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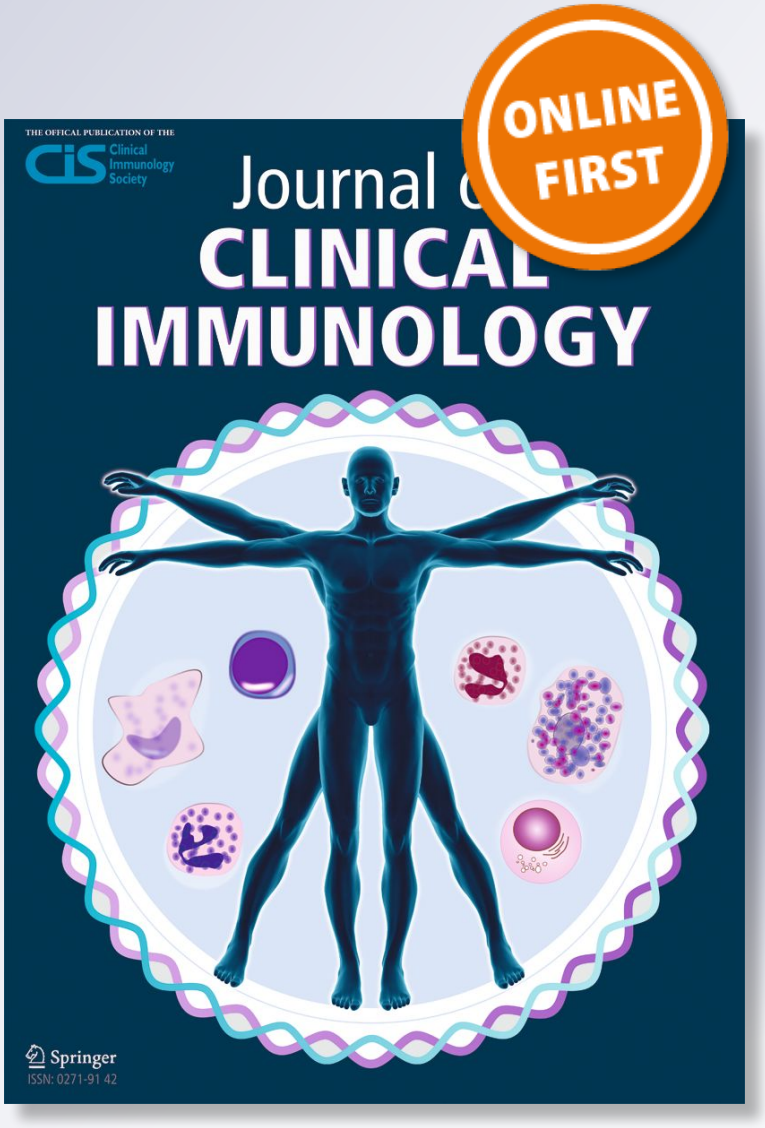

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BRIEF COMMUNICATION

Elevated Serum Resistin in Juvenile IdiopathicArthritis: Relation to Categories and Disease Activity

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Abstract
Background Juvenile Idiopathic Arthritis (JIA) is one of the more common chronic diseases of childhood that often persists into adulthood and can result in significant long-term morbidity, including physical disability. The aim of the present study was to assess the serum level of resistin in JIA patients and compare its levels according to the categories, clinical manifestations and disease activity.
Methods Sixty-eight JIA patients and 33 age and sex matched control children were included in the present study. All patients included in this study were subjected to full history taking, clinical examination. Juvenile arthritis disease activity score in 27 joints (JADAS-27) was calculated and Childhood Health Assessment Questionnaire (CHAQ) was used to measure the functional status. Serum resistin levels were measured by enzyme-linked immunosorbent assay (ELISA).
Results The mean serum resistin was significantly higher in the JIA patients (4.01±2.46 ng/ml) compared to the control (2.08±1.23 ng/ml) ($p<0.001$) especially those with systemic-onset. Its level was significantly higher in those receiving steroids and those with a positive antinuclear antibody. Resistin significantly correlated with the JADAS27 (r 0.26, p 0.035) and CHAQ (r 0.4, p 0.001). The JIA patients were 50 females and 18 males; however, the level of resistin was insignificantly different according to the gender although there was a tendency to be higher in females.
Conclusion Our results reinforce the proposition of an important role for resistin in JIA and may be considered an interesting biomarker for disease activity especially those with systemic onset.

