The relationship between anthropometric status and rheumatoid arthritis. Exploring the role of nesfatin and asymmetric dimethylarginine

Naghashian F[1], Hosseinzadeh-Attar MJ[2], Akhlaghi M[3], Yekaninejad MS[4], Aryaeian N[5], Derakhshanian H[6]

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ABSTRACT

Objective: The aim of this study was to explore the anthropometric status of rheumatoid arthritis (RA) patients, as well as two controversial adipokines, namely nesfatin-1 and asymmetric dimethylarginine (ADMA), to reveal the possible relationships between them and RA.

Methods: This study included RA patients who fulfilled the American college of rheumatology classification criteria. Anthropometric parameters including height, weight, and waist circumference (WC) were measured and body mass index (BMI) was calculated. Disease activity was assessed by 28 joints disease activity score (DAS28). Fasting plasma samples were collected and erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), nesfatin-1 and asymmetric dimethylarginine (ADMA) were determined using commercial kits. Statistical analyses were done using the BMI SPSS Statistics.

Results: A total of 77 patients including 63 females, with an average age of 48.45±11.26 and disease duration of 9.99±5.80 years participated the study, 62% of whom were overweight or obese. Disease activity was significantly higher in obese patients. In addition, BMI and WC were correlated with CRP and ESR, indicating higher level of inflammation in obese patients. DAS28 was also found to be correlated with CRP, ESR and ADMA (r=0.38, 0.61, 0.21 respectively). Higher protein intake was accompanied with higher CRP and ESR and higher carbohydrate intake was related to higher CRP and lower nesfatin-1.

Conclusions: Weight, BMI, and WC were correlated with the activity of RA and the concentrations of CRP and ESR went up in tandem with BMI. In addition, ADMA, but not nesfatin-1, was associated with BMI and disease activity in RA patients.

Keywords: Rheumatoid arthritis (RA); Body mass index (BMI); Nutrition; Inflammation; Adipokine

1. Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
2. Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran/ Center of Research Excellence in Translating Nutritional Science to Good Health, Royal Adelaide Hospital, University of Adelaide, Adelaide, Australia
3. Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran
4. Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran;
5. Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran
6. Dietary Supplements and Probiotic Research Center, Alborz University of Medical Sciences, Karaj, Iran/ Department of Biochemistry Genetics and Nutrition, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, and autoimmune disease that affects around one percent of adults worldwide and is associated with disability, loss of productivity, and decreased life expectancy and quality[1]. The etiology of RA is not clear, while the development of disease may be affected by both genetic susceptibility and life style risk factors including nutrition[2, 3].

There has been a long-standing debate whether diet plays a pivotal role in autoimmune diseases including RA[4, 5]. Various dietary patterns and some specific nutrients are speculated to be relevant to the occurrence of the disease. Although none of these diets or nutrients has been proven to be clinically effective so far, there is no doubt all RA patients can benefit from a balanced diet. One of the common consequents of imbalanced diet is obesity which is shown to have a correlation with the activity of RA. In a population-based prospective cohort study, it has been recently reported that overall RA risk was 10% higher for each 5% increment of total body fat, 5% higher for each 5cm increment of waist circumference (WC), and nearly 50% higher in those

with an obese compared to normal body mass index (BMI)[6, 7]. Obesity-induced chronic inflammation might be an important contributor of developing and worsening inflammatory diseases such as RA. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can be considered as inflammation indicators in RA patients. In addition, most of adipokines are involved in modulation of inflammation and thus might hypothetically play a role in RA pathogenesis[8]. Some studies have shown that adipokines including leptin, resistin, and visfatin may contribute to RA pathophysiology. Obesity and increased body fat mass are associated with higher production of adipokines with pro-inflammatory characteristics[9-11].

In this study, two other controversial adipokines, namely nesfatin-1 and asymmetric dimethylarginine (ADMA), were evaluated to reveal the possible relationships between them and RA activity[12]. The relationship between nesfatin-1 and body fat mass is still controversial. This anorexigenic peptide is also involved in glucose homeostasis, regulation of cardiovascular functions, and responses to stressors[13]; however, little is known about the role of nesfatin-1 in rheumatic diseases. ADMA, which is reported to increases in obesity and RA, inhibits vascular nitric oxide production endogenously and, in high levels, could contribute to impaired endothelium function and cardiovascular diseases[14-16].

