ORIGINAL ARTICLE

The relation between serum visfatin levels and cardiovascular involvement in rheumatoid arthritis

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Abstract *Objectives:* To investigate the effect of visfatin on the cardiovascular system in rheumatoid arthritis (RA) patients.

Methods: Twenty patients diagnosed with RA were recruited, as well as 15 age and sex-matched healthy controls. The RA patients underwent thorough clinical examination including body mass index (BMI) and waist/hip ratio measurement. The disease activity score (DAS 28) was calculated. Echocardiography and coronary artery calcium scoring (CACS) were performed, as well as measurement of serum visfatin levels, total cholesterol, high density lipoproteins (HDL), low density lipoproteins (LDL), and serum triglycerides. The healthy control group had serum visfatin levels measured. Another group for risk stratification (RS) included 30 non-RA female patients who were referred for calcium scoring to exclude coronary artery disease and for lipid profile assessment.

Results: RA patients' ages ranged from 27 to 61 years (mean: 43.9 ± 11.6). They all had normal echocardiographic findings. Serum visfatin levels were significantly higher in the RA group (58.8 ± 6.6 ng/ml) versus the controls (13.8 ± 8.11 ng/ml). Eleven RA patients (55%) had evidence of coronary atherosclerotic changes with a mean CACS of 86.4 ± 360. There was a significant correlation between serum triglycerides and CACS ($P = 0.014$); however, there was no significant correlation of the CACS with the visfatin level, disease duration and DAS. Serum visfatin levels did not correlate with BMI or waist/hip ratio. Compared to the RS group, the RA group was significantly younger (43.9 ± 11.6 versus 56.8 ± 11.6 years, $P < 0.0001$). However, there was no statistically significant difference in the frequency of coronary artery calcification between the RA group (55%) and the RS group (32%) ($P = 0.65$) and no significant difference between the two groups in the CACS.

Conclusion: Coronary atherosclerosis occurs at least 10 years earlier in female patients with RA. Serum visfatin levels are elevated in RA patients; however, it does not explain early subclinical atherosclerosis.

1. Introduction

Rheumatoid arthritis (RA) is characterized by a systemic inflammatory state, involving several organs, including joints, skin, eyes, lungs, and blood vessels.[1] Coronary artery disease (CAD) and heart failure represent the most common causes of death in RA.[2] Patients with RA have a higher morbidity and mortality from myocardial infarction and allied disorders as accelerated atherosclerosis than the general population.[3] The risk of CAD in RA patients which precedes the ACR criteria-based diagnosis of RA cannot be explained by an increased incidence of traditional CAD risk factors in RA patients.[2]

Immune cells and soluble inflammatory mediators play a crucial role in RA pathogenesis.[4] These inflammatory processes resemble those in other chronic inflammatory diseases, such as atherosclerosis.[5] Expression of proinflammatory cytokines and inflammatory mediators influences all stages of atherosclerosis development, from early atheroma formation to thrombus development responsible for events as myocardial infarction.[6] The chronic systemic inflammation in RA can be considered as an independent risk factor for the development of atherosclerosis.[7–9]

Visfatin is one of the adipokines produced and secreted primarily by visceral white adipose tissue.[10] Overexpression of visfatin in disease is thought to be more than simply a biomarker of inflammation.[11] It has pro-inflammatory as well as immunomodulating properties through its extracellular form.[12] In rheumatoid arthritis, visfatin level was found to be elevated in plasma and synovial fluid of patients compared to control subjects.[13–15] In one study, serum and synovial fluid visfatin was found to be correlated with the degree of inflammation and clinical disease activity.[15]

On the other hand, visfatin was recently shown to play a role in plaque destabilization.[16] Its role in atherosclerosis was studied and its plasma levels were significantly higher in chronic CAD and acute coronary syndromes compared with control patients[17] and correlated with the presence of CAD independent of other cardiovascular risk factors.[18]

Unlike atherosclerotic non-RA patients, the role of visfatin in accelerating atherosclerosis in RA patients was not clearly defined and needs further elucidation owing to the scarceness of available research. It was found by some authors to be elevated in RA patients without being correlated with carotid intima-media thickness; a predictor of atherosclerosis[19] and by others to be not independently associated with the coronary artery calcium score (which detects CAD).[20] Identification of the role of visfatin in atherosclerosis in RA patients should add to better recognition and management of cardiovascular risk in RA and hence it may be a future therapeutic target.

