

Characterization of the Metrnl Serum Levels in Patients with Inflammatory Bowel Disease and its Association with Inflammatory Cytokines

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Abstract

Background

Meteorin-like (Metrl) is a newly discovered adipokine with the anti-inflammatory and insulin sensitizing properties. Accordingly, Metrl regulates glucose tolerance, enhances metabolism in body tissues, and induces thermogenesis in white adipose tissue. However, the correlation among Metrl, IBD, and obesity still remains unexplored.

Methods

The present study was conducted on 54 healthy control, 42 Ulcerative Colitis (UC), and 43 Crohn's disease (CD) patients who were diagnosed by pathological examination. In these patients, serum levels of adiponectin, Metrl, IL-6, and TNF- α were measured using ELISA kits.

Results

Metrl concentration significantly decreased in both of the UC (85.25 ± 36.55 pg/mL) and CD (76.93 ± 27.92 pg/mL) patients compared to control group (107.52 ± 35.33 pg/mL). Similarly, adiponectin has also decreased in these two patient groups compared to the controls. However, IL-6 and TNF- α significantly increased in both of the patient groups. Moreover, Metrl indicated an inverse relationship with BMI in the controls and both of the patient groups. In addition, there was an inverse correlation among Metrl, IL-6, and TNF- α in both of the patient groups.

Conclusions

The current study is the first one reporting the decreased Metrl serum level in the patients with IBD, which is inversely related to BMI, TNF- α , and IL-6. These results suggested a possible role for Metrl in the pathogenesis of IBD, particularly through inflammation modulating.

Introduction

Inflammatory Bowel Disease (IBD) is known as one of the causes of mortality in modern societies, with the characteristics of gastrointestinal chronic inflammation (1, 2). Moreover, IBD includes two pathogenic form Crohn's disease (CD) and ulcerative colitis (UC). In this regard, the exact etiology of IBD is not well-understood yet, which resulted in identifying no-definitive cure (3). Although underweight and malnutrition are historically associated with IBD, new studies have revealed a rising prevalence of the IBD obese patients (15–40% are obese, and 20–40% are overweight) in general population (4). Recent epidemiological studies have also shown that, the increasing rate of IBD is parallel with the obesity prevalence (4, 5). Moreover, hospitalization and surgery are more frequent among the obese IBD patients

(6). Although it is not fully understood yet, scientist studies have suggested that, genetics, the gut microbiome, and the immune system may play critical roles in IBD (7). IBD (UC and CD disease) also displays the characteristics of chronic inflammation and metabolic syndrome, which is affectedly altered in metabolism (8, 9). Adipocytokines are secreted by white adipose tissue affecting the gut microbiome, inflammation, and metabolism pathways (10, 11). Conversely, IBD can be considered as a risk factor for obesity by changes in the intestinal microbial metabolism (9, 12).

On the other hand, the inflammatory condition of colon tissue can be affected by the impaired white adipose tissue (WAT) function such as abnormal adipocytokine secretion from adipocytes [12]. For example, leptin has decreased in the serum sample obtained from the IBD patients (with or without overweight). While the levels of resistin, adiponectin, and active ghrelin have remarkably increased(13).

Meteorin-like (Metrl, known as Subfatin) is a novel adipo-myokine that is mainly expressed in WAT. In addition, some studies have shown that, Metrl is expressed in the colon epithelium. Recently, it has been revealed that, Metrl exerts an anti-inflammatory activity (14). Moreover, it can enhance lipid metabolism, decrease adipose inflammation, and ameliorate obesity-mediated insulin resistance. Notably, in this study, Metrl expression was higher in mesenteric WAT of the CD patients in comparison to the controls(15). Studies reported that, the expression of Metrl is high in intestinal cells, white adipose tissue, and skin. In addition, Metrl express in various other tissues including muscle, liver, heart, spleen, and central nervous system (CNS). Moreover, Metrl is produced by the activated macrophages, thus it can be associated with the inflammatory disorders such as IBD(16). A few studies have been done on tissue Metrl and IBD disease. However, up to now, no studies have been performed on investigating the association between serum Metrl and IBD disease as well as the association among this protein, obesity, and the pro-inflammatory cytokines. In this study, we examined the serum levels of Metrl in the patients with inflammatory bowel disease and also its association with the hall-markers of inflammatory cytokines (TNF- α and IL-6) in IBD.