The aim of this study was to analyze the correlation between disease activity with inflammation indicators, and some adipokines, namely nesfatin-1 and ADMA.

MATERIALS AND METHODS

STUDY POPULATION

This study included RA patients with the age range of 20-70 years, who fulfilled the 1987 American college of rheumatology classification criteria[17]. All patients had RA for at least 2 years and were treated in the clinic of rheumatology. This study was approved by the ethics committee and an informed consent was obtained from all participants. Patients with cardiovascular disease, kidney disease, liver disease, metabolic disease, cancer, diabetes, pregnancy and lactation, smoking, and taking drugs (such as biologics, hormones, cyclophosphamide and mycophenolate) were excluded from the study to include patients with more homogeneity and comparability.

Anthropometric parameters including height, weight, and waist circumference and body mass index were measured for all patients. Height and weight were measured without shoes and with light clothes. Waist circumference was measured at umbilicus level. BMI was calculated as the ratio of weight in kilograms and squared height in meter. Nutritional data were collected by a trained nutritionist using food frequency questionnaire (FFQ) and three-day dietary records and were analyzed by Nutritionist-4 software. Disease activity was assessed by 28 joints disease activity score (DAS28)[18]. DAS28 is a validated index that can be calculated using the number of tender (TJC28) and swollen joint count (SJC28), erythrocyte sedimentation rate (ESR), and patient's global assessment which is measured by a visual analog scale (VAS). The formula is: DAS28 = 0.56*√ (28 TJC) + 0.28*√ (28SJC) + 0.70*Ln (ESR/CRP) + 0.014*VAS. DAS28 index ranges from 0 to 10 and is graded to low (DAS28<3.2), moderate (3.2<DAS28<5.1), and severe (DAS28>5.1). A DAS28 of less than 2.6 considered as remission.

LABORATORY PARAMETERS

Blood samples were collected after 10-12 hours fasting between 9:00-10:00 AM. Collected samples were centrifuged for 10 minutes at 1500g with the purpose of separating serum and the serum stored in -80°C. ESR was measured via Convergys device (Convergent Technologies GmbH, Marburg, Germany). Plasma level of nesfatin-1, ADMA, and high sensitivity C-reactive protein (hs-CRP) were determined using enzyme-linked immunosorbent assay (ELISA) commercial kits and according to the manufacturer's instructions (Cusabio Biotech., China; Monobind Inc., USA).

STATISTICAL ANALYSIS

Statistical analyses were done using the IBM SPSS® Statistics) version 21, SPSS Inc., Chicago, IL, USA). The continuous and categorical variables were expressed as mean and percentages, respectively. Besides, the correlation study was done using bivariate Pearson test. Obese and non-obese patients were compared by student's t-test. P <0.05 was considered statistically significant.

RESULTS

A total of 86 patients were approached and 9 were excluded due to changes in medications and travel. Finally, 77 patients including 63 females with the average

age of 48.45 ± 11.26 and disease duration of 9.99 ± 5.80 years were assessed in this study (Table I). Mean BMI was 28.13±5.69 kg/m^2 and 62% of the patients were overweight or obese according to the definition given for obesity by the World Health Organization (WHO) which categorizes BMI>25 as overweight and BMI>30 as obese. WC was 93.81±12.58 centimeters and, based on National Institutes of Health (NIH) classification (>102 cm for men and >88 cm for women), 61% were obese. 82% of participants were taking disease-modifying anti-rheumatic drugs (DMARDs), 6% were nonsteroidal anti-inflammatory drugs (NSAIDs) users and 93% were treated with glucocorticoids. There was no difference in treatment type of obese and non-obese patients. Disease activity (DAS28) was evaluated which was significantly higher in obese patients (P=0.04). There was a positive correlation between BMI and disease activity (Table II). In addition, BMI was correlated with CRP and ESR (r=0.36 and 0.31; P<0.01), indicating higher level of inflammation in obese patients. The correlation between DAS28 and ADMA was marginally significant (P=0.05). In contrast, no relation was observed between nesfatin-1 and disease activity. Obviously, good correlations are observed between DAS28 and ESR or with CRP. Analysis of nutritional data showed that higher protein intake was accompanied by higher CRP and ESR and higher carbohydrate intake was related to higher CRP and lower nesfatin-1 (Table III). A complete network of relationships is depicted in Figure 1. It should be noticed that being a cross-sectional study, the causal effects relations may not be concluded.