1.1. Aim

To investigate the effect of visfatin on the cardiovascular system in patients with rheumatoid arthritis.

2. Methods

The study included 20 female patients diagnosed with RA, according to the 1988 revised ACR criteria,[21] who attended the Physical Medicine, Rheumatology and Rehabilitation department at the Faculty of Medicine, Alexandria University. Exclusion criteria included any systemic illness as endocrine disorders, other associated rheumatic diseases, history of myocardial infarction, any malignancy, chronic kidney or liver disease.

Detailed history taking about their condition including disease duration, morning stiffness and drug history was carried out. All patients underwent thorough clinical examination with special attention to cardiac and articular examination. Body mass index (BMI) (weight in kilograms/height in square meters) was determined. Waist and hip circumference measurement was performed to calculate the waist/hip ratio.[22] Disease activity assessment by the disease activity score (DAS 28) was carried out.[23] The formula employed in this study was the DAS28 with four variables:

$$DAS28 = 0.56\sqrt{(TEN28)} + 0.28\sqrt{(SW28)} + 0.70\ln(ESR) + 0.014\,(GH).$$ (TEN 28: 28 joint count for tenderness, SW 28: 28 joint count for swelling, Ln ESR: the natural logarithm of Westergren's erythrocyte sedimentation rate, GH: general health or patient's global assessment of disease activity on the visual analog scale (VAS) of 100 mm).

Laboratory investigations were performed, which included complete blood count and ESR. Serum visfatin levels were measured (visfatin was assayed using a commercially available ELISA kit, Phoenix Pharmaceuticals, Belmont, CA) (interassay coefficient of variation 4.9%) drawn after an overnight fast and stored at −70 °C). Lipid profile assessment, which included total cholesterol (TC), high and low density lipopro-

teins (HDL and LDL, respectively) and serum triglycerides (TG) was performed.

2.1. Cardiac assessment included

- Echocardiography: using HP envisor 1500 for the evaluation of left ventricular dimension and function and to exclude valvular lesions and pericardial involvement.
- Detection of early atherosclerosis: by identifying the coronary artery calcium score (CACS): multislice computed tomography (MSCT) data acquisition: examinations were performed using Toshiba 64-slice multislice aquilion systems (Toshiba Medical Systems, Tokyo, Japan).[24] A prospectively triggered coronary calcium scan was acquired with the following parameters: collimation 4×3.0 mm, gantry rotation time 400 ms, tube voltage and tube current 120 kV and 200 mA, respectively, and the temporal window was set at 75% after the R-wave. CACS was assessed with the application of dedicated software (Vitrea 2). Coronary artery calcium was identified as a dense exceeding the threshold of 130 HU. An overall Agatston score was recorded for each patient.

A control group of 15 healthy females matching in age, BMI and waist/hip ratio had their serum visfatin level measured. In addition to a risk stratification (RS) group of 30 female patients referred for calcium scoring. The study was explained to the participants and an informed consent was given by each one. The study was approved by the local ethics committee.

2.2. Statistics

Data was statistically analyzed using SPSS (Statistical Package for the Social Sciences) version 11 for windows. Descriptive data were presented as range, mean ± SD and frequencies. Mann–Whitney test was used to compare between groups. Spearman correlation coefficient was used to test the relationship between various variables. P-value $\leqslant 0.05$ was considered significant. The cut off value of the serum visfatin level = -mean ± 1 SD. Moreover, patients were considered to have an abnormal lipid profile if the serum level exceeded the upper limit of normality.

3. Results

The mean age of the patients was 43.9 ± 11.6 years (range: 27–60 years). The mean disease duration was 3.5 ± 3.4 years (range: 3–14 years) and the mean DAS28 was 5.4 ± 0.46 (range: 4.5–6.4). None of the examined patients had extra-articular involvement. Regarding the lipid profile of the studied RA patients, it was found that the mean serum level of the TC, HDL, LDL, and TG were 220.65 ± 43.9, 48.45 ± 8.5, 145 ± 38.23, and 109.3 ± 29.1 mg/dl, respectively. Furthermore, individual data analysis revealed that 12 patients (60%) had elevated serum TC level (> 200 mg/dl). Two patients (10%) had low serum HDL levels (< 40 mg/dl) i.e. high risk for the development of atherosclerosis, while 18 patients (90%) had moderate risk (40–65 mg/dl). Moreover, 19 patients (95%) had elevated serum LDL (> 100 mg/dl). None of the studied patients had elevated serum TG. The mean ESR (first hour) was 31.6 ± 13.5 mm (range: 18–55). All patients were treated with appropriate doses of methotexate with concomitant non-steroidal anti-inflammatory drugs (NSAIDs).

