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Changes in Visfatin, Adiponectin, Leptin and Ghrelin Levels in Patients with Rheumatoid Arthritis and Their Correlation with Disease Activity

[Romatoid Artritli Hastalarda Visfatin, Adiponektin, Leptin ve Grelin Düzeyindeki Değişiklikler ve Bunların Hastalık Aktivitesi ile İlişkisi]

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ABSTRACT

Purpose: The aim of the present study was to determine the levels of visfatin, adiponectin, leptin and ghrelin in patients with rheumatoid arthritis and to find whether they have the potential to act as proinflammatory mediators and to correlate them with disease activity.
Material and Methods: This study included 30 female patients divided into two groups: patients with inactive rheumatoid arthritis (group I) and patients with active rheumatoid arthritis (group II). In addition 15 healthy females of similar age were used as controls. Fasting plasma visfatin, adiponectin, leptin and ghrelin were determined with ELISA kits.
Results: Rheumatoid arthritis patients had significantly higher plasma visfatin, adiponectin, leptin levels than controls with more significant increase in group II than I. Ghrelin was significantly decreased in rheumatoid arthritis patients (group I and II) than controls with no significant difference between the two groups of patients. Disease activity score, erythrocyte sedimentation rate and C-reactive protein were significantly positively correlated with plasma visfatin and adiponectin but not with either leptin or ghrelin.
Conclusion: The present study suggested a relevant role of visfatin, adiponectin and leptin, as proinflammatory mediators in rheumatoid arthritis. Therefore, approaches that reduce adipose tissue depots may reduce the severity of their resultant pathologies. Furthermore, this study has shown that the blood levels of proinflammatory mediators are different. Additionally, "Grelin" as well as being a growth hormone releasing factor is also a leptin antagonist. Therefore ghrelin-substitutive therapy should be revised and softened as; can be considered in control of leptin regulation.
Key Words: adiponectin, ghrelin, leptin, rheumatoid arthritis, visfatin

ÖZET

Amaç: Bu çalışmanın amacı romatoid artritli hastalarda visfatin, adiponektin, leptin ve grelin düzeylerini saptamak, proenflamatuvar aracı olarak görev yapabilecek potansiyele sahip olup olmadıklarını anlamak ve hastalık aktivitesi ile olan ilişkilerini araştırmaktır.
Gereç ve Yöntem: Çalışmaya dahil edilen 30 kadın hasta inaktif (grup I) ve aktif (grup II) romatoid artrit hastalığına sahip olmalarına göre iki gruba ayrılmıştır. Ayrıca aynı yaşlarda 15 sağlıklı kadın, kontrol grubu olarak değerlendirilmiştir. Açlık visfatin, adiponektin, leptin ve grelin düzeylerine ELISA yöntemi ile bakılmıştır.
Bulgular: Romatoid artrit hastalarında plazma visfatin, adiponektin, leptin düzeyleri kontrol grubuna kıyasla yüksek bulunmuştur. Grup II'de bu artış grup I'e nazaran daha yüksektir. Grelin, grup I ve II romatoid artrit hastalarında kontrol grubuna göre azalma göstermektedir. İki grup arasında grelin düzeyi bakımından farklılık bulunmamaktadır. Hastalık aktivite skoru, eritrosit sedimantasyon hızı ve C-reaktif protein, plazma visfatin ve adiponektin düzeyleri ile pozitif korelasyon gösterirken; leptin ve grelin ile aralarında bir ilişki bulunmamaktadır.
Sonuç: Bu çalışma visfatin, adiponektin ve leptinin proenflamatuvar aracı olarak romatoid artritte önemli rolü olduğunu göstermektedir. Bu nedenle adipoz dokudaki depoları azaltmaya yönelik yaklaşımlar patolojik sonuçların ortaya çıkmasını önleyebilmektedir. Ayrıca, çalışma proenflamatuvar aracıların kan düzeylerinin farklı olduğunu göstermektedir. Ek olarak "Grelin" büyüme hormonu salgılatıcı faktör olmasının yanı sıra leptin antagonisti olarak da görev yapmaktadır. Bu yüzden grelinin yerini alan tedavi gözden geçirilmeli ve leptin düzeyinin kontrolünü sağlayacak şekilde ayarlanmalıdır.
Anahtar Kelimeler: adiponektin, grelin, leptin, romatoid artrit, visfatin