Keywords Childhood HAQ · JADAS27 · juvenile idiopathic arthritis · resistin · categories

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Introduction

Juvenile idiopathic arthritis (JIA) is defined by the International League of Associations for Rheumatology (ILAR) as arthritis of unknown etiology that begins before the sixteenth birthday and persists for at least 6 weeks with other known conditions excluded [1]. Juvenile Idiopathic Arthritis (JIA) is one of the more common chronic diseases of childhood that often persists into adulthood and can result in significant long-term morbidity, including physical disability [2].

Important advances in our understanding of the relationships between adipose derived products (adipokines), inflammation and the immune response have been achieved in the past 10 years. White adipose tissue has emerged as an active endocrine organ that releases an excess of immune and inflammatory mediators involved in rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [3–5].

Resistin belongs to a family of proteins found in foci of inflammation, where they contribute to the inflammatory

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response and in RA has been found in the inflammatory processes [3, 6]. Resistin, one of the major adipokines, participates in inflammation and immunity [4]. It can contribute to the inflammatory processes by triggering cytokine production [7]. In addition to its association with increased inflammation, resistin is also associated with insulin resistance and cardiovascular risk [8]. The proinflammatory properties of resistin are superior to its insulin resistance-inducing effects in RA as it was found to be upregulated on TNFα stimulation and activates NF-κB-dependent pathways. Resistin is an important member of the cytokine family with potent regulatory functions that might be involved in the pathogenesis of RA and considered an interesting biomarker of inflammation [9, 10]. A possible metabolic role of adipose tissue in arthritis and rheumatologic diseases was suggested by the involvement of resistin in the inflammatory and metabolic pathways [11].

Synovial resistin levels are 10 times higher than its level in serum [11]. Immunocompetent cells, especially lymphocytes, in the adipose tissue rather than adipocytes seem to be another major source of resistin in humans [10]. Resistin exerts potent modulatory actions on target tissues and cells involved in rheumatic disease, including cartilage, synovium, bone and various immune cells [5]. Adipokines are predictors of radiographic progression in RA, possibly through distinct underlying biologic mechanisms [12].

The aim of the present study was to assess the serum level of resistin in JIA patients and compare its levels according to the categories, clinical manifestations and disease activity.

Methods

Sixty-eight Juvenile Idiopathic Arthritis (JIA) patients diagnosed according to the International League Against Rheumatism (ILAR) classification [1] were consecutively recruited from the Rheumatology clinics, Faculty of Medicine, Cairo University Hospitals. Thirty-three completely healthy children served as controls. All children or their parents gave informed consents and the study approved by the local ethical committee. All patients included in this study were subjected to full history taking, clinical examination. Juvenile arthritis disease activity score in 27 joints (JADAS-27) was calculated [13] and Childhood Health Assessment Questionnaire (CHAQ) was used to measure the functional status [14]. Drugs being taken were recorded, and doses of corticosteroids other than prednisone were converted to and reported as daily.

Patients and controls were matched for age, sex and Body Mass Index (BMI) and all participants reported no alterations of body weight for at least 3 months before the study. JIA cases with current infections, diabetes or with cardiac, hepatic, renal, gastrointestinal or other diseases—which might affect the parameters to be investigated- were excluded from the study. Serum resistin levels were measured by enzyme-linked immunosorbent assay (ELISA) according to the protocol provided by the manufacturer (BioVendor Laboratory Medicine, Inc., Brno, Czech Republic) and expressed as ng/ml. The study was approved by the local university ethical committee and the study performed in accordance with the ethical standards of the 1964 Helsinki declaration. All patients gave their informed consent prior to their inclusion in the study.