Methods

Study population

This case-control study was conducted on 54 control subjects and 85 IBD patients including 42 CD and 43 UC who were recruited from endoscopy unit of Valiasr Hospital, Birjand, Iran. The patient and control groups were selected by clinical examination, radiologic, endoscopic, and pathologic criteria. All the individuals aged between 35 and 60 years old. Moreover, the subjects with any history of cancer, diabetes, autoimmune diseases or active infectious disease were excluded from this study.

Anthropometric data and laboratory measurements

All the participants filled out a questionnaire to report their demographic data and medical history. Furthermore, weight and height were measured and body mass index (BMI) was also calculated using the following formula: [height (m)²/weight (kg)]. Afterward, systolic and diastolic blood pressures of all the

participants were evaluated using a standard sphygmomanometer after 15 min resting in sitting posture. After 12 hours of fasting, 5 ml of blood was obtained from all the participants and the serum was then separated by centrifugation. Subsequently, blood glucose serum levels (FBS) and lipid profiles including triglycerides (TG), cholesterol (Chol), HDL, and LDL were measured using auto-analyzer and the commercially available kits (Pars Azmoon, Iran).

Serum adipokine and cytokines

Circulating levels of METRNL were determined using an immunoassay kit (R&D Systems, USA, Cat#DY7867). Moreover, the inter-assay and intra-assay variations were calculated as 6 and 8%, respectively. Adiponectin serum levels were measured using an ELISA kit (Adipogen, South Korea, Cat#AG-45A-0001YEK-K101) with inter- and intra-assay variations of 4.4% and 4.6%, respectively. Afterward, the ultrasensitive ELISA kits were used to measure the serum levels of interleukin-6 (IL-6) (R & D Systems, USA, Cat# HS600B) and TNF- α (R & D Systems, USA, Cat# DTA00C). Notably, the minimum detectable ranges of IL-6 and TNF- α were obtained as 0.7 and 1.6 pg/ml, respectively.

Statistical analysis

Statistical analysis was performed using SPSS version 18. Categorical data were presented by frequency and percentage, which were tested by chi-square test. Continuous variables were also examined by student t-test and one-way ANOVA, and were then presented by mean and standard deviation (SD). Correlation analysis was performed by Pearson correlation test. Furthermore, multinomial logistic regression was conducted to estimate the risk of diseases status in terms of the Metrnl levels.

Results

Anthropometric and biochemical measurement

The details of anthropometric and biochemical variables of the studied population are given in Table 1. In this regard, the studied groups showed no significant difference in terms of age, sex, and BMI. Similarly, SBP and DPB indicated no considerable difference among these 3 groups. Although FBG illustrated no significant difference between the controls and patients with UC and CD, insulin and HOMA-IR significantly increased in the patients with CD compared to the controls. It should be noted that, higher levels of insulin and HOMA-IR in the UC patients compared to the controls did not reach the significant threshold. Furthermore, lipids profile including TG, TC, HDL-C, and LDL-C demonstrated no considerable variation between the patients and controls.

Table 1
Anthropometric and biochemical characteristic of studied population.

	Control (n = 54)	UC (n = 43)	CD (n = 42)	p value
BMI (kg/m ²)	24.12 ± 3.56	23.45 ± 3.64	24.43 ± 4.61	0.502
Age (year)	39.02 ± 4.6	38.24 ± 5.32	38.74 ± 5.7	0.763
SBP (mmHg)	131.17 ± 20.79	133.40 ± 24.26	131.65 ± 23.97	0.887
DBP (mmHg)	81.63 ± 13.11	83.10 ± 14.48	83.16 ± 14.26	0.825
FBG (mg/dl)	90.26 ± 9.03	93.65 ± 13.27	94.28 ± 12.05	0.172
Insulin (μU/ml)	4.03 ± 0.31	5.66 ± 0.5	5.93 ± 0.64 ^{a*}	0.014
HOMA-IR	0.89 ± 0.07	1.31 ± 0.14	1.43 ± 0.17 ^{a**}	0.005
TG (mg/dl)	117.41 ± 44.83	128.76 ± 47.64	126.08 ± 38.15	0.409
TC (mg/dl)	157.22 ± 35.41	164.54 ± 47.49	162.25 ± 30.83	0.629
LDL-C (mg/dl)	94.70 ± 26.95	100.64 ± 35.84	104.93 ± 21.74	0.212
HDL-C (mg/dl)	43.53 ± 6.20	42.11 ± 9.07	41.46 ± 7.76	0.394
Abbreviations: UC, ulcerative colitis; CD, Crohn's disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.				
^a Comparison between control and CD.				
*p < 0.05.				
**p < 0.01.				