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory condition characterized by polyarthritis and high concentrations of proinflammatory cytokines. Chronic inflammation in RA triggers body energy adjustments that include, fat mobilization, enhanced gluconeogenesis, protein catabolism and negative nitrogen balance (1). RA-associated wasting syndrome is characterized by a considerable loss of body cell mass (BCM). Loss of BCM is often accompanied by increased fat mass and stable body weight. In patients with RA, these changes predispose to an apparently contradictory condition, termed 'rheumatoid cachectic obesity which increases the morbidity and mortality (2). Obesity may increase susceptibility to RA, and at present is considered to be a chronic metabolic disorder characterized by systemic low-grade inflammation, with increasing levels of inflammatory markers in the blood, most of them produced by the white adipose tissue (WAT) (3). WAT is now considered to be a dynamic endocrine organ that secretes a number of factors, collectively referred to as adipokines. These include for example; tumor necrosis factor-a (TNF-α), leptin, interleukin-6 (IL-6), resistin, adiponectin and visfatin (4). Visfatin is identical to pre-B cell colony-enhancing factor (PBEF) that exhibits insulin-mimetic properties. Although the connection between the insulin-mimetic and antiapoptotic effects of visfatin still have to be investigated, that protein clearly represents an additional link between adipose tissue and inflammation. (5,6). Adiponectin, a recently described adipokine of emerging importance, is distinct from other known adipokines in that it alone among them appears to improve insulin sensitivity and is postulated to be associated in the modulation of inflammatory responses as it attenuates the inflammatory response mediated by TNF-α, inhibits macrophage phagocytic activity and TNF-α production (7). Leptin is a 16 kDa adipocyte-derived hormone. It has recently been recognized as a modulator of inflammatory and immune responses. Leptin has a dual role in inflammation. On one hand, it activates monocyte/macrophage cells and potentiates production of the proinflammatory cytokines, and directs T cell differentiation to Th1 phenotype, expressing interferon γ and IL-2. On the other hand, it expresses certain anti-inflammatory properties by releasing IL-1 receptor antagonist (8).

These metabolic abnormalities in RA are associated not only with increased production of inflammatory cytokines but also, mediated by disturbances of the endocrine system particularly those related to the adrenal axis and pituitary (9).

Ghrelin is a recently described growth hormone (GH)-releasing molecule produced by the stomach. It acts on the lateral hypothalamus and theoretically inhibits proinflammatory cytokine secretion and antagonizes leptin. It also, antagonizes leptin through the activation of the hypothalamic neuropeptide Y/Y1 receptor pathway**.** These findings raise the possibility that ghrelin may play an important role in the regulation of metabolic balance in inflammatory diseases such as RA (10, 11).

Therefore, the aim of the present study was to determine the levels of visfatin, adiponectin, leptin and ghrelin in patients with rheumatoid arthritis and to determine if they had any correlation with the disease activity.

Subjects and Methods

Patients

30 female patients selected from the Outpatient Clinic of the Physical Medicine/Rehabilitation and Internal Medicine Departments of Tanta University Hospital and fulfilled the 1987 American College of Rheumatology revised criteria for the diagnosis of RA (12). All patients were informed about this study and their consent was recorded. RA activity was assessed according to the 28 Joint Count Disease Activity Score (DAS28) (13) and patients were divided into: patients with inactive RA (DAS < 3.2) (group I, n=15), and patients with active RA (DAS ≥ 3.2) (group II, n=15) (14). RA patients were treated with disease modifying ant rheumatic drugs and suitable dosages of non-steroidal anti-inflammatory drugs were allowed during the study. In addition, 15 healthy volunteer female of similar age were recruited for participation as controls (group III). None was taking any medication. None of the control subjects or the RA patients had clinical or laboratory evidence of any disease that might have affected the parameters to be measured. Exclusion criteria include, post-menopausal women, cases with diabetes mellitus, other endocrine disorders (Cushing syndrome, thyroid diseases), those who were obese (Body mass index (BMI) >30 kg/m^2) caused by endocrine disorders or psychiatric disorders, those who were underweight (BMI <18 kg/m^2), history of myocardial infarction during the last 6 months, any malignancy, chronic kidney or liver disease, seizure. No patient had psoriasis, inflammatory bowel disease or history of ankylosing spondylitis (15). All cases included in this study were subjected to the detailed history taking and laboratory investigations.

