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Relation of serum resistin to subclinical atherosclerosis in multiple sclerosis

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Abstract

Background Resistin is a small protein that has pro-inflammatory and atherogenic effects. This study aimed to evaluate the level of serum resistin as a marker of subclinical atherosclerosis in multiple sclerosis (MS) sufferers. 114 MS sufferers and 114 age, sex and body mass index matched controls were enrolled in this study, subjected to detailed history taking, general, neurological examination, assessment of anthropometric measurements, serum resistin level, and carotid duplex to asses subclinical atherosclerosis.

Results MS sufferers showed a higher cholesterol, and triglycerides levels as compared to controls. Progressive MS sufferers (SPMS, and PPMS) showed a higher cholesterol level as compared to RRMS sufferers. SPMS sufferers showed a higher cholesterol level as compared to PPMS sufferers. RRMS sufferers showed a higher triglycerides level as compared to progressive MS sufferers. Sufferers had significantly higher mean levels of resistin and right carotid intimal medial thickness (CIMT) as compared to controls. There was a significant positive correlation in MS sufferers between serum resistin and the following parameters: age, and disease duration, body mass index, triglycerides, cholesterol and low-density lipoprotein. There were significant positive correlations between carotid intimal medial thickness and body mass index, disease duration, age, expanded disability status scale, levels of triglycerides, low-density lipoprotein, and cholesterol. The risk factors of subclinical atherosclerosis in MS sufferers were higher mean levels of resistin, triglycerides, low-density lipoprotein, cholesterol, and disease duration. Subclinical atherosclerosis in MS sufferers was significantly associated with higher mean levels of resistin, and triglycerides.

Conclusions Higher mean levels of resistin might reflect the predisposition to subclinical atherosclerosis in MS sufferers.

Keywords Multiple sclerosis, Resistin, Atherosclerosis, Carotid intimal–medial thickness, Carotid duplex and lipid profile

Background

The role of resistin in the occurrence of early stages of atherosclerosis has been documented; however, data concerning their consequence on multiple sclerosis (MS) are deficient. Resistin is a small protein that is secreted in the great amount by macrophages, monocytes and in smaller amounts by fat cells in humans. Resistin is a proinflammatory cytokine that is involved in the mechanism of vascular inflammation, immune response, and inflammatory process in various disease via production of cytokines [1]. The resistin gene is located on chromosome number 19 in humans [2].

Inflammatory leukocytes infiltrate the central nervous system (CNS) of MS sufferers to mediate the initiation and maintenance of disease leading to tissue damage involving both demyelination and neuronal degeneration. Increased interleukin 6 (IL-6) levels were found in active plaques of individuals suffering from MS. In addition, interleukin 12 (IL-12) is a master-regulator in the polarization of T_H1 cells. A pathogenic T_H subset has

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been implicated in driving MS development. This was supported by the finding that elevated IL-12 levels are observed in the cerebrospinal fluid (CSF) and lesions of MS sufferers. Increased TNF-α levels can be found in active lesions within the CNS, serum and CSF of MS sufferers. Increased tumor necrosis factor α (TNF-α) in CSF also correlates with MS severity and progression [3].

Moreover, some pro-inflammatory agents, such as IL-6 and TNF-α can influence the secretion of resistin [2]. Resistin mRNA was strongly increased by IL-6 and TNF-α in human peripheral blood mononuclear cells (PBMC). Resistin strongly upregulated IL-6 and TNF-α in human PBMC via NF-κB pathway. Addition of recombinant human resistin protein to macrophages from both mouse and human resulted in enhanced secretion of pro-inflammatory cytokines, TNF-α and IL-12. Furthermore, resistin can stimulate the endothelial cells and modulate indirectly the process of expression of adhesion molecules that is considered as a marker of inflammation in vascular endothelial cell, especially VCAM-1 that plays an important role in the occurrence of early stages of atherosclerosis [4].