Table 1 demonstrates the comparison between RA patients and the healthy control group regarding their age, anthropometric measurements and serum visfatin level. There was a statistically significant increase in the mean serum visfatin level of RA patients compared to the control group ($Z = -5.096$, $P = 0.000$).

All RA patients had elevated serum visfatin levels (exceeding the high cut off value i.e. 21.43 ng/ml). However, no statistically significant correlations were found for the serum visfatin level with the clinical measurements and lipid profile of the RA patients (Table 2).

In the current study, although all RA patients had no clinical evidence of cardiac involvement or echocardiographic changes, their mean CACS was 86.4 ± 360.3 Agatston score. Among the studied patients, 11 (55%) had evidence of coronary atherosclerotic changes with a mean CACS of 157.1 ± 484.2 Agatston score. However, comparison between RA patients with coronary artery calcification (CAC) and those with no CAC revealed no significant differences regarding clinical findings, anthropometric measurements and laboratory findings apart from a significant increase in serum TG in patients with CAC ($Z = -2.091$, $P = 0.037$) (Table 3).

CACS had a significant positive correlation with serum triglycerides ($P = 0.014$), whereas, it had no significant correlations with other clinical and laboratory parameters as disease duration, disease activity, and serum visfatin levels ($P < 0.05$).

Compared to the risk stratification group (RS), the RA patients were significantly younger; their mean age was 43.85 ± 11.56, while that of RS group was 56.8 ± 11.6 years ($P = 0.0001$). However, there was no significant difference between both groups regarding the frequency of coronary artery calcification (55% in RA versus 32% in RS groups; $P = 0.65$). Moreover, there was no significant difference between both groups regarding the mean CACS (157.1 ± 484.2 for RA versus 111.2 ± 286.5 Agatston score for RS).

4. Discussion

Atherogenesis is accelerated in RA patients[5] and increases mortality from acute cardiovascular events.[25–27] Several immune cells and soluble mediators play a crucial role in the pathogenesis of atherosclerosis in RA.[4] Among these mediators is visfatin which is an adipokine produced and secreted primarily by visceral white adipose tissue (WAT)[10] and represents an additional link between adipose tissue and inflammation.[28]

In the current study, serum visfatin levels were significantly elevated in RA patients compared to controls (58.82 ± 6.58 versus 13.54 ± 7.9) and the serum level exceeded the high cut off value in all patients. This is in agreement with Otero et al.[13] Brentano et al.[15] and Rho et al.[29] However, in the present study, serum visfatin levels did not correlate with DAS 28 or with ESR. This signifies that in spite of being elevated, serum visfatin may not directly reflect the pathological changes (the inflammatory process) of RA in this study. In fact, the role of visfatin in the context of RA is unclear; it might involve the modulation of the inflammatory or immune response or the increased level could simply be an epiphenomenon.[30] Nevertheless, assessment of synovial fluid visfatin, or its

Table 1 Comparison between RA patients and the healthy control group regarding their age, anthropometric measurements and serum visfatin level (Mann–Whitney test).

Parameters	RA patients mean ± SD	Controls mean ± SD	Z	P
Age (years)	43.85 ± 11.56	38.75 ± 9.53	−1.307	0.191
Serum visfatin level (ng/ml)	58.82 ± 6.58	13.54 ± 7.9	−5.096*	0.000
Weight (kg)	78.1 ± 14.9	73.1 ± 16.04	−1.402	0.161
Height (meter)	157.1 ± 4.37	160.94 ± 7.1	−1.882	0.06
BMI (kg/m²)	31.28 ± 6.6	28.17 ± 5.55	−1.64	0.101
Waist circumference (cm)	94.43 ± 12.3	93 ± 12	−0.383	0.702
Hip circumference (cm)	111.73 ± 14.9	105.06 ± 13.3	−1.817	0.69
Waist/hip ratio	0.85 ± 0.07	0.89 ± 0.13	−0.877	0.38

Kg, kilogram; ng/ml, nanogram/milliliter; BMI, body mass index; cm, centimeter.
* Significant if $P < 0.05$.