TABLE I. DEMOGRAPHIC, DISEASE ACTIVITY AND BIOCHEMICAL CHARACTERISTICS OF RHEUMATOID ARTHRITIS PATIENTS

Demographic and disease activity	Mean+/-SD	Biochemical factors	Mean+/-SD
Age (y)	48.4 ± 11.2	CRP (mg/l)	12.18 ± 11.64
BMI (kg/m2)	28.1 ± 5.6	ESR (mm/hr)	33.81 ± 29.17
WC (cm)	93.8 ± 12.5	Nesfatin-1 (pg/ml)	522.72 ± 483.51
Duration of disease (y)	9.9 ± 5.8	ADMA (ng/ml)	29.72 ± 28.86
DAS	4.2 ± 1.0		
Number of swollen joints	5.2 ± 5.1		

Data are described as Mean ± SD. BMI: body mass index, WC: waist circumference, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, ADMA: asymmetric dimethylarginine, DAS: disease activity score.

TABLE II. CORRELATION BETWEEN DISEASE ACTIVITY AND OTHER VARIABLES

	Weight	BMI	WC	CRP	ESR	ADMA	Nesfatin
R	0.21	0.29	0.26	0.38	0.61	0.21	-0.04
P	0.05	0.01	0.02	0.001	<0.001	0.05	0.73

Disease activity is described with disease activity score 28 (DAS28), BMI: body mass index, WC: waist circumference, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, ADMA: asymmetric dimethylarginine, R: Pearson correlation, P: P value. Statistical correlations were determined using Pearson test, P < 0.05 is considered as significant.

TABLE III. CORRELATION BETWEEN NUTRITIONAL AND BIOCHEMICAL FACTORS

	Energy	Protein	Carbohydrate	Fat	Fiber
CRP	0.17	0.22 *	0.30 **	0.25 *	-0.03
ESR	0.10	0.30 **	0.16	0.16	-0.10
ADMA	0.002	0.13	0.12	0.07	-0.01
Nesfatin	-0.01	-0.03	-0.24 *	-0.17	-0.03

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, ADMA: asymmetric dimethylarginine. Statistical correlations were determined using Pearson test, P < 0.05 is considered as significant. * P < 0.01, ** P < 0.01

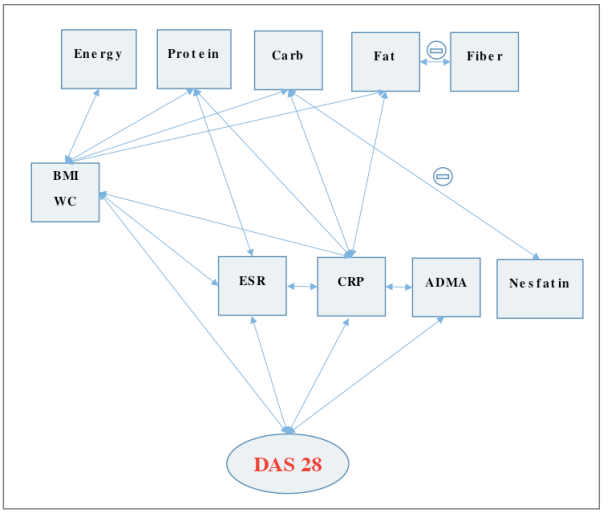

FIGURE 1. Correlation between disease activity (DAS), anthropometric, nutritional and biochemical factors in rheumatoid arthritis patients. BMI: body mass index, WC: waist circumference, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, ADMA: asymmetric dimethylarginine, ⊖ : negative correlation. $p < 0.05$ is considered for significant correlations.

DISCUSSION

In the present study, a positive but modest correlation was found between BMI and RA activity. Numerous studies have attempted to identify RA risk factors such as lifestyle and body composition[3]. In this context, obesity, as a potential risk factor for the development of RA, has been an area of interest for many years[19]. Previous study results have been controversial, with some showing an increased risk of RA among obese individuals and others showing no association. Even, a part of the literature showed that obesity may have a protective role in RA. For instance, Westhoff *et al*. showed people who were overweight or obese at the time of diagnosis had less joint damage than those with normal weight after 3 years of follow-up[20]. One hypothesis is that the protective effect of obesity may be due to the lower level of adiponectin in obese individuals[21]. On the other hand, several studies of long time monitoring have shown that overweight and obesity are associated with increased activity of RA and greater levels of disability[8]. It seems that the possible protective effect of obesity can disappear over time. A recent meta-analysis reported that obesity decreases the odds of remission in RA and negatively affects patient-reported disease activity[22].