Atherosclerosis is a chronic process that involves the arterial walls and remains silent until rupture or stenosis occurs [5]. Thus, it is the underlying process of death, cerebrovascular and cardiovascular disease in multiple sclerosis sufferers. Therefore, early screening of multiple sclerosis sufferers for subclinical atherosclerosis is important in prevention of cardiovascular disease. The carotid intimal medial thickness (CIMT) is a valid screening method for cardiovascular disease and early stage of subclinical atherosclerosis [6].

Up to our knowledge, the prognostic significance of resistin as a marker of subclinical atherosclerosis in MS sufferers is not well-established. Therefore, the current study aimed to evaluate the level of resistin as a marker of subclinical atherosclerosis in MS sufferers.

Methods

This is a case control study conducted on 228 subjects during the period from February 2020 to October 2021. Samples were collected by the systematic random method.

Sample size calculation: a sample size of 89 patients and 89 controls was found to provide 80% power, at 0.05 alpha level of significance. We used a sample of 114 MS patients and 114 controls to increase the power of our study. Epi Info version 7 was used for this calculation [7].

One hundred and fourteen sufferers with clinically defined MS were recruited from Neurology department, of Zagazig university hospital, 114 healthy controls matched for age, sex and body mass index (BMI) with MS sufferers were recruited from the outpatient clinics during the same study period and enrolled in this study. Healthy controls were free from MS and other inflammatory diseases in their medical history, as well as free from acute or chronic internal and neurological diseases as determined by physical examinations. Their laboratory investigations did not demonstrate infection, inflammatory diseases or chronic illness.

MS sufferers and controls were informed with the design of the study and a written informed consent was obtained from all of them. An approval for performing this study was obtained from Institutional Review Board of our university.

This study included sufferers aged ≥ 18 years and diagnosed as MS according to the McDonald criteria of 2017 [8], with no previous history of cardiovascular disease. All types of MS were included.

We excluded MS sufferers with hepatic and renal failure; neoplasm, other autoimmune diseases or acute inflammatory process, and those presented with acute relapses or corticosteroid treatment within 3 months prior to enrollment in the study.

MS sufferers and controls were subjected to thorough history taking (with special emphasis on past history of other medical conditions, the date of onset of MS, duration of the disease, type of MS, number of relapses, and detailed drug history), complete general, neurological examination, assessment of the anthropometric measurements, such as height and weight, and calculation of body mass index (BMI).

The neurological disability of the MS sufferers was assessed using the Kurtzke Expanded Disability Status Scale (EDSS) scores; it provides a total score on a scale that ranges from zero that means normal examination to ten that means death from MS [9].

We conducted brain and spinal magnetic resonance imaging MRI) on all MS sufferers using one and half Tesla superconducting MR imager [Achieva, Philips Medical System].

Carotid doppler ultrasound was done for MS sufferers and controls to measure the CIMT (using Philips Affiniti 70, Philps Ultrasound System, USA). The gray-scale US was done with the real-time sector scanner by a high-frequency linear array transducer (7.5/10 MHz). The radiologist optimized the settings of the US machine, such as depth, gain, zoom, focal zone, frequency, pre- and post-processing, dynamic range, frame averaging, and compounding. MS sufferers were placed in supine position with their chin extended, arms down by their side, and head turned about 45∘ away from the side being examined. The right and left common carotid arteries were scanned longitudinally thorough gray-scale examination. There were two echogenic parallel lines generated by the lumen intimal interface and media–adventitia interfaces.

We measured the distance between these two lines to get a reliable index of the CIMT measurement that was taken approximately one cm proximal to the carotid bulb (distal one cm of the carotid artery) in areas without carotid plaque at end diastole. CIMT was determined from an average value of six measurements (three for the left and three for the right) at the time of carotid doppler ultrasound scanning on unfrozen images of longitudinal scans using the electronic caliper of the machine, as shown in Fig. 1. The measurements were performed by the same licensed and trained radiologist who was blinded to the clinical characteristics of the participants. A cutoff value of CIMT was 0.72 mm, participants who had CIMT above this value were considered to have atherosclerosis [10].