Detailed history taking

Systemic and rheumatologic examinations were performed. BMI was calculated as weight [in kilograms] divided by squared height [in meters], (kg/m^2).

Laboratory investigations

A. Routine laboratory investigations including:

1. Complete blood count (CBC)
2. Erythrocyte sedimentation rate (ESR) mm/1st h was determined by Westergren according to Dacie and Lemis (16), ESR > 28 mm/1st h was considered as criteria of disease activity.

3. Serum C-reactive protein (CRP) was determined by semi-quantitative latex agglutination using AVITEX-CRPLATEX kit (Omega Diagnostics, Scotland, UK) according to Hind and Pepys (17). CRP value > 6mg/L was considered positive.

B. Specific laboratory investigations including :

1. Plasma level of visfatin was determined by the enzyme immunoassay kit purchased from Phoenix Pharmaceuticals (Belmont, California, USA) according to manufacturer's instructions (18).
2. Plasma adiponectin concentration was determined using Quntikine Human Adiponectin ELISA kit supplied by R and D systems, Germany (19).
3. Plasma leptin concentration was measured using Human Leptin ELISA kit supplied by Diagnostic System Laboratories, INC, USA (20).
4. Serum total ghrelin was measured using commercially available total ghrelin ELISA kit supplied by DSL-10-33700, INC. USA (21).

Overnight fasting-state blood samples [K_2EDTA(1mg/ml) treated and not] were drawn from patients and controls, then centrifuged as soon as possible at 2 000 × g for 10 minutes at 4 ºC. Serum and plasma samples were stored at −70 °C until the analysis.

Statistical Analysis

Statistical analyses were performed with a Statistical Package for the Social Sciences (SPSS version 8.0 Package (SPSS, USA)). Values were expressed as range, mean ±SD and median. Comparisons of parameters between the two groups were made by non parametric t-test (Mann-Whitney). Comparisons of parameters among three groups were made by non parametric ANOVA (Kruskal Wallis test) followed by Dunn's Multiple comparison test.

The relationships between the different variables (BMI, DAS, CRP, ESR on one hand and visfatin, adiponectin, leptin and ghrelin on other-hand) were analyzed using Spearman non-parametric correlation coefficient. A P value ≤ 0.05 was considered significant.

Results

Characteristics of the RA patients and controls are summarized in (Tables 1 and 2). They did not differ significantly with respect to age and BMI but RA patients had significantly higher CRP levels and ESR than healthy controls. Patients with RA (groups I and II) showed significantly higher plasma levels of visfatin, adiponectin and leptin than control group (group III) with more significant increase in group II than I (only in visfatin and adiponectin), with no significant difference

Table 1. Anthropometric and laboratory characteristics of RA patients and control subjects

Parameters	RA patients (n=30)	Healthy controls (n=15)	P
	Range Mean ±SD median	Range Mean ±SD median	
Age (years)	38-62 49.4±10.1 52	38-59 48.1±10.6 51	0.691
Duration of RA(years)	6-26 (months) 1.5±1.1(years) 11(months)	-	
DAS	1.2-6.3 3.35±1.04 4.4	-	
BMI (kg/m2)	17.4-30.2 24.60±4.65 22.2	16.5-27.6 22.74±4.25 20.3	0.201
CRP (mg/l)	12.5-70.2 36.50±21.39 45.3	3.3-8.4 4.8±2.13 6.1	<0.0001
ESR(mm/1st h)	14.5-74.5 41.36±21.01 50.7	5.7-16.6 9.60±4.38 11.3	<0.001
Visfatin(ng/ml)	43.7-113.4 78.50±26.50 70.5	25.7-43.4 34.33±6.58 30.4	<0.0001
Adiponectin(μg/ml)	8.8-32.4 19.09 ± 6.20 22.6	9.57 ± 3.29 (5.5-16.3)11.2	<0.001
Leptin (ng/ml)	14.5-28.8 20.50±4.16 22.3	8.5-18.4 12.20±2.34 14.4	<0.001
Ghrelin (pg/ml)	18.2-36.2 25.69±6.24 28.5	30.3-46.1 39.01±8.09 37.2	<0.001

Disease Activity Score (DAS), Body mass index (BMI), C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR)

