Progress in Nutrition 2018; Vol. 20, Supplement 2: 132-136 DOI: 10.23751/pn.v20i2-S.6560

Original article

Circulating resistin in ulcerative colitis, relation with anthropometric, body composition and inflammatory parameters

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Summary. *Background:* Chronic inflammation, altered body composition and development of abdominal obesity are distinct characteristic of Inflammatory Bowel Diseases (IBDs). Resistin, a white adipose tissue-secreted protein, play an important role in metabolism and inflammation. *Aim:* To evaluate serum resistin in ulcerative colitis (UC) and healthy controls and its association with anthropometric, body composition, inflammatory parameters and clinical disease activity in UC. *Methods***:** Fifty UC patients and 43 healthy age and sex matched participants were recruited for this case-control study. Clinical disease activity of UC patients was determined according to the Powell-Tuck activity index. Anthropometric parameters and body composition were assessed in UC patients. Serum resistin, hs-CRP and white blood cell (WBC) count were evaluated, too. Univariate and multivariate regression analyses used to determine the association between parameters. *Results:* Serum resistin levels were significantly increased in UC patients compared with controls (P= 0.004). It was correlated with disease activity scores (P= 0.016), hs-CRP levels (P= 0.009) and fat mass (P= 0.023) in UC patients but not with anthropometric factors and lean body mass. Results have showed that the most sensitive independent predictors of resistin among patients with UC were inflammatory parameters (P= 0.015). *Conclusion:* We found elevated levels of resistin in mild to moderate UC patients compared to healthy subjects. It was strongly correlated with inflammatory parameters but not anthropometric factors and body composition.

Key word: resistin, body composition, inflammation, fat mass, ulcerative colitis

Introduction

Resistin is a 12.5 kDa cysteine-rich peptide with different biological effects. The major cell populations that express and produce resistin in humans are PBMC, macrophages, bone marrow cells and also at very low levels in adipose cells (1-3). During last few years the role of resistin as an inflammatory marker has been studied (4-6). It considers as a link between inflammatory and metabolic pathways in humans (7).

Chronic inflammation, altered body composition and development of mesenteric WAT hypertrophy (accumulation of intra-abdominal WAT) are distinct characteristic of IBDs. These indicating an important role for WAT-secreted proteins such as resistin (8).

The role of resistin in IBDs and its correlation with systemic inflammatory markers and disease activity was investigated in few studies in recent years (9-13). We aimed to evaluate the serum levels of resistin in ulcerative colitis and compare with healthy controls

and its association with anthropometric, body composition, inflammatory parameters and clinical disease activity in UC.

Material and methods

Patients and healthy controls

Fifty UC patients (22 females, 28 males) were recruited for the study. Diagnosis of UC was established by endoscopic, histologic and clinical criteria. Patients were recruited by convenience sampling during their regular visits at the university related clinic of Tabriz, Iran University of Medical Sciences during spring and summer 2016. Forty three (19 females, 24 males) healthy age and sex matched volunteers (without known history of acute or chronic inflammatory disease, liver disease, kidney disease or use of anti-inflammatory drugs) agreed to participate in this case-control study. They were randomly selected from clinic personnel. Clinical disease activity of UC patients was determined according to the Powell-Tuck activity index with a score 3-5 defining mild, 6-8 moderate and >8 sever disease activity (14). During last six months patients did not experience any relapse episode and all were treated with their routine medication (mesalazine with or without azathioprine). A therapy with TNF-α antibody led to an exclusion from the study. All study participants gave their informed consent and the study protocol was approved by the ethics committee of the Tabriz University of Medical Sciences.

Biochemical parameters

Serum resistin concentrations were measured by ELISA (Mediagnost E50, Germany) with a sensitivity of 12 pg/ml with a normal range of 4-12 ng/ml. Determination of white blood cell (WBC) count was performed at the hematology laboratory of shahid ghazi hospital during 2 hours after withdrawal using an automatic blood cell counter (TechniconH.1 system). Serum high sensitive-CRP (hs-CRP) concentrations were measured using a turbidimetric Immunoassay (Stanbio WR, Germany).

Nutritional assessment and body composition

Height and weight of the patients and controls were measured on the day of assessment, and their BMI was calculated as weight (in kilograms) divided by square height (in meters). Waist circumference was measured at the narrowest level between the lowest rib and the iliac crest and hip circumference was measured at the maximum level over light clothing, with the use of an unstretched tape measure without any pressure to body surface. Measurements were recorded to the nearest 0.1 cm and the waist-to-hip ratio was calculated.