Blood samples for assessment of serum resistin, cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein level were taken from all participants in the morning after 12 h of fasting under aseptic conditions. Blood specimens were centrifuged immediately at 4 °C and plasma was frozen at –70 °C for further analysis. Level of resistin was measured using a sandwich enzyme-linked immunosorbent assay (R, and D Systems, Inc., Minneapolis, MN, USA) kits. The intra- and inter-assay coefficients of variability of serum resistin were 4.5% and 7.8%, respectively.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using the statistical package for the social sciences (SPSS) version 24 (Released 2016 by the International Business Machines Corporation, USA). Quantitative data of this study were expressed as mean and standard deviation, whereas categorical data were expressed as number (n) and percentages (%). Unpaired *t* test or Chi-square (χ^2) test, one-way analysis of variance (ANOVA) analyses, post hoc, Spearman correlation, multiple regression analysis and logistic regression analysis were applied when appropriate in this study. *P* values were considered as significant and highly significant if it were less than 0.05 and 0.001, respectively. The sensitivity and specificity of serum resistin as a diagnostic marker in multiple sclerosis was also assessed by a receiver operating characteristic (ROC) curve (Figs. 2 and 3). We found a significant resistin cutoff for MS was 7.8 ng/mL with a sensitivity of 98% and a specificity of 88.52%, respectively (AUC was 0.924).

Results

MS sufferers were 78 (68%) female and 36 (32%) male and their age ranged from 19 to 48 years with a mean age (± standard deviation) of 37.13 (± 7.61) years. While the controls included 74 females and 40 males with a mean age (± standard deviation) was 35.11 (± 6.53) years. The MS sufferers were grouped into 75% relapsing–remitting (RR), 18% secondary progressive (SP) and 7% primary progressive (PP) on the basis of their clinical course. The mean age at onset of MS sufferers was 27.39 ± 6.79 years, their mean disease duration was 4.43 ± 3.31 years and their mean number of relapses was 3.46 ± 1.36 years. Regarding the type of treatment, 43 patients (38%) received interferon [intramuscular interferon β1a (8%), subcutaneous interferon β1a (14%), subcutaneous interferon β1b (16%)], 31 (27%) patients received fingolimod, 14 patients (12%) received rituximab, 10 patients (9%) received dimethyl fumarate, 6 patients (5%) received ocrelizumab, 5 patients (4%) received teriflunomide, 2 patients (2%) received monthly methylprednisolone, one patients (1%) received methotrexate, one patients (1%) received azathioprine, and one (1%) patient received

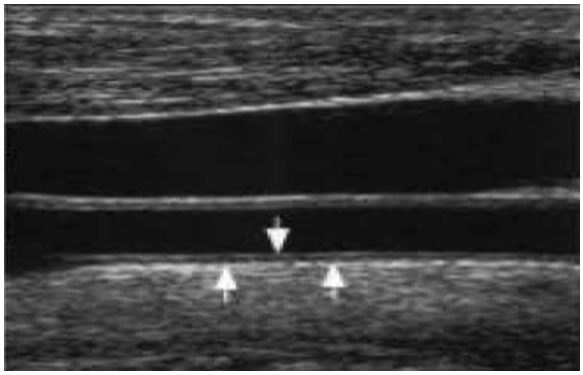

Fig. 1 Gray-scale carotid doppler ultrasound shows the normal vascular diameter with normal intimal media complex is less than 0.8 mm

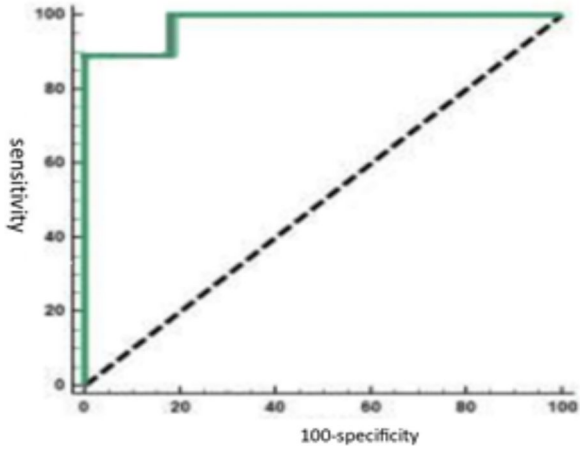

Fig. 2 Receiver operating characteristic (ROC) curve of serum resistin as a diagnostic marker in multiple sclerosis

cyclophosphamide. MS patients showed a higher cholesterol, and triglycerides levels as compared to controls. MS Sufferers had significantly higher mean levels of resistin and right CIMT as compared to controls ($P < 0.05$) (Table 1).