Statistics The Statistical Package for Social Sciences (SPSS) version 10 (LEAD Technology Inc., Charlotte, NC, USA) was used to analyze the data. Continuous variables were summarized through the median (range) and categorical variables using absolute values and percentages. Nonparametric Mann–Whitney *U* test compared two independent groups and Kruskal–Wallis test compared more than two groups. Spearman's rank correlation test was used as a measure of association of quantitative variables. Two-tailed p values<0.05 was considered to be statistically significant.

Results

The study included 68 JIA patients with a mean age of 12.21±3.07 years while the controls were 33 with a matched age of 12.76±3.24 years. The mean serum resistin was significantly higher in the JIA patients (4.01±2.46 ng/ml) compared to the control (2.08±1.23 ng/ml) ($p<0.001$). The demographic, clinical and laboratory features of the JIA patients according to the categories are shown in Table I. All the patients were receiving methotrexate (MTX), while 17 of the systemic onset, 17 of the polyarticular and 7 of the oligoarticular onset were receiving prednisolone. All patients were treated, however the follow-up data before and after treatment are unavailable.

In the JIA patients there were 50 females and 18 males with a matched control of 26 females and 7 males. The serum resistin level was insignificantly different according to the gender although the tendency was to be higher in the females.

The laboratory investigations of for the JIA patients showed the following mean results: hemoglobin (Hb) (11.7±1.27 g/dl), white blood cell (WBC) count (7.51±2.15×10^3/mm^3), platelets (343.44±74.3×10^3/mm^3), erythrocyte sedimentation rate (ESR) (50.71±22.65 mm/1st hr). There were no significant differences among the JIA categories in the Hb level or WBC count, while the platelet level was significantly higher in the systemic-onset category ($p<$ 0.001) and the ESR was significantly higher in the polyarticular and systemic-onset patients (p 0.001).

Table I The JIA patients characteristics

Parameter median (range)	Systemic (19)	Oligo (28)	Poly (21)
Age (yrs)	10 (5–16)	12 (6–16)	14 (9–16)
Gender Female:Male (no.)	12:7	24:4	14:7
Disease duration (yrs)	5(1–11)	5(2–10)	5 (2–12)
Body Mass Index (BMI)	23.2 (21.9–26.8)[a]	22.1 (18.9–25.4)	22.6 (18.7–26.8)
JADAS-27	19(6–24)	15(6.4–16)	18.3(11–38)[a]
C-HAQ	1.3(1–1.9)[a]	0.55 (0–1)	1.2 (0–1.9)
RF+ ve no (%)	0 (0)	0 (0)	5 (21.74)
ANA+ ve no (%)	3 (15.79)	18 (64.29)	7 (30.43)
Clinical manifestation no (%)			
Fever	19 (100)	0 (0)	4 (19.05)
Fatigue	15 (78.9)	2 (7.14)	3 (14.29)
Arthritis	19 (100)	28 (100)	21 (100)
Rash	15 (78.9)	0 (0)	0 (0)
Uveitis	0 (0)	5 (17.86)	1 (4.76)
Radiological findings no (%)			
Juxtarticular osteopenia	0 (0)	3 (10.71)	3 (14.29)
Avascular necrosis	0 (0)	0 (0)	2 (9.52)
Erosions of the hands	0 (0)	3 (10.71)	3 (14.29)
Medications			
Methotrexate	19 (100)	28 (100)	21 (100)
Prednisone>1 mg/kg/day	9 (47.37)	0 (0)	4 (19.05)
Hydroxychloroquine	15 (78.9)	25 (89.29)	21 (100)
Leflunomide	0 (0)	0 (0)	6 (28.57)