Table 2. Anthropometric and laboratory characteristics of the studied groups

Variables	RA patients (n=30)		Healthy controls (n=15) (III)	P
	DAS<3.2 (n=15) (I)	DAS≥3.2 (n=15) (II)		
	Range Mean±SD median	Range Mean±SD median	Range Mean±SD median	
Age (years)	38-58 48.6±10.1 51	39-62 50.2±12.4 53	38-59 48.1±10.6 51	0.86
Duration of RA(years) Range in months	6- 24 (months) 1.2±0.7 10 (months)	8-26 1.7±0.9 12		p=0.10
DAS	1.2-3.1 2.50±0.41 1.8	3.5-6.3 4.20±0.73 5.3		p<0.001
BMI(kg/m^2)	17.4-30.2 24.40±4.93 22.2	18-29.7 24.80±4.62 22.1	16.5-27.6 22.74±4.25 20.3	0.433
CRP(mg/l)	12.5-24.2 17.40±4.60 19.7	30.4-70.2 55.60±12.04 48.5	3.3-8.4 4.8±2.13 6.1	<0.0001 All groups are significantly different by Dunn's Multiple comparison tests.
ESR (mm/1st h)	14.5-28.2 22.50±5.31 18	48.3-74.5 60.22±11.15 55.2	5.7-16.6 9.60±4.38 11.3	<0.0001 All groups are significantly different by Dunn's Multiple comparison tests
Visfatin (ng/ml)	43.7- 90.2 68.80±22.14 63.6	55.6- 113.4 88.21±27.61 80.2	25.7-43.4 34.33±6.58 30.4	<0.0001 All groups are significantly different by Dunn's Multiple comparison tests
Adiponectin (μg/ml)	8.8-22.3 15.64±4.79 17.8	13.3-32.4 22.55±5.58 24.2	5.5-16.3 9.57± 3.29 11.2	<0.0001 All groups are significantly different by Dunn's Multiple comparison tests
Leptin (ng/ml)	14.5-26.3 19.7±3.26 21.1	15.4-28.8 21.3±4.34 23.1	8.5-18.4 12.2±2.34 14.4	<0.0001 All groups are significantly different by Dunn's Multiple comparison tests except I vs. II
Ghrelin (pg/ml)	20.2-36.2 27.28±5.33 29.3	18.2-35.6 24.10±5.05 26.6	30.3-46.1 39.01±8.09 37.2	<0.0001 All groups are significantly different by Dunn's Multiple comparison tests except I vs. II

Disease Activity Score (DAS), Body mass index (BMI), C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR)

between groups I and II as regards leptin. But ghrelin was significantly decreased in RA patients (groups I and II) than control group with no significant difference between group I and II.

As regards correlation matrix; DAS, ESR and CRP were significantly positively correlated with plasma visfatin (r=0.58, 0.62 and 0.61, p<0.001, respectively) and adiponectin (r=0.58, 0.53 and 0.53 p<0.001, respectively) (Table 3) but with no significant correlation with either leptin or ghrelin (Table 3). As regards BMI; it was significantly positively correlated with plasma leptin (r=0.66 p<0.001) and significantly negatively correlated with serum ghrelin level (r=-0.79 p<0.05) (Table 3), with no significant correlation with both adiponectin and visfatin in patient groups (Table 3).

Discussion

Adipocytokines are now considered important players in the etiopathogenesis of numerous metabolic and inflammatory disorders including RA (3). Clinical studies have shown a relationship between serum concentrations of various markers of inflammation, such as CRP and IL-6, and the risk of development of insulin resistance. RA have reduced peripheral insulin action but the mechanism is still unknown, however excess TNF-α production may inhibit tyrosine kinase phosphorylation of the insulin receptor, resulting in defects in insulin signaling that leads to insulin resistance (22,23). Recently, it has been suggested that visfatin may be involved in the development of insulin resistance, because it is expressed predominantly in the visceral adipose tissue and exhibits insulin mimetic effects .This new adipokine facilitates adipogenesis (24). It is unclear what would be its physiological role in RA.

In the present study, visfatin level was significantly increased in patients with RA as compared to controls with higher levels in patients with DAS ≥ 3.2 than those with DAS < 3.2. These results came in accordance with the results of Luk et al (24). Also, Brentano et al reported significantly higher visfatin level in serum and synovial fluid samples from RA patients compared with those from patients with osteoarthritis (6).