Progressive MS sufferers (SPMS, and PPMS) showed a higher cholesterol level as compared to RRMS sufferers. SPMS sufferers showed a higher cholesterol level as compared to PPMS sufferers. RRMS sufferers showed a higher triglycerides level as compared to progressive MS sufferers (SPMS, PPMS) (Table 2).

There were significant positive correlations in MS sufferers between serum resistin and the following parameters: age, and disease duration, body mass index, triglycerides, cholesterol and low-density lipoprotein ($P < 0.05$) (Table 3).

There were significant positive correlations between carotid intimal medial thickness and body mass index, disease duration, age of the patients, expanded disability status scale, levels of triglycerides, low-density lipoprotein, and cholesterol ($P < 0.05$) (Table 4).

Multiple regression analysis revealed that the risk factors of atherosclerosis in multiple sclerosis sufferers were higher level of resistin, triglycerides, low-density lipoprotein, cholesterol, and disease duration (Table 5).

Logistic regression analysis revealed that higher mean level of resistin and triglycerides were risk factors of subclinical atherosclerosis in multiple sclerosis sufferers (Table 6).

Discussion

In spite the improved treatments of MS, MS sufferers experience premature atherosclerosis and the rate of mortality among them remains high. Low-grade and chronic inflammation and oxidative stress in sufferers contribute to endothelial dysfunction and higher risk of atherosclerosis [11].

Also, resistin is an adipocyte-specific hormone that has been suggested as a novel biomarker for early prediction of subclinical atherosclerosis in MS suffers as in the current study the level of resistin was significantly higher in the MS sufferers than in controls. This finding is compatible with that finding of Emamgholipour and colleagues [12]. They found that serum levels of resistin in MS sufferers were significantly higher in comparison with controls. Kraszula and colleagues as well as Michalak and colleagues [13, 14] reported significantly higher resistin levels were found in relapsing–remitting multiple sclerosis sufferers in comparison with the controls.

An increase in resistin concentrations may reflect the activation of monocytes and macrophages in multiple sclerosis sufferers. As during the pathogenesis of MS, monocytes and macrophages are involved in both brain injury and repair. The clearance of myelin debris in demyelinating lesions by macrophage phagocytosis is required for effective remyelination. The phagocytosis of myelin debris modulates the function of macrophages and monocytes [14].

MS sufferers showed a higher cholesterol, and triglycerides levels as compared to controls. Progressive MS sufferers (SPMS, and PPMS) showed a higher cholesterol level as compared to RRMS sufferers. SPMS sufferers showed a higher cholesterol level as compared to PPMS sufferers. RRMS sufferers showed a higher triglycerides level as compared to progressive MS sufferers (SPMS, PPMS). This finding met with that of Jorissen and colleagues [15] who found that progressive MS sufferers (SPMS, and PPMS) showed a higher cholesterol level as compared to RRMS sufferers. RRMS sufferers showed a higher triglycerides level as compared to progressive MS sufferers (SPMS, PPMS).

We found that MS sufferers had significantly higher right carotid intimal medial thickness (CIMT) as compared to controls. In the same context Yuksel and colleagues [16] found that MS sufferers had significantly higher right CIMT as compared to controls.

There was a positive correlation between serum level of resistin and patient age. This may be attributable to aging process with increase in fat content as reported by Oliver and colleagues [17]. In addition, serum resistin level correlated positively with disease duration in MS sufferers. This met with the finding of Michalak and colleagues [14] who found that resistin concentration correlated positively with the duration of relapsing-remittent MS sufferers.