Table 2 Correlation between the serum visfatin level and the clinical data, anthropometric measurements and laboratory data of the RA patients (Spearman's correlation coefficient test).

Parameters	r	P
Age (years)	−0.153	0.521
Disease duration	0.011	0.962
DAS28	0.150	0.529
BMI (kg/m²)	−0.185	0.435
Waist/hip ratio	0.104	0.662
Serum cholesterol	0.119	0.617
Serum triglycerides	−0.092	0.700
Serum HDL	0.068	0.776
Serum LDL	0.140	0.556
ESR (1st hour)	0.2	0.397

BMI, body mass index; HDL; high density lipoproteins; LDL, low density lipoproteins.

expression in synovial tissue cells[14,15] may be more relevant to the pathological events taking place inside the joint and may reflect disease activity. Moreover, serum visfatin levels did not correlate with the anthropometric measurements of the studied RA patients including waist/hip ratio and waist circumference which is a simple indicator of abdominal visceral adipose mass.[22,31] Although visfatin is secreted by visceral WAT[10], the lack of correlation between both points out to other possible sources and or causes which modulate serum visfatin levels in RA. As visfatin synthesis is regulated by several factors including IL-6 and TNFα,[30] it is possible that visfatin levels increase in RA as a direct consequence of increased IL-6 and TNFα.[30,32] Moreover, it may be secreted by activated peripheral lymphocytes[33] monocytes, macrophages and dendritic cells in response to inflammatory stimuli.[16,34,35] Altogether, this may increase the level of serum visfatin independent of visceral WAT in RA.

Another speculation is that the high level of serum visfatin in RA patients may be due to a sort of alteration in the gene encoding visfatin as a result of the RA triggering factors: a condition which may lead to an increase in its production autonomously independent of disease activity or visceral obesity. Our results also revealed that serum visfatin levels did not correlate with patients' ages or disease duration denoting that its level is not a cumulative phenomenon related to time lapse,

rather it may be influenced by short-term fluctuating factors like inflammatory mediators. Gonzalez-Gay et al.[36] also did not find any correlation between serum visfatin levels and patients' ages, disease duration, BMI, ESR, CRP, lipids, and DAS 28 in non-diabetic RA patients.

In the current study, none of the RA patients had clinical or echocardiographic evidence of cardiovascular involvement, yet 55% had CAC denoting subclinical atherosclerosis, detected by MSCT, a technique that provides a reproducible and quantitative method for the detection of subclinical coronary artery sclerosis and yields information about additional future cardiovascular risk.[37,38] CAC provides a better estimate of the disease than luminal stenosis[39] because less obstructive plaques give rise to more occlusion than the more obstructive plaques due to their greater number.[40] Although CAC directly detects hard or calcified plaques only, it serves as a marker for soft and non-calcified plaques as in the majority of patients both types of plaques coexist proportionately.[41] Therefore, a CACS of zero is a technically acceptable result that makes the presence of atherosclerotic plaques including unstable ones very unlikely.[42] Thus, in the present study, the 45% of RA patients who had a CACS of zero were unlikely to have subclinical atherosclerosis. On the other hand, the 55% of RA patients who had CAC (though asymptomatic) had the risk to develop CAD as in some studies CACS provided an incremental progressive value when added to the conventional risk factors of CAD.[43,44]

The development of preclinical atherosclerosis is more prevalent and accelerated in RA patients and occurs independently of the traditional risk factors.[45] In the current study, two important factors related to atherosclerosis were investigated, namely visfatin and the lipid profile.

Dyslipidaemia (as a traditional atherosclerotic risk factor) plays a crucial role in the development of atherosclerosis, a process which is accelerated by the endothelial dysfunction characterizing RA. The increased spaces between altered endothelial cells in RA patients permit the entry of LDL, which is retained in the intima, oxidized with subsequent recruitment of circulating leukocytes within atherosclerotic plaques.[46,47] On the other hand, decreased levels of HDL may accelerate atherosclerosis because they exert atheroprotective functions.[48,49]

In this study, almost all RA patients had increased serum TC and increased serum LDL together with a general tendency to low levels of HDL. Thus, the dyslipidaemia of the studied RA patients was matching to a great extent with the atherogenic lipid profile which is typically characterized by

Table 3 Comparison between RA patients with coronary artery calcification (CAC) and those with no CAC regarding the clinical, anthropometric and laboratory data (Mann–Whitney test).

