, in our study, was significantly correlated with the higher levels of resistin, visfatin, and CIMT. Older patients had more inflammation, which may be due to less β-cell function and production of adipocytokines due to consequent adipose tissue inflammation. On the contrary, Senolt et al. reported that there is no relation between age and serum levels of resistin and visfatin in RA patients [29]. Rizi et al. postulated ethnic heterogeneity as a possible cause for these contradictory results [30].

Our RA/MetS+ cases had significantly lower disease duration than RA/ MetS- cases. Cases of RA that developed MetS probably tended to develop it earlier, or they might have developed it before they showed the symptoms of RA. However, there is no proven causal relationship between RA and MetS [31].

Our results revealed no correlation between resistin, visfatin, and CIMT levels with the disease duration. This finding was consistent with van Sijil et al., who postulated that visfatin production is not a cumulative phenomenon related to the time-lapse. Instead, it may be influenced by short-term factors like inflammatory mediators and drugs [32].

In our study, though insignificant, resistin serum levels were higher in RA/MetS+ than in RA/MetS- than in control subjects. In a survey by Alkady et al. [33] and Otero et al. [17], no significant difference was found between resistin levels in RA patients and controls. On the other hand, Forsblad et al. showed a significant relationship between resistin and inflammatory markers like ESR, CRP, and TNF-α [34], and Senolt et al. proposed the relationship between resistin and disease activity using CRP and disease activity score (DAS28) [29]. The significantly high serum resistin levels in the latter studies may be explained by their relation to disease activity rather than the presence or absence of the disease. Senolt et al. got the same conclusion and stated that in humans, resistin is more directly related to inflammation. In addition, they demonstrated that increased resistin levels in RA patients may be directly linked to enhanced disease activity [29].

Numerous hormonal factors, including glucocorticoids, can regulate resistin levels. As glucocorticoids can increase resistin production [35], we may speculate that the increased resistin level in patients with RA can be partly due to glucocorticoid treatment. This postulation was denied by Senolt et al. [29].

There are other suggested mechanisms -other than stimulation by exogenous glucocorticoids- that may be responsible for the increase of resistin levels in patients with RA; Bokarewa et al., for instance, suggested other pro-inflammatory cytokines and a positive feedback loop (resistin itself) as possible causes for resistin levels upregulation in inflammatory conditions such as RA [36].

Our work showed a positive correlation between resistin levels and waist circumference, but not IR.

Rizi et al. did not support a key role for resistin in abdominal adiposity and IR [30]. Straburzyńska-Lupa et al. also found no correlation between resistin levels, insulin levels, and IR, but, unlike our study, no correlation between resistin and WC [26]. On the contrary, Heilbronn et al.'s study indicated a potential role of resistin in the pathogenesis of IR [37].

Some authors reported that resistin concentration increases with obesity [38], whereas others have not [39]. Some authors suggested that resistin impacts adipose tissues and systemic inflammation [40]. Our study confirmed that resistin has a positive correlation with waist circumference but not IR.

Rizi et al. attributed these differences to variations in the measurement techniques for these adipocytokines, challenges in data interpretation, and heterogeneity among the studied populations. Additionally, the concentration of these adipocytokines may differ between acute and chronic exposure, and finally, the effect of these adipocytokines may be tissue-specific [30].

Unlike resistin, visfatin levels in our work were significantly higher in RA cases compared to control subjects, which may indicate that visfatin is a better marker of inflammation in such a group of patients.

A meta-analysis by Lee and Bae also showed that visfatin levels in RA patients were significantly higher than those in the control group, and they also found a positive correlation with disease activity measured by DAS28 and CRP levels [41].

Neumann et al. reported that visfatin activates leukocytes and protects them from apoptosis [42]. Furthermore, in a study by Busso et al., blocking visfatin activity was shown to reduce the severity of arthritis in the collagen-induced arthritis mouse model [43].

On the other side, in a study by Gonzalez-Gay et al., serum visfatin levels were not associated with most clinical and laboratory parameters of disease activity and inflammation, nor were they correlated with metabolic characteristics in patients with RA [44].

Our study marked a significant drop in visfatin in RA/MetS+ compared to RA/MetS- patients, which might be related to the downregulation of visfatin production ensued by the high metabolic activity.

We could not find a relation between visfatin and any parameter of MetS, which may confirm the postulation that visfatin is affected mainly by the inflammatory reaction of RA rather than by the metabolic derangement of MetS.

Close to our findings, Straburzyńska-Lupa et al. showed significantly lower visfatin levels in patients with RA and abdominal obesity in comparison to those without abdominal obesity [26], which may be the result of disturbed adipokine secretion and action during obesity as postulated by Trayhurn and Wood [45]. It may also be possible that visfatin in peripheral tissues is influenced by negative feedback from other adipokines or other factors released by adipose tissue in RA.

From another point of view, serum visfatin levels had also been correlated with fat mass and the presence of the MetS [22]. Therefore, they may be the mediators of metabolic abnormalities detected in inflammatory conditions like RA.