Moreover, there were significant positive correlations in MS sufferers between serum resistin and body mass index, triglycerides, cholesterol and low-density lipoprotein. Our result was supported by the findings obtained by Lu et and colleagues [18]. They found that plasma

(See figure on next page.)

Fig. 3 Illustrated case of a 42 female patient known to have multiple sclerosis. MRI. (**A**) Axial T1. (**B**) Axial T2 WI at the same level. (**C**) Axial FLAIR in a lower level. (**D**) Sagittal FLAIR shows multiple periventricular abnormal low T1, high T2 and FLAIR signal foci with a characteristic perpendicular alignment to the ventricle (best seen on sagittal view). **E** Gray-scale carotid doppler ultrasound exam at the right side distal carotid artery 1.5 cm from the bifurcation revealed an irregular parallel alignment of the vessel wall with early intimal media complex hyperplasia with lost hypo-echoic component revealing subclinical atherosclerotic changes

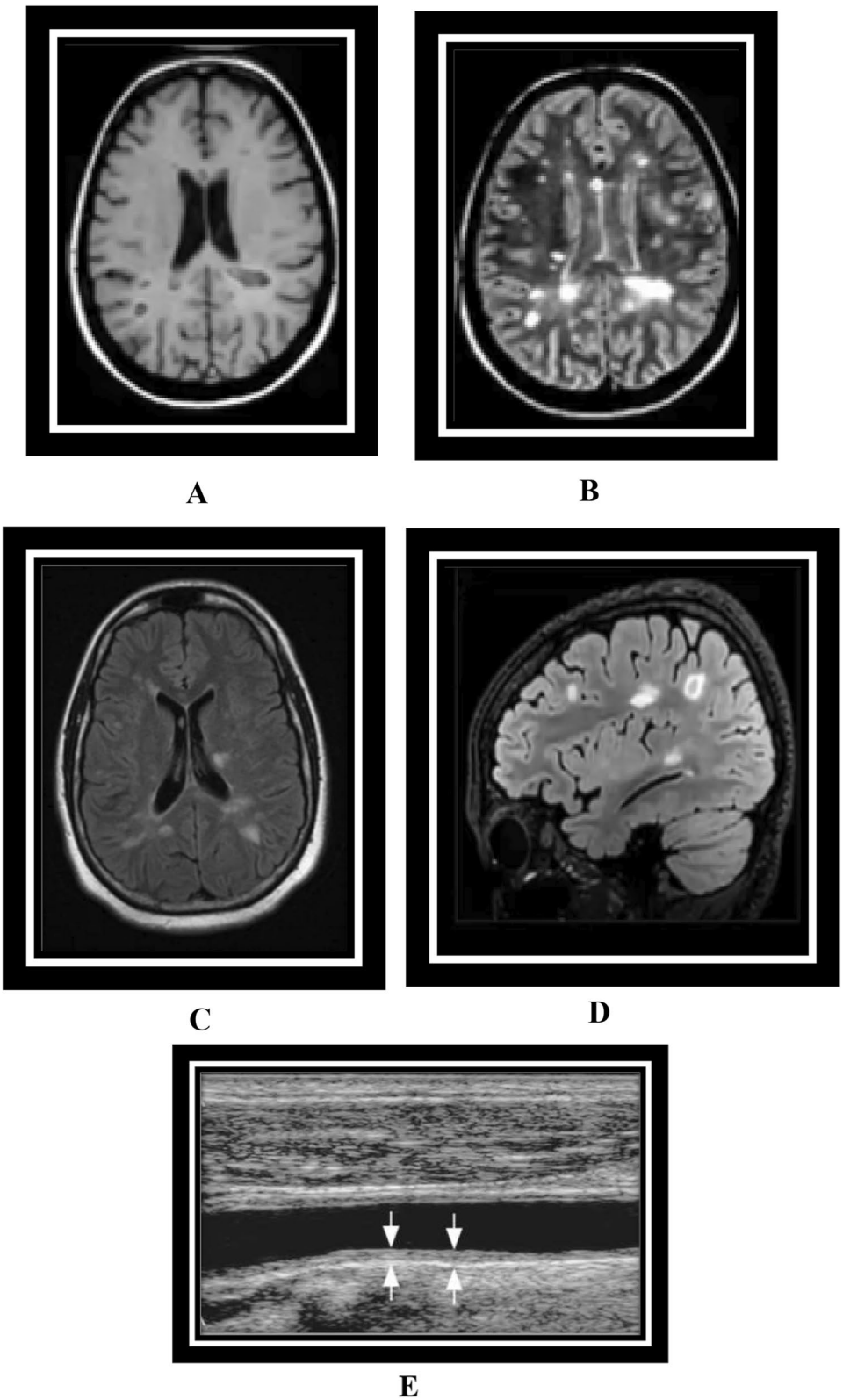

Fig. 3 (See legend on previous page.)

Table 1 Clinical profile, laboratory investigation and carotid intimal medial thickness of the participants

Variables	MS sufferers (*n* = 114)	Controls (*n* = 114)	*p* value
Age	37.13 ± 7.61	35.11 ± 6.53	0.13
Gender			
Male	36 (32%)	40 (35%)	0.57
Female	78 (68%)	74 (65%)	
Disease course			
RR	86 (75%)	–	–
SP	20 (18%)	–	
PP	8 (7%)	–	
Smoking	28 (24%)	29 (25%)	0.9
Age of MS onset (years)	27.39 ± 6.79	–	–
Disease duration (years)	4.43 ± 3.31	–	–
Number of relapses	3.46 ± 1.36	–	–
EDSS	2.54 ± 1.81	–	–
Body mass index (kg/m2)	27.68 ± 6.93	26.34 ± 6.91	0.30