Data are no (%) unless stated otherwise

JADAS Juvenile arthritis disease activity score, *C-HAQ* Childhood health assessment questionnaire, *RF* Rheumatoid factor, *ANA* anti nuclear antibody

[a]significantly different at $p<0.05$

The mean disease activity (JADAS-27) was significantly higher in the polyarticular JIA patients compared to the other categories ($p<0.001$). The functional capacity (CHAQ) was obviously impaired in those with systemic onset JIA compared to the other categories. Moreover, the serum resistin level was significantly higher in the systemic-onset JIA patients (6.26±2.35 ng/ml) compared to those with polyarticular (4.74±2.41 ng/ml) and oligoarticular (2.92±1.67 ng/ml) involvement (<0.001) and to the control (2.08±1.23 ng/ml) (<0.001) as graphically presented in Fig. 1. The levels of resistin were close between those with

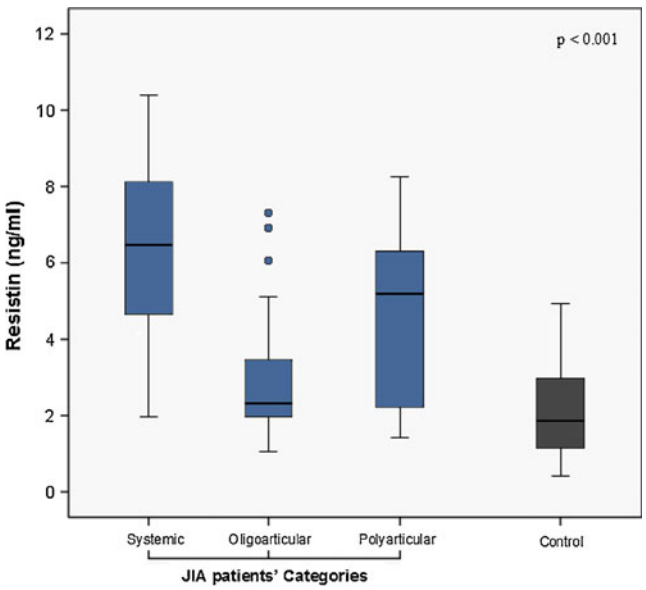

Fig. 1 Serum resistin level in Juvenile idiopathic arthritis patients according to the subtypes and control

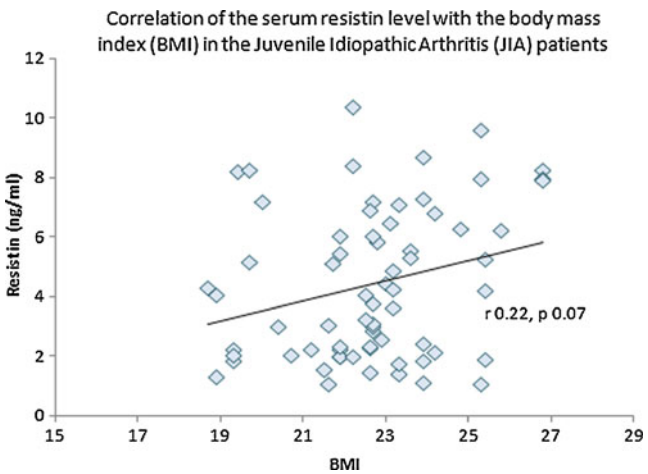

Fig. 2 Correlation of the serum resistin level with the body mass index (BMI) in the juvenile idiopathic arthritis (JIA) patients

oligoarticular JIA and the control, yet still difference was significant (p 0.03).