Body composition was assessed with body electrical bio-impedance analysis (BIA; Maltron Bioscan 916, England). An electric current of 0.8 mA and 50 kHz was produced by a calibrated signal generator and applied to the skin using adhesive electrodes placed on right-side limbs. Resistance and reactance were used to calculate total fat and lean body mass.

Statistical analysis

Statistical analysis was carried out using SPSS 13 (SPSS Inc., Chicago, IL, USA). Data were expressed mean (standard deviation). The normal distribution of variables was assessed using the Kolmogorov-Smirnov test. Univariate analyses were used to compare groups (chi-square test for categorical data and Student's *T*-test for continuous data). Correlations were calculated using Pearson for parametric and Spearman's rank-order correlation coefficient for non-normal data. Multivariate linear regression analysis was used to determine the relationship of serum resistin with inflammatory, anthropometric and body composition parameters in UC patients. An acceptable level of statistical significance was established a priori at $P \leq 0.05$.

Results

Baseline descriptive and anthropometric characteristics of participating individuals are shown in Table 1. Just waist circumference was slightly high in patients suffering from UC. No significant differences were seen among other parameters.

As expected, hs-CRP was significantly elevated in UC patients compared with control participants (P= 0.001). Likewise, serum resistin levels were significantly increased in UC patients compared with controls (P= 0.004) (Table 2).

Serum resistin well correlated with disease activity scores, hs-CRP levels and fat mass in UC patients.

Table 1. Comparison of descriptive and anthropometric characteristic between controls and ulcerative colitis

Characteristics	Controls n= 43	UC n= 50	P*
Sex (male/female)	24/19	28/22	0.323
Age (years)	33.19 ± 8.81	33.27 ± 9.70	0.724
Duration (years)		5.42 ± 3.35	
Mean of age at diagnosis (years)		27.44 ± 9.63	
Weight (kg)	68.24 ± 13.74	70.15 ± 14.56	0.641
BMI (kg/m²)	23.13 ± 6.17	24.76 ± 5.08	0.102
Waist (cm)	81.24 ± 12.40	84.68 ± 11.19	**0.041**
WHR	0.82 ± 0.07	0.81 ± 0.04	0.213
Fat mass (kg)	19.63 ± 5.41	20.2 ± 9.86	0.406
Lean body mass (kg)	43.4 ± 7.2	41.2 ± 8.8	0.134
Powell-Tuck activity index		6.02 ± 3.06	

*BMI: Body Mass Index, WHR: Waist to Hip Ratio; * Student's T-test*

It did not correlate with anthropometric factors and lean body mass (Table 3).

Results showed that the most sensitive independent predictors of resistin among patients with UC were inflammatory parameters (P= 0.015). R square in first model was 0.217 and R square change and P-value were 0.200 and 0.015, respectively (Table 4).

Table 2. Inflammatory parameters of healthy controls and UC patients

Parameters	Controls n= 43	UC n= 50	P*
WBC (× 10^3/µl)	7.19 ± 3.1	7.71 ± 2.17	0.203
hs-CRP (mg/L)	0.97 ± 0.86	2.04 ± 2.18	**0.001**
Resistin (ng/dl)	14.11 ± 9.34	17.90 ± 10.32	**0.004**

*WBC: White Blood Cell, hs-CRP: High-Sensitivity C-Reactive Protein; * Student's T-test*

Table 3. Association of serum resistin levels with inflammatory, anthropometric and body composition parameters in UC patients

Parameters	r	P*
Inflammatory factors		
WBC	0.155	0.322
hs-CRP	0.391	**0.009**
Clinical disease activity index	0.360	**0.016**
Anthropometric factors		
BMI	-0.087	0.579
Waist	-0.020	0.897
WHR	0.060	0.703
Body composition		
Fat mass	0.173	**0.023**
Lean body mass	0.085	0.268

*WBC: White Blood Cell, hs-CRP: High-Sensitivity C-Reactive Protein, BMI: Body Mass Index, WHR: Waist to Hip Ratio, *Pearson correlation*

Discussion

In the present study we investigated serum resistin in UC patients and healthy controls. We found that serum resistin was increased in UC and well correlated with disease activity index, hs-CRP levels and rather fat mass in these patients by using univariate regression but not with anthropometric parameters such as

Table 4. Linear multivariate regression analysis of serum resistin levels with inflammatory, anthropometric and body composition parameters in UC patients