Total cholesterol (mg/dl)	184.68 ± 4.13	182.65 ± 4.16	0.0003*
Triglycerides (mg/dl)	138.59 ± 8.94	135.58 ± 8.83	0.01*
High-density lipoprotein (mg/dl)	59.59 ± 6.2	61.17 ± 6.1	0.05
Low-density lipoprotein (mg/dl)	109.23 ± 3.53	108.54 ± 2.39	0.053
Resistin (ng/mL)	15.29 ± 2.76	7.39 ± 2.16	< 0.0001**
Mean CIMT (mm)	0.57 ± 0.13	0.56 ± 0.11	0.65
Right CIMT (mm)	0.61 ± 0.09	0.57 ± 0.08	0.01*
Left CIMT (mm)	0.53 ± 0.11	0.54 ± 0.11	0.63

MS multiple sclerosis; *n* number, *%* percentages; *RR* relapsing–remitting, *SP* secondary progressive, *PP* primary progressive, *EDSS* expanded disability status scale, *CIMT* carotid intimal medial thickness

*Significant, **Highly significant

Table 2 Comparison of demographic characteristics, laboratory findings, and carotid intimal medial thickness in MS sufferers respect to clinical subtypes

Variables	RRMS (*n* = 86)	SPMS (*n* = 20)	PPMS (*n* = 8)
Age	37.33 ± 7.41	35.22 ± 6.42	36.63 ± 9.15
Gender			
Male	27 (31%)	7 (35%)	2 (25%)
Female	59 (69%)	13 (65%)	6 (75%)
Smoking	21 (24%)	4 (20%)	2 (25%)
Age of MS onset (years)	27.39 ± 6.79	27.39 ± 6.79	27.39 ± 6.79
Body mass index(kg/m2)	27.68 ± 6.93	25.18 ± 5.03	25.34 ± 6.19
Total cholesterol (mg/dl)	171.68 ± 2.13	186.45 ± 2.67 +*	182.45 ± 2.76 *
Triglycerides (mg/dl)	138.95 ± 16.52*	108.18 ± 5.13	107.59 ± 5.45
HDL (mg/dl)	59.57 ± 6.4	60.51 ± 5.9	60.49 ± 5.8
LDL (mg/dl)	109.32 ± 3.35	112.32 ± 3.53	113.23 ± 3.55
Resistin (ng/mL)	14.29 ± 4.66	14.16 ± 4.19	15.39 ± 4.12
Mean CIMT (mm)	0.57 ± 0.13	0.56 ± 0.12	0.56 ± 0.11
Right CIMT (mm)	0.59 ± 0.09	0.58 ± 0.19	0.57 ± 0.08
Left CIMT (mm)	0.53 ± 0.11	0.53 ± 0.9	0.54 ± 0.11