Serum levels of adipokines and cytokines

The ELISA results (Fig. 1) showed that, adiponectin concentration significantly decreased in the patients with UC and CD compared to the controls. Furthermore, TNF-α considerably elevated in the patients with UC and CD in comparison to the controls. Moreover, the patients with CD showed higher IL-6 levels compared to the controls, while the serum levels of IL-6 did not reach the significant threshold in the patients with UC compared to the controls. Furthermore, Metrnl serum concentration considerably diminished in the patients with UC and CD compared to the controls.

Regarding the crucial role of adipose tissue on Metrnl levels, analysis was performed according to the BMI cutoff (Over Wight, BMI ≥ 25 and normal weight, BMI < 25). In this regard, Metrnl serum levels were found to be lower in all the overweight subgroups (Table 2).

Table 2
Serum levels of Metrnl according to BMI cutoff.

Group	Normal weight	Over weight	p
All participants	102.27 ± 36.23	78.13 ± 31.04	< 0.001
Control	117.84 ± 37.53	95.56 ± 28.90	0.019
UC	96.92 ± 35.63	66.29 ± 30.25	0.007
CD	87.40 ± 27.24	66.93 ± 25.24	0.014
Abbreviations: UC, ulcerative colitis; CD, Crohn's disease.			

Association of serum Metrnl with the risk of diseases status

Multinomial logistic regression demonstrated an association between the decreased serum levels of Metrnl with the risk of UC and CD diseases. Furthermore, these associations have been adjusted for confounding factors including age, sex and BMI and the relationships remained as significant for both UC and CD diseases (Table 3).

Table 3
Odd ratio of disease status according to 10 unit change in serum levels of Metrnl.

Model	Group	Odd Ratio	95% CI	P value
Crude	UC	0.833	(0.735–0.944)	0.004
	CD	0.760	(0.661–0.874)	< 0.001
Model 1	UC	0.794	(0.692–0.912)	0.001
	CD	0.738	(0.636–0.858)	< 0.001
Model 1. Adjusted for age, sex and BMI.				

Correlation analysis

Correlation analyses were performed in 2 subgroups, as controls and patients. In the control group, Metrnl was found to be inversely correlated with BMI. Also, in the patient groups, Metrnl had an inverse correlation with BMI, IL-6, and TNF- α (Table 4).

Table 4
Correlation analysis of serum Metrnl levels
with anthropometric and biochemical
variables.

	Metrnl	
	Control	IBD
BMI (kg/m ²)	-0.298*	-0.391**
Age	0.174	-0.146
SBP	-0.026	0.032
DBP	-0.110	-0.061
FBG (mg/dl)	0.023	0.222*
Insulin (uU/ml)	-0.184	0.085
HOMA-IR	-0.175	0.127
TG (mg/dl)	0.202	-0.004
TC (mg/dl)	0.082	-0.016
LDL-C (mg/dl)	0.026	-0.061
HDL-C (mg/dl)	0.085	-0.029
Adiponectin (ug/ml)	-0.012	-0.076
TNF-alpha	0.137	-0.380**
IL-6 (pg/ml)	-0.027	-0.324**

Discussion

Adipokines have several effects on the immune system through regulating the expression and secretion of various cytokines. Therefore, they can play a crucial role in inflammatory diseases like IBD, which also have a metabolic background (17). Several studies have shown that, adipokines such as leptin, resistin, visfatin, retinol-binding protein-4, adiponectin, glucose, and insulin are deregulated in the IBD patients (13). Metrnl is a novel adipokine, which plays a key role in inflammation and insulin resistance improvement (18). Accordingly, this adipokine has been investigated in several metabolic and inflammatory diseases. Lee et al. showed that, the levels of Metrnl were lower in the serum samples of the T2DM patients(19). Moreover, Dadmanesh et al. found lower serum levels of Metrnl in the patients with coronary artery disease and type 2 diabetes mellitus(20). While, Chung et al. reported an increased serum level of Metrnl in the patients with T2DM(21). Most of the previous studies determined the tissues level of Metrnl in inflammatory disorders, so there is no data on the serum levels of Metrnl in these complications. Bridgwood et al. investigated the Metrnl in synovial tissue in the patients with