The possible mechanisms by which visfatin exerts its proinflammatory effects in the arthritic joint are incompletely understood. As an extracellular cytokine; visfatin can induce the cellular expression of inflammatory cytokines such as TNF-alpha, IL-1 beta, and IL-6**.** In addition, visfatin is known to activate nuclear factor-kappaB (NF-kB), which plays an important role in triggering and coordinating immune responses in mice (25). It was recently suggested that visfatin expression is upregulated in a variety of acute and chronic inflammatory diseases including sepsis, acute lung injury, inflammatory bowel disease, and plays a key role in the persistence of inflammation through its capacity to inhibit neutrophil apoptosis (24).

In the present study, the presence of correlation between visfatin and markers of inflammation such as the CRP and ESR levels provided support for an important role of that cytokine in inflammatory reactions. The current results came in accordance with those of Oki et al who suggested the existence of positive correlations between serum visfatin levels and serum levels of IL-6 or CRP in humans (26). Furthermore, the higher level of visfatin in group II than in group I and its correlation with DAS in the current study suggests that visfatin is a marker of the severity of inflammation in patients with RA. Finally, the absence of correlation between visfatin and BMI may suggest that serum visfatin increases in RA regardless of the presences of obesity.

As regards adiponectin, in the current study, patients with RA had considerably higher adiponectin levels than controls with higher levels in patients with DAS ≥ 3.2 than those with DAS<3.2. The results of the present study came in accordance with those of Ebina et al (27) and Senolt et al (7). Presle et al also demonstrated that both serum and synovial fluid adiponectin levels were significantly higher in RA compared to healthy controls (28). However, its synovial fluid level was lower as compared to serum indicating that peripheral fat stores are major producers of adiponectin into the blood stream, and that increased synovial fluid adiponectin in RA patients may counterpart the local inflammatory process. The reasons for adiponectin higher levels are not evident, but it may represent an attempt to antagonize the anorexigenic and well-known pro-inflammatory effect of leptin, suggesting that these two adipokines may act in parallel as opposing metabolic counterparts. Furthermore, adiponectin may have a role in modulating the inflammatory response by inhibiting the expression of adhesion molecules on endothelial cells, suppressing macrophage function and inhibiting NF-kB signal-

Table 3. Correlation between the studied parameters and DAS, ESR, CRP in RA groups (n=30)

Parameters	BMI		DAS		ESR		CRP	
	r	p	r	p	r	p	r	P
Visfatin	0.102	0.592	0.588	<0.001	0.621	<0.001	0.613	<0.001
Adiponectin	0.203	0.282	0.587	<0.001	0.537	0.002	0.534	0.002
Leptin	0.664	<0.001	0.235	>0.05	0.199	0.291	0.296	0.112
Ghrelin	-0.795	<0.001	-0.236	>0.05	-0.211	0.264	-0.209	0.269

ling, as reviewed by Fantuzzi et al (29). It is also, believed that adiponectin has anti-inflammatory properties and can counteract the pro-inflammatory effects of TNF-α, a pro-inflammatory cytokine, which may influence the production of IL-6 and CRP in RA (30). The putative anti-inflammatory role of adiponectin needs further evaluation. This discrepancy may be explained by the fact that adiponectin circulates mainly as a low molecular weight (LMW) hexamer and a high molecular weight (HMW) multimer that induce isoform-specific responses. It has recently been discovered that only LMW adiponectin displays anti-inflammatory properties and HMW adiponectin may be responsible for pro-inflammatory effects (31). Thereby, analysis of specific adiponectin isoforms may be of great importance in determining those diverse effects.

In the present study there was a significant positive correlation between adiponectin and markers of inflammation (CRP and ESR) which came in accordance with the results of Ebina et al (27) and Fantuzzi et al (29). In contrast to those of Popa et al (32) and Senolt et al (7) who concluded that adiponectin was not related to age, disease duration, BMI, or disease activity of RA patients.