RRMS relapsing–remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *PPMS* primary progressive multiple sclerosis, *n* number, *%* percentages, *HDL* high-density lipoprotein; LDL: low-density lipoprotein; CIMT: carotid intimal medial thickness

*Significant comparing either RRMS versus PPMS or SPMS, + significant comparing SPMS versus PPMS

Table 3 Correlation between serum resistin and other studied parameters in MS sufferers

	Serum resistin (ng/ml)	
	R	*p* value
Age (years)	0.29	0.002**
Disease duration (years)	0.43	0.03*
body mass index	0.41	0.02*
Age of MS onset (years)	0.12	0.45
EDSS	0.25	0.58
Triglycerides (mg/dl)	0.48	0.02*
Cholesterol (mg/dl)	0.39	0.011*
Low-density lipoprotein (mg/dl)	0.15	0.01*
High-density lipoprotein (mg/dl)	-0.28	0.32

EDSS expanded disability status scale

**Highly significant, *Significant

resistin correlated positively with body mass index, and triglyceride. An increased resistin levels result in accumulation of triglycerides via insulin resistance and inhibiting adiponectin action.

In addition, resistin down regulates low-density lipoprotein receptors in primary hepatocytes, through increasing the intracellular expression of the recently identified protease, proprotein convertase subtilisin/kexin type 9, which enhances intracellular lysosomal degradation of low-density lipoprotein receptors, leading to a decrease in hepatic clearance of low-density lipoprotein with subsequent prolongation of its plasma half-life[19].

There were significant positive correlations between carotid intimal medial thickness and body mass index, disease duration, age, expanded disability status scale, levels of triglycerides, low-density lipoprotein, and cholesterol. In concordance with our result Omerzu and colleagues [20] found that common carotid arteries intima media thickness values were positively correlated with age, body mass index expanded disability status scale, serum cholesterol, low-density lipoprotein, and triglycerides levels of relapsing–remitting multiple sclerosis patients. Similarly, Yuksel and colleagues [16] found that common carotid arteries intima media thickness values were positively correlated with age in MS patients.

Table 4 Correlation between carotid intimal medial thickness and other studied parameters in MS patients

	Carotid intimal medial thickness	
	R	***p* value**
Age (years)	0.43	0.02*
Body mass index (kg/m^2)	0.39	0.003**
Disease duration (years)	0.41	0.04*
EDSS	0.32	0.02*
Triglycerides (mg/dl)	0.43	0.021*
Cholesterol (mg/dl)	0.46	0.01*
Low-density lipoprotein (mg/dl)	0.47	0.020*
High-density lipoprotein (mg/dl)	0.22	0.55
Resistin (ng/mL)	0.20	0.11

EDSS expanded disability status scale

**Highly significant, *Significant

Table 5 Multiple regression analysis for risk factors of atherosclerosis in multiple sclerosis sufferers

Risk factor	OR (95% CI)	*p* value
Body mass index (kg/m^2)	1.06 (0.62–1.51)	0.56
Triglycerides (mg/dl)	1.21 (2–2.36)	0.02*
Cholesterol (mg/dl)	1.43 (1.43–1.91)	0.01*
Low-density lipoprotein (mg/dl)	1.27 (1.21–2.81)	0.02*
Higher resistin level (ng/mL)	1.27 (2–2.39)	0.002**
Disease duration (years)	1.47 (1.23–1.81)	0.01*
EDSS	1.09 (0.72–1.61)	0.65
Number of relapses	0.24 (0.12–0.46)	0.14