Parameters	RA patients with no CAC N = 9 (45%)	RA patients with CAC N = 11(55%)	Z	P
Age (years)	39.7 ± 10.3	47.27 ± 11.8	−1.446	0.148
Disease duration (years)	2.5 ± 2.37	4.3 ± 4.9	−0.384	0.701
DAS28	5.5 ± 0.52	5.4 ± 0.42	−0.117	0.907
Pulse (beats/minutes)	65.78 ± 2.3	66.1 ± 1.92	−0.236	0.813
Ejection fraction (%)	69 ± 3.6	69 ± 4.7	0.00	1
CACS	0	157.1 ± 484.2	−3.946	0.000
BMI	30.1 ± 6.2	32.3 ± 7	−0.57	0.569
Waist/hip ratio	0.84 ± 0.07	0.86 ± 0.07	−0.381	0.703
Serum visfatin level (ng/ml)	58.3 ± 6	59.3 ± 7.3	−0.418	0.138
Serum cholesterol (mg/dl)	212.2 ± 38.67	227.6 ± 48.4	−0.722	0.470
Serum triglycerides (mg/dl)	98.9 ± 31.6	117.82 ± 25.2	−2.091[*]	0.037
Serum HDL (mg/dl)	49.4 ± 7.9	47.6 ± 9.2	−0.228	0.819
Serum LDL (mg/dl)	132.5 ± 26.8	155.3 ± 44.1	−1.178	0.239
ESR(1st hour)	32.11 ± 15.6	31.1 ± 12.23	−0.233	0.816

BMI, body mass index; HDL, high density lipoproteins; LDL, low density lipoproteins; ng/ml, nanogram/milliliter; mg/dl, milligram/deciliter.
[*] Significant if $P < 0.05$.

an increase in TC, LDL, and serum TG levels and a reduction in serum HDL levels.[50] Specifically, an increase in the TC/HDL ratio, which represents an atherogenic index, is an important prognostic marker for cardiovascular disease.[51] The risk of myocardial infarct (MI) increases considerably when this ratio is higher than 5, and it should ideally be 4 or less.[51] In this study, 25% of the RA patients had an atherogenic index > 5 (data not shown), denoting a higher risk of atherosclerosis.[51]

Despite having an atherogenic lipid profile in almost all RA patients, only 55% had CAC. Thus, the role of dyslipidaemia as a mechanism of CAD is doubtful in those patients because the rest of our patients had no CAC in spite of having a pro-atherogenic lipid profile. Furthermore, comparison between patients with and without CAC revealed no significant difference regarding TC, HDL, and LDL. However, there was a tendency for the lipid profile of the patients with no CAC to be less pro-atherogenic though not significant. Thus, it can be concluded that the role of dyslipidaemia in the pathogenesis of subclinical atherosclerosis in RA patients should be viewed in the context of other operating mechanisms.[4] Moreover, it is possible that other fractions of specific lipoprotein particles such as very low density lipoproteins (VLDL) or sub-fractions of HDL[52,53] may play a significant role in atherogenesis in RA.

On the other hand, although all the studied RA patients showed normal serum TG levels, patients with CAC showed a significant increase in its mean value (117.82 ± 25.2) compared to those without CAC (98.9 ± 31.6). Moreover, there was a significant positive correlation between CACS and the serum TG levels in RA patients denoting that serum TG is probably relevant to atherogenesis. In non-RA patients, hypertriglyceridemia is considered to be a risk factor for CAD. The possible causes include increased production of atherogenic chylomicrons, VLDL remnants and more dense atherogenic LDL particles, in addition to the interaction between serum TG and the fibrinolytic/coagulation system.[54]

An association between moderately high TG levels within the normal range and the development of CAD was demonstrated suggesting a cumulative effect of exposure to high TG levels.[55] Nevertheless, it is to be noted that TG levels are subjected to variations by many factors including life style modifications, BMI changes and aerobic exercise.[56–58] Therefore, a single measurement of TG levels may not be a reliable indicator for the long term effects of hypertriglyceridemia. While our study demonstrated a significant positive correlation between serum TG and CAD in RA, others did not.[59,60]