Rheumatoid Arthritis, Psoriatic Arthritis, and Osteoarthritis. As a result, they found the elevated level of Metrnl in Psoriatic Arthritis (22). To the best of knowledge, this is the first report on the serum levels of Metrnl in the IBD patients. In addition, our results show the lower serum levels of Metrnl in the IBD patients compared to the controls. However, Metrnl was not different between the patients with UC and CD. LI et al. demonstrated that, Metrnl is highly expressed in the gastrointestinal tract of normal donors as well as mice. On the other hand, they produced intestinal epithelial cell-specific knockout mice, which showed no significant serum reduction, despite the reduction in the GUT expression of Metrnl (16). A recent study performed by Zuo et al. reported that Metrnl expression is higher in mesenteric adipose tissue (MAT) of the CD patients compared to the controls. They also showed that, systemic treatment of Metrnl can improve the adipocyte function, and reduce the macrophage infiltration and inflammation by acting on the PPAR γ pathway in mice. Therefore, they suggested that, Metrnl upregulation in the MAT of these patients may be caused by a compensatory response ((14). Regarding the inconvenient results, it seems likely that, Metrnl expression can have an organ dependent pattern; however, establishing this concept needs more studies.

Furthermore, in the present study, Metrnl indicated an inverse relationship with the inflammatory cytokines in the IBD patients. Also, recent studies observed that, Metrnl displays a function in inflammation pathways. Zuo et al. administered the Metrnl in IL-10 $^{-/-}$ mice and then observed a significant decrease in the score of inflammation and pro-inflammatory factors such as tumor necrosis factor (TNF)- α , interferon (IFN)- γ , and IL-6 (12). Additionally, Zhi-yong LI et al. reported that, Metrnl plays a regulatory role in the expression of antimicrobial peptides such as islet-derived 3 gamma (Reg3g), lactotransferrin, and amyloid A-3 (SAA3) (22). Since TNF- α and IL-6 are considered as the markers of inflammation, our results suggest a relationship between Metrnl and IBD pathogenesis

When we stratified the population based on obesity, the serum level of Metrnl was significantly lower in obese subjects than in non-obese ones. Consistently, AlKhairi et al. reported that, Metrnl is significantly higher in the T2D obese patients, in a way that this elevation can be considered as a compensatory response (23). However, Zhi-Yong Li et al. showed no correlation between serum Metrnl level and BMI (24). As the adipose tissue is the main source of Metrnl secretion, it is expected that, BMI can affect the levels of this adipokine, and adipose tissue inflammation and dysfunction might be considered as the causes for the decrease in Metrnl levels.

Conclusion

In conclusion, the current study is the first to show that serum level of Metrnl has decreased in the IBD patients. Moreover, it was found that, serum level of Metrnl has a negative correlation with serum levels of TNF- α , IL-6 and BMI in the patients with IBD. Altogether, the present study demonstrated a relationship among Metrnl, inflammation, and obesity that suggested a possible role of Metrnl in the pathogenesis of IBD. However, the cross-sectional design of the study limited us in concluding a cause and effect relationship, so further studies are needed to dissect the possible mechanism for the reported relationship.

Abbreviations

Metrl: Meteorin-like; IBD:Inflammatory bowel disease; CD:Crohn's disease ; IL-6:Interleukine 6; TNF- α :Tumor necrosis factor α ; WAT:white adipose tissue ; TG:triglyceride; Chol:Cholesterol ; FBS:Fasting blood sugars; SD:standard deviations.

Declarations

Availability of data and material

Additional data are available from the corresponding authors for reasonable requesting.

Ethics approval and consent to participate

The written informed consent was signed by all the participants and the research was confirmed by the Ethics Committee of Birjand University of Medical Sciences.

Consent for publication

No applicable

Competing interest

The authors declare no conflict of interest.

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Author's contribution

Afsane Gholamrezayi & Maryam Mohamadinarab: Design and performed experiments, analyzed data and co-wrote the paper. Pegah Rahbarinejad, Shekufe Rezghi Barez ,Leila Setayesh:Performed experiments; Soudabeh Fallah: super vision and revised final manuscript and confirmed; Nariman Moradi and Reza Fadaei : Design experiment, Monitoring the experiment &written the manuscript and revision; *Elham Chamani & Tahmine Tavakili: Performed Endoscopy, collected samples, supervision, financial support & corresponding Authors. All authors read and approved final manuscript.