Leptin is a novel proinflammatory adipocyte-derived factor that operates in the cytokine network by linking immune and inflammatory processes to the neuroendocrine (33). In the present study the plasma levels of leptin is significantly increased in patients with RA as compared with controls with no significant differences between patients with DAS < 3.2 and those with DAS ≥ 3.2 and it is correlated with BMI with no significant correlation with both ESR and CRP. The results of the present study came in accordance with Popa et al (32), Lago et al (33) and Gunaydin et al (34) who concluded that serum leptin in RA patients reflects BMI but not joint inflammation. The increase in leptin production during infection and inflammation strongly suggests that leptin is a part of the cytokine cascade, which orchestrates the innate immune response and host defense mechanisms. Also, leptin may promote inflammatory response via production of nitric oxide synthase type 2 (8). In addition, Targońska-Stepniak et al found that leptin levels were significantly higher in patients with higher disease activity; also there was a positive correlation between serum leptin concentration and the value of DAS, ESR and the number of tender joints (35). Their results suggested that some important dependence exists between the risk of aggressive course of RA and increased leptin levels. In contrast, Hizmetli et al stated that there wasn't any significant difference in plasma leptin levels between RA patients and controls (36). Furthermore, Nishiya et al reported lower plasma leptin levels in patients with RA than in controls, because TNF-α may inhibit leptin secretion via TNF-α receptor type 1 in the absence of transforming growth factor-beta (37). Taken together, the data of different clinical studies indicate that leptin levels cannot be used to assess the disease activity in RA (38). However, the results of Bokarewa et al suggested that leptin may influence the outcome of RA (39). Thus, longitudinal studies including patients with early RA are still needed to clarify the potential influence of leptin on disease outcome.

In addition, bi-directional neuroendocrine–immune relationships are accountable for some of the homeostatic perturbations. In fact, defective hypothalamic–pituitary–adrenal axis functions are found in RA (40).

Ghrelin is a powerful, endogenous orexigenic peptide. In addition, ghrelin has anti-inflammatory effects, and it has been reported that ghrelin down-regulates pro-inflammatory cytokines, including interleukin (IL)-1beta and tumor necrosis factor (TNF)-alpha (11).

In the present work, there was a significant decrease in serum concentrations of ghrelin in RA patients as compared to the control. It is possible that serum concentration of ghrelin decreased in the early phase of the arthritis and increased in the chronic phase as a consequence of the associated relative weight loss (41). Such results came in accordance with the results of Koca et al (11) and Otero et al (9) who stated that low ghrelin concentrations could reflect the presence of an inhibitory anorexigenic signal/s. Whether this anorexigenic signal is evoked by leptin or other factors remains to be established.

Ghrelin and leptin are negatively related: leptin is able to negatively regulate ghrelin and vice versa; and thus, balance between ghrelin and leptin influences body weight. This hypothesis is consistent with observations of other authors showing that increases of ghrelin induced by weight loss arise because of diminished inhibitory input from leptin (41).These data suggest the existence of a reciprocal regulatory network by which ghrelin and leptin control immune cell activation and inflammation. Zhao et al strongly suggested that ghrelin may be a pro-inflammatory peptide in the colon and it may participate in the pathophysiology of colonic inflammation by inducing protein kinase C (PKC)-dependent NF-kappaB activation and IL-8 production at the colonocyte level (42). Ghrelin also inhibited endotoxin-induced systemic cytokine production in vivo. These findings may help to explain the beneficial effects of ghrelin administration in various pathological states associated with inflammation.

In conclusion, the current work suggested that patients with RA have a significant increase in plasma levels of visfatin, adiponectin and leptin but a significant decrease in serum ghrelin. These data confirm a relevant role for adipokines produced by WAT in the metabolic changes of autoimmune articular diseases such as RA. Not surprisingly, approaches that reduce adipose tissue depots improve proinflammatory adipokine levels and reduce the severity of their resultant pathologies. Also, this study suggested and couldn't rule out that an increase in visfatin levels may be related to the modulation of inflammatory response, contribute to the pat-

hology observed; however, it remains to be determined how the high levels of visfatin affect disease progression clinically. In addition chronic imbalance in ghrelin levels suggests that this gastric hormone may participate, together with other factors, in alterations of metabolic status during inflammatory stress. Furthermore, the potential of ghrelin-substitutive therapy, in association with other anti-inflammatory treatments, needs to be explored further.

Recommendation: In the current study based on single measurements of blood visfatin, may not reflect the relationship over time. It would be interesting to measure serial changes of plasma visfatin levels in RA patients to further clarify the role of visfatin in the pathogenesis of RA. Whether visfatin is related to plasma insulin or insulin resistance in these subjects is not determined. Further studies with large population are needed to investigate the role of visfatin in association with insulin resistance may help to clarify the role of visfatin in RA.

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