Parameters	B	SE	Beta	P*
Model 1				
Inflammatory factors				
hs-CRP	0.481	0.241	0.311	0.053
Clinical disease activity index	0.264	0.175	0.236	0.141
Model 2				
Anthropometric factors				
BMI	-0.077	0.354	-0.114	0.830
Waist	-0.031	0.244	-0.010	0.990
WHR	0.048	22.42	0.106	0.830
Model 3				
Body composition				
Fat mass	0.092	0.387	0.135	0.274
Lean body mass	0.043	0.206	0.028	0.455

*hs-CRP: High-Sensitivity C-Reactive Protein, BMI: Body Mass Index, WHR: Waist to Hip Ratio; *Herarchical linear regression*

waist, WHR and BMI. Multivariate regression analyses have showed that the most sensitive independent predictors of resistin among patients with UC were inflammatory parameters.

Few studies investigated circulating levels of adipokines and reported increased levels of resistin in IBDs (9-12). According to disease activity index, our patients were mild to moderate and in accordance to Konrad et al (10) and kader et al (13) serum resistin levels were correlated with disease activity scores.

Resistin is a protein hormone secreted by adipocytes, which leads to insulin resistance (IR) in vivo an in vitro but recently more evidence indicates that it might also be involved in inflammatory processes (6, 7, 15, 16). It acts in a pro-inflammatory manner through activation of nuclear factor-kappa B inflammatory pathways (6). Human resistin, among other tissues, is expressed in the nonfat cells of WAT, mainly in macrophages and in peripheral blood mononuclear cells (PBMC), and minimally in adipocytes (2, 3). The association of blood resistin with adiposity markers, especially central obesity and body composition was investigated frequently but the results were not consistence (17-21). To our knowledge, relation of resistin with anthropometric and body composition in IBD have been evaluated previously once by Valentini et al (11). They reported that resistin correlated with disease activity scores and all inflammatory markers except interleukin-6 but not with body fat mass or plasma fatty acids. In this report we found no correlation between serum resistin with anthropometric parameters (BMI, waist circumference, WHR) but with fat mass by using univariate regression. Two investigations have shown higher serum resistin levels in obese subjects compared with lean subjects (22, 23). Yannakoulia et al (19) observed a positive correlation between resistin levels and body fat mass in healthy subjects similar to present study. Another study was conducted among Chinese children and adolescents (17) and authors reported a significant correlation between resistin and waist circumference, WHR, BMI and body fat percentages. Similarly, some investigations on diabetes mellitus type 2 patients suggested such correlation between resistin and adiposity markers (23, 24). Some human studies have shown no correlation between serum or plasma resistin with adiposity markers (20, 21).

Inflammatory bowel disease was associated with alterations in circulating adipokines and insulin (11). Resistin, a kind of adipocytokine, is a link between inflammation and metabolic pathways. Concerning inflammation-related diseases, resistin levels have been found to be elevated in the synovial fluid of rheumatoid arthritis patients (25), in the serum of patients with chronic liver diseases (26), and IBD (9-12). Human resistin has a pro-inflammatory role and also stimulates the secretion of TNF-α and IL-12, IL-6 and IL-1b (6, 7). Kader et al (13) found that resistin level was correlated with disease activity, WBC, ESR and CRP in UC patients, while Konrad et al (10) found similar results just in Crohn's disease while, Karmiris et al (9) did not find such an association. In present study we found a positive association between hs-CRP and serum resistin in accordance to Kunnari et al (27). According to multivariate regression results, hs-CRP did not show significant relation with serum resistin. Limited number of patients could. More detailed studies are needed to clarify the possible role of resistin in IBD.

Assessment of more inflammatory parameters such as TNF-α and pro-inflammatory cytokines and adipokines would be valuable for understanding the clear correlation. Adipocytokines affect function of immune cells, the differences in their circulating levels may be related to the distinct clinical features of IBD. The other limitation of present study was relatively small sample size.

Conclusions

In conclusion, we found elevated levels of resistin in mild to moderate UC patients compared to healthy subjects. In our study the strongest association from the tested variables emerged between resistin level and inflammatory factors. Regardless of the association with inflammation, we did not find a significant association between resistin level and obesity measured with body composition and anthropometric parameters when using multivariate linear regression.

Funding source

This work was supported by Student Research Center and Nutrition Research Center, Tabriz University of Medical Sciences.

Ethical approval

The study protocol was approved by the ethics committee of the Tabriz University of Medical Sciences.

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