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Figures

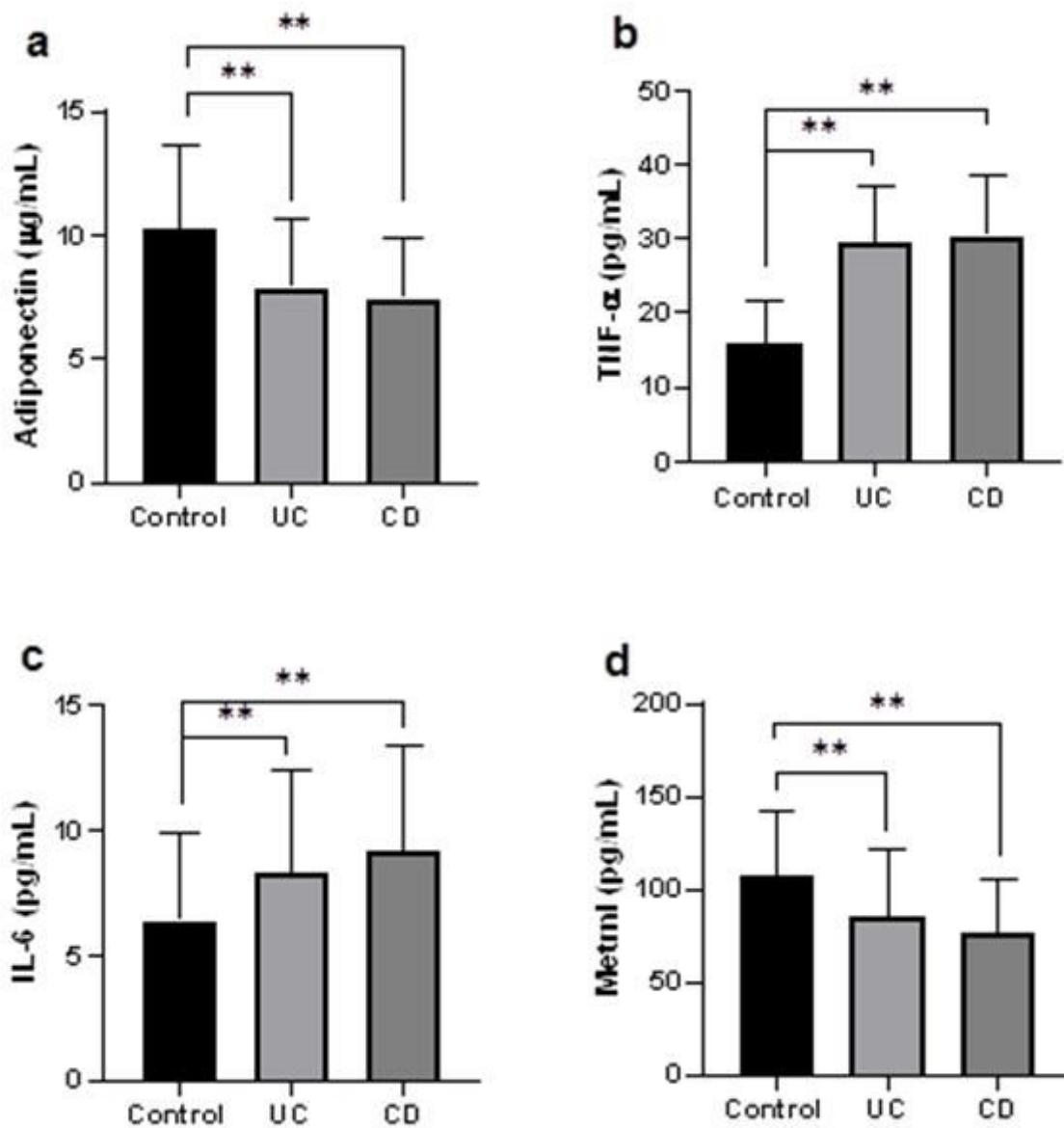


Figure 1

Serum levels of adipokines and cytokines. a) Serum levels of adiponectin decreased significantly in both UC and CD patients compared to controls. b) Serum levels of TNF-alpha were found to be lower in both patient groups compared to controls. c) IL-6 serum concentration indicated a considerable increase in both patient groups compared to controls. d) MetrnI serum levels demonstrated a significant decline in UC and CD patients compared to controls. CD, Crohn's disease; IL-6, Interleukin 6; TNF-α, Tumor Necrosis Factor Alpha; UC, ulcerative colitis.