OR Odds Ratio, *CI* confidence interval, *%* percentages, *EDSS* expanded disability status scale. **Highly significant, *Significant

Table 6 Logistic regression analysis of risk factors of subclinical atherosclerosis in multiple sclerosis sufferers

Risk factor	OR (95% CI)	*p* value
Disease duration (years)	1.37 (0.22–1.71)	0.11
Triglycerides (mg/dl)	1.12 (2–2.31)	0.01*
Cholesterol (mg/dl)	1.73 (0.20–1.91)	0.71
Low-density lipoprotein (mg/dl)	1.67 (0.32–1.51)	0.55
Resistin level (ng/mL)	1.26 (1–1.37)	0.02*

OR Odds Ratio, *CI* confidence interval, *%* percentages

*Significant

The predictors of subclinical atherosclerosis in multiple sclerosis sufferers in the current study were disease duration, and higher mean levels of resistin, triglycerides, low-density lipoprotein, cholesterol, and disease duration. Subclinical atherosclerosis in multiple sclerosis sufferers was significantly associated with higher mean levels of resistin, and triglycerides.

This should raise the awareness of potential risk for cardiovascular diseases in young adults MS sufferers who have no other identifiable risk factors. Early identification of such changes could modify therapies of MS sufferers accordingly and have a significant impact on outcome.

Conclusions

Multiple sclerosis sufferers have predisposition to subclinical atherosclerosis. Early diagnosis is important in these young MS sufferers to prevent occurrence of vascular diseases in them. Higher mean levels of resistin, and triglycerides can reflect the predisposition to subclinical atherosclerosis in multiple sclerosis sufferers.

Points of strengths of this study were that multiple sclerosis is a challenging area of interest. We are searching for atherogenic substrate in multiple sclerosis, even though the age of the patients not the age corresponding to atherosclerosis, nor the symptomatology can be explained by it. This is the first study found that higher mean levels of resistin, and triglycerides can reflect the predisposition to subclinical atherosclerosis in multiple sclerosis sufferers.

Limitations were that it is a single center study, and multiple measurements of serum resistin level over time are likely to provide additional information. Therefore, findings cannot be generalized to population or community (hospital-based study). Therefore, further multicenter studies with a larger sample size are urged for validation of the current evidence. However, our findings are still preliminary in nature and future studies are needed to replicate these findings.

Abbreviations

MS	Multiple sclerosis
IL-6	Interleukin 6
IL-12	Interleukin 12
CNS	Central nervous system
CSF	Cerebrospinal fluid
PBMC	Peripheral blood mononuclear cells
TNF-α	Tumor necrosis factor α
CIMT	Carotid intima–media thickness
BMI	Body mass index
EDSS	Expanded Disability Status Scale
MRI	Magnetic resonance imaging
SPSS	Statistical package for the social sciences
n	Number
%	Percentages
χ2	Chi-square
OR	Odds ratio
CI	Confidence interval
SP	Secondary progressive
PP	Primary progressive
RR	Relapsing–remitting
RRMS	Relapsing–remitting multiple sclerosis
SPMS	Secondary progressive multiple sclerosis
PPMS	Primary progressive multiple sclerosis

HDL High-density lipoprotein
LDL Low-density lipoprotein

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Author contributions
RSN, HFT, AF and MAA carried out the work. RSN designed the study, wrote the manuscript, coordinated the research team, collected the patients, gathered clinical data, had done the statistical analysis and reviewed the manuscript. HFT had done the imaging work in the present study and reviewed the manuscript. AF and MAA helped the laboratory work of the study. All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final manuscript.

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Availability of data and materials
From the corresponding author.

Declarations

Ethics approval and consent to participate
The study was approved from the institute research board of Faculty of Medicine, Zagazig University, Egypt (ZU-IRB#:9178/2-4-2018). A written informed consent was obtained from all the participants or their responsible relatives after informing them about the study rationale and their right to withdraw from the study at any time without any consequences.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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