In the current study, almost all patients received methotrexate and NSAIDs which may influence serum lipid levels as reported by some studies.[61,62] Accordingly, the detection of serum lipids in early RA or before the commencement of therapy may be more representative of the lipid profile in RA as shown in a study performed by Georgiadis et al.[50] For the same reason i.e. the effect of treatment, rheumatoid factor seropositivity was not considered in our study.[63,64]

The second factor studied in the current work in the context of atherosclerosis was serum visfatin. Through cytokine-like activity, visfatin is suggested to play a role in unstable atherosclerosis. Dahl et al.[16] found increased visfatin expression from the carotid artery of patients with stroke and at the sites of plaque rupture in patients with acute MI. They also found upregulation of visfatin in macrophages from human unstable atherosclerotic lesions and suggested that visfatin plays an important role in atherogenesis and plaque destabilization.

In RA, the permanent over-expression of cellular adhesion molecules and proinflammatory cytokines may participate in accelerated atherogenesis.[19] In this context, visfatin was found to enhance the expression of ICAM-1 and VCAM-1 and others[65] whose expression on the endothelial cell surface is the initial step in atherogenesis.[65,66] Thus, it can be assumed that visfatin may play a role in the acceleration of atherogenesis in RA. However, in the current study, CACS did not correlate with serum visfatin levels in RA patients. There was also no significant difference between the mean serum visfatin level in RA patients with and without CAC (59.3 ± 7.3 versus 58.3 ± 6). This signifies that visfatin did not play a direct role in atherosclerosis in RA patients. This is in agreement with Rho et al.[20] who studied the effect of adipokines on atherosclerosis in RA patients using electron beam CT to detect CAC. They found that serum visfatin was not associated with CAC. Moreover, Ozgen et al.[19] studied the association

between serum visfatin levels and common carotid intima-media thickness in some rheumatic diseases including RA. They found increased serum visfatin levels in RA patients compared to other rheumatic diseases, yet its level was not correlated with intima-media thickness. Thus, based on this, it seems that the role of visfatin in atherogenesis is different in RA patients. This can be attributed to the highly complicated multifactorial pathogenesis of atherosclerosis in RA. These factors include various leukocytic populations orchestrated by several cytokines (among which TNFα is of particular importance), chemokines, growth factors, and hormones.[46] Therefore, the contribution of each factor to atherogenesis in RA may differ among individuals. Hence, the role of visfatin as a single factor is not stereotyped in all patients.

On the other hand, 45% of our patients were not atherosclerotic in spite of having increased serum visfatin levels suggesting that it is unlikely to play a direct role in CAD and another mechanism may be involved such as a relative increase in serum TG.[55] It is worth mentioning that visfatin may exert a variety of insulin-mimetic effects, including enhancing glucose uptake and increasing TG synthesis,[67] an issue which may represent an indirect link between visfatin and atherosclerosis in some patients.

In the present study, CACS did not correlate with patients' anthropometric measurements supporting the multifactorial nature of atherogenesis in RA (not dependant mainly on BMI or visceral fat). CACS also was not correlated with patients' ages or disease duration. This is unlike the study performed by Del Rincón et al.[8] who concluded that patients with prolonged RA have more atherosclerosis than age-matched patients with more recent disease onset. They suggested that systemic inflammation may amplify the age-related risk of cardiovascular diseases. Moreover, CACS did not correlate with DAS28. This may be related to the inherent nature of DAS which considers mainly the articular involvement as an indicator of RA disease activity, while CAD is an extraarticular manifestation. Accordingly, it is conceivable that DAS cannot reflect the degree of CAC.

Comparison between the RA patients and the RS group recruited for determination of CACS revealed that RA patients were significantly younger and had comparable CACS. This supports the notion that RA is a risk factor that causes premature atherosclerosis[45] (independent of other risk factors). This should encourage aggressive therapy to induce remission and hence arrest or prevent the development of CAD.[45]

From this study it can be concluded that serum visfatin levels are significantly elevated in RA patients. However, this could not be explained in terms of increased disease activity, visceral obesity or inflammatory markers. It could not also be considered as a factor responsible for CAC in the studied RA patients. Thus, the source of its production, factors influencing its serum level and its pathogenetic role in RA especially in CAD remain to be clarified. A longitudinal study on a larger number of RA patients is needed to further study the role of visfatin in CAD taking into consideration the role of the other confounding risk factors.

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