In our study, patients with high fasting blood sugar showed higher levels of resistin, visfatin, and CIMT as markers for inflammation, although the increase is not significant. Impaired fasting glucose and diabetes are clinical hallmarks of impaired βcell function and adipose tissue inflammation.

In a study by Dogru and his colleagues, visfatin levels were higher in patients with diabetes mellitus compared to healthy controls [46]. However, they were not related to either BMI or HOMA IR, findings that are consistent with our study. Moreover, McGee et al. suggested that visfatin is regulated by rosiglitazone in Type 2 Diabetes [47]. Ozgen et al. also demonstrated that although serum visfatin levels were higher in RA patients, it was not associated with IR [48], and Pagano et al. determined that circulating visfatin levels are correlated with inflammatory status but do not reflect the degree of insulin resistance [49].

Our work showed a significant increase in CIMT in RA patients compared to controls, which makes it an excellent indicator of CV risk. However, CIMT had no significant direct correlation with either IR or MetS in RA patients, which may give the impression that the inflammation rather than metabolic derangement is responsible for the increase in CIMT and CV risk.

In the meta-analysis done by van Sijil et al., the key finding is a statistically significant increase in CIMT in RA patients compared to control subjects, supporting epidemiological evidence for an increased CV burden in these patients [32], which was also confirmed by Kim et al. [50].

In another study by Gonzalez-Juanatey et al., CIMT could highly predict the development of CV events in patients with RA who were followed up for 5 years. They added that higher CIMT as a marker of "subclinical atherosclerosis" was associated with a higher incidence of silent heart ischemia and sudden cardiac death in RA patients [51], a finding confirmed by Maradit-Kremers et al. [52].

In our work, CIMT positively correlated with both IR and MetS, though results were statistically nonsignificant, with higher values in RA/MetS+ compared to RA/ MetS- patients. These two findings together may indicate the "add-on harm" of RA/MetS/IR co-morbidity on subclinical atherosclerosis, hence CV morbidities and mortality.

This study demonstrated that 58.6% of our RA patients had MetS, which is higher than previous studies (22-44%) [53,54,55]. Using time-varying BMI, Lu et al. observed that obese nurses in the NHS (Nurse Health Society) with a BMI ≥30 kg/m2 (according to the WHO definition) tend to have a higher risk of RA [25]. In the same study, being overweight (BMI ≥25 kg/m2, based on a retrospective self-assessment) at the age of 18 was a significant predictor of RA [25]. Furthermore, according to a population-based control study from Olmsted County, Minnesota, obesity was associated with an increased risk of RA diagnosis before, but not after, the age of 60 [56].

In our study, there was a significant increase in WC in cases of RA/MetS+ and RA/MetS- compared to control subjects. Therefore, we can postulate that increased WC may accompany the inflammatory process of RA independent of the presence of MetS, a postulation confirmed by Dessein and Joffee [57].

In our study, there was a significant difference between the values of BP, HDL, TG, FBG, and WC among our three groups. An increase in both TG and WC in our RA patients compared to controls may highlight the importance of diet control to decrease CV risk, which is known to increase with high TG and/or WC.

Our study also revealed a significant increase in systolic BP over diastolic BP in RA patients compared to controls. An increase in systolic BP has a greater effect on the occurrence of atherosclerosis, especially in old age with high CV risk [58], which may contribute to the premature atherosclerosis and CV risk noticed in young patients with RA.

Our results showed that SBP, TG, and FBG had a significant increase in cases compared to controls. However, we did not find a significant difference between RA/MetS+ and RA/MetS-. Whether RA per se may increase the level of blood sugar independent of the presence of MetS due to different factors such as medications, IR, βcell dysfunction, or through the inflammatory adipokines themselves, as postulated by Dessein and Joffee [57] and Karakoca et al. [55]. This question needs to be further investigated.

Cases of RA with IR showed a significant increase in TG and FBG. At the same time, there was no increase in WC, as expected to be high due to the increase in IR, a finding which indicates that IR may be related to the inflammatory process of RA rather than the increase in body weight [57].

Limitations

1- Further studies with a greater number of patients are to be done, including separate arms of patients with isolated MetS to highlight the isolated effect of MetS more precisely.
2- We encourage repeating this study on males, as our study included only females.

Conclusions

-Resistin was more correlated with the inflammatory effect of RA, while visfatin was correlated with both the inflammatory and metabolic effects of RA.
-Resistin showed the highest correlation to waist circumference
-RA may be related to the increase in FBG and waist circumference, independent of the add-on effect of metabolic syndrome.
- An increase in insulin resistance and metabolic syndrome accompanied RA.
- Visfatin was significantly correlated with the add-on effect of metabolic syndrome on RA.
-The combination of RA with MetS increases CV risk, which is proven by an increase in CIMT
-Our study encourages applying the CIMT test for patients with RA to determine subclinical atherosclerosis as an early indicator of CV risk.

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