On comparing the parameters according to the presence and absence of RF positivity, uveitis or erosions, there were no differences of significance. However, in those receiving steroids, the serum level of resistin was significantly higher (5.08±2.56 ng/ml) to those not receiving (3.47±2.14 ng/ml) (p 0.006). Again, those receiving steroids had a higher JADAS-27 and CHAQ (19.234±5.84 and 1.16±0.52) compared to those not receiving steroids (12.71±4.53 and 0.55±0.44 respectively) ($p<0.001$). Moreover, the serum resistin level was significantly higher in those with positive ANA (5.19±2.62 ng/ml) compared to those with a negative test (3.88±2.3 ng/ml) (p 0.038).

The serum level of resistin significantly correlated with the duration of MS (r 0.38, p 0.002), steroid dose (r 0.3, p 0.012), JADAS27 (r 0.26, p 0.035) and CHAQ (r 0.4, p 0.001). There was a tendency to correlate with the ESR (r 0.2, p 0.1) and BMI (0.22, p 0.07) (Fig. 2). In the control, there was no significant correlation of the resistin level and the BMI (r 0.17, p 0.34).

Discussion

The rapidly growing understanding of resistin biology is revealing the complexity of this remarkable protein, thereby redefining white adipose tissue as a key element of the inflammatory and immune response in rheumatic diseases [5].

In the present study the serum resistin level was significantly higher in the JIA patients especially those with systemic onset. A role for resistin in the pathogenesis of RA has been suggested by its upregulation at local sites of inflammation and its link to inflammation and disease activity [10, 15]. Serum resistin levels were significantly increased in RA patients and correlated with inflammatory markers and TNF-α, suggesting that it may play a role in the rheumatoid inflammatory process [16]. Resistin was reported to be elevated in both the serum and synovial fluid of RA patients and even shown to induce *de novo* arthritis when injected in animal models [17]. Its potential role in the inflammatory cascade in RA was supported [18]. In the present study, there was no significant difference in the resistin level according to the gender of the children although there was tendency to be higher in females. In a study in adults, resistin concentrations did not differ significantly among men and women [8]. Others found that the serum levels of resistin were also associated with female sex [19].

In the current study, the serum level of resistin significantly correlated with the disease activity, steroid dose and CHAQ with a tendency to correlate with the ESR. Similarly, in RA patients, the increased serum resistin correlated with the DAS28 [10]. In another study, the levels of resistin positively correlated with systemic markers of inflammation such as ESR [11, 20] and even correlated better with the degree of subclinical inflammation [10]. The serum level of resistin was positively associated with CRP level in RA patients, suggesting that it may act as pro-inflammatory cytokines in this disease [19]. It was found that elevated serum levels of resistin was associated with the use of prednisolone [15, 19, 21]. Markedly distinct pathogenesis of oligo/polyarticular and systemic JIA implies that they might need different treatment strategies [22].

In latest American College of Rheumatology recommendations, prednisolone is key drug for systemic JIA but not oligo/polyarticular JIA. Additionally, systemic JIA patients need higher dose of prednisolone to control the disease than other JIA patients do [23]. Therefore, it is possible that the use and dose of prednisolone in few JIA patients with oligo/polyarticular involvement had an effect on the present results. In the patients, there was a tendency of resistin to correlate with the BMI.

The interrelationship between rheumatoid arthritis activity and resistin has been reported. However, there are no reports regarding resistin in JIA yet. This seems to be the first report showing the relationship between resistin and JIA categories/disease activity. Other studied the level of resistin in another rheumatic disease of children, Kawasaki disease [24, 25].

The sample size and unavailable follow-up treatment data were limitations for this study. However, our results reinforce the proposition of an important role for resistin in JIA and may be considered an interesting biomarker for disease activity especially those with systemic onset. It is recommended that a longitudinal study is conducted on a larger scale and including other adipokines to confirm the results and elucidate their role in the pathogenesis of this debilitating disease and value as a treatment biomarker. The next step to confirming its role as a biomarker is to establish it as a marker of disease activity and considering the study in untreated patients and follow-up before and after treatment.

Conflict of Interest None.

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