The underlying mechanisms of the association between obesity and RA have yet to be determined. However, we know obesity as a pro-inflammatory condition in which adipocytes and adipose tissue-resident immune cells contribute to increased circulating levels of pro-inflammatory cytokines. In this study, there was a significant correlation between weight, BMI, WC and inflammation indicators such as hs-CRP and ESR. However, the causal relations may not be concluded based on bivariate correlations. Some adipocytokines, due to their association with adiposity and their pro-inflammatory effects, have been proposed as potential mediators[23]. High concentrations of inflammatory cytokines such as IL-6, IL-1, TNF-α, and many of adipocytokines such as adiponectin, leptin, and visfatin have been reported previously[24-26]. In addition, a positive correlation was shown between DAS28 and ESR/CRP which was expected since these inflammatory markers are used for DAS28 calculation.

Nesfatin-1 is a novel peptide which can be expressed in the hypothalamus, pancreatic islets, gastric endocrine cells, and adipocytes and might be related to obesity[27,28]. To the best of our knowledge, this is the first study that evaluates nesfatin-1 in RA patients. We could not find any significant relationship between nesfatin-1 level and obesity in RA. There is no data about concentration of nesfatin-1 in RA and the data about nesfatin-1 and obesity association is controversial. Ozkan *et al*. could not find any correlation between BMI and nesfatin-1 in normal and overweight subjects. However, nesfatin level dropped in obese patients. Similarly, there is another study showing that nesfatin-1 is not associated with BMI in diabetic patients[29,30]. On the other hand, some authors have reported that nesfatin-1 circulating levels are positively correlated with BMI[31] and some others reported negative correlation.[32] It seems that changes in the serum levels of nesfatin-1 depend on several other factors such as age, insulin resistance, disease control and etc[29,33,34]. Therefore, using the bivariate correlation may cause some biases if other variables are neglected.

Several studies have shown that higher levels of ADMA are associated with an increased risk of heart disease[35]. Previous studies have shown that ADMA levels are higher in RA patient that may result in increased risk of heart disease. In this study, disease activity was correlated with both BMI and ADMA. However, no direct significant correlation was detected

between body weight and ADMA concentration. The studies by Türkçüo lu *et al.*[36] on lean and obese women with polycystic ovary syndrome and studies by Cetinalp *et al*[37]. about postmenopausal women report that ADMA concentrations had not any correlation with BMI. Nevertheless, Koc *et al.*[38] showed that the ADMA levels are significantly higher in normotensive obese individuals than healthy controls. There are different hypotheses with regard to the higher levels of ADMA in obesity. It seems that reduction in activity of dimethylarginine dimethylaminohydrolase (DDAH) or increased activity of protein arginine N-methyltransferase (PRMT) may lead to increased ADMA levels in obesity[39,40]. DDAH is responsible for 80% of ADMA metabolism and is inversely associated with inflammation and TNF-a level in obesity[41]. We observed a correlation between fat and protein intake and inflammatory cytokines. The relationship between inflammation and dietary intake has been studied in the recent years. It seems that an adequate intake of vegetables, fruit, fish and dietary fiber may reduce CRP level. On the other hand, a Westernized dietary pattern that involves high intake of fat, red meat and refined grains has been reported to increase levels of CRP and inflammation[42]. Our study had several limitations. The relationship between variables could be better detected if we had a larger sample size. Conducting a case control study for comparing normal and obese RA patients may result in better interpretation of data. It is also recommended to measure body fat percentage and distribution in the future investigations.

CONCLUSION

The present study showed that weight, BMI and WC were correlated with the RA activity and the concentrations of CRP and ESR went up correspondingly with BMI. In addition, ADMA, but not nesfatin-1, was modestly associated with BMI and the disease activity in RA patients.

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CORRESPONDENCE TO

Mohammad Javad Hosseinzadeh-Attar
Department of Clinical Nutrition,
School of Nutritional Sciences and Dietetics,
Tehran University of Medical Sciences,
No. 44, Hojjatdost St.,
Naderi Ave., Keshavarz Blvd., Tehran, Iran.

E-mail: hosseinzadeh.md.phd@gmail.com

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