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Plasma levels of CTRP-3, CTRP-9 and apelin in women with multiple sclerosis

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ABSTRACT

Background: Recently, adipocytokines have been shown to play a pivotal role in autoimmune and inflammatory-related disease. The purpose of this study was to compare the levels of CTRP3, CTRP9, adiponectin and apelin- in Multiple Sclerosis (MS) patients with healthy subjects and their relationship with clinical parameters and the levels of pro-inflammatory mediators.
Methods: Plasma levels of CTRP3, CTRP9, apelin, TNF-α, hs-CRP, and adiponectin were evaluated in 24 healthy women and 26 women with relapsing–remitting MS using immunoassay methods.
Results: The plasma apelin level of the MS patients was significantly lower than that of healthy controls. The concentration of TNF-α and adiponectin were significantly higher in MS patients compared to the healthy controls. Plasma CTRP3, CTRP9 and hs-CRP levels were not significantly different between the two groups. There was no correlation between these adipokines and inflammatory mediators. A statistically significant negative correlation was observed between plasma concentrations of apelin with expanded disability status scale (EDSS) scores and number of relapse.
Conclusions: Our findings suggest that adipokines, particularly apelin and adiponectin, may contribute to the pathogenesis of MS and can be considered as a biomarker or as a therapeutic target for the treatment of this disease.

1. Background

Multiple Sclerosis (MS) is an autoimmune, inflammatory and disabling disease of the central nervous system, although the cause of MS is unknown, evidence revealed that dysregulation of the immune system and cytokines are involved in its pathogenesis (Bennett and Stüve, 2009; D'Angelo et al., 2018; Graber and Dhib-Jalbut, 2011; Kasper and Shoemaker, 2010). Recent studies suggest that adipocytokines, cytokines mainly produced by adipose tissue, including leptin, resistin, adiponectin, and visfatin may contribute in the pathogenesis and development of autoimmune disease such as MS (De Rosa et al., 2007; Dikbas et al., 2016; Dini et al., 2017; Emamgholiour et al., 2013; Reale and Sanchez-Ramon, 2017).

The Complement C1q Tumor necrosis factor-Related Proteins (CTRPs) are a novel family of adipocytokines that exerts a dual function in immunity and metabolism (Schäffler and Buechler, 2012). Adiponectin is a member of this family, which is predominantly expressed in adipose tissue and has anti-atherosclerosis, anti-diabetes, anti-inflammatory and immune suppressive effects in metabolic disorders (Fantuzzi, 2008; Fantuzzi, 2013; Ouchi and Walsh, 2007). Furthermore, adiponectin plays an important role in the development of immune-mediated diseases, but its role in inflammatory/autoimmune diseases may be controversial and remain largely unknown. Various studies have examined adiponectin levels in MS patients, with different results (Hietaharju et al., 2010; Kraszula et al., 2019; Musabak et al., 2011; Penesova et al., 2015).

CTRP-3 and CTRP-9 are also other members of this family that have anti-inflammatory effects. CTRP-3 is secreted by adipocytes and

monocytes (Hofmann et al., 2011; Weigert et al., 2005) and inhibits the proinflammatory pathways induced by lipopolysaccharides (LPS), toll-like receptor (TLR) ligands, and fatty acids in these cells (Compton and Cheatham, 2010; Kopp et al., 2010). CTRP9, expressed mainly by adipose tissue, regulates glucose and lipid metabolism (Wei et al., 2014; Yang et al., 2016), and also has anti-inflammatory and protective effects against oxidative (Cheng et al., 2016; Jung et al., 2016; Li et al., 2016) and ischemia–reperfusion damage (Bai et al., 2016; Kambara et al., 2012).

Apelin is another novel member of adipokines that secretes by various tissues and organs, such as adipose tissues, heart muscle, liver, lymphocytes and central nervous system. Apelin and its receptor APJ have multiple functions, including the regulation of blood pressure, cardiac contractility, glucose metabolism, body fluid homeostasis, cell proliferation, immune response and neuroprotective effects (Wu et al., 2017). Apelin also has anti-inflammatory effects through inhibition of inflammatory factors such as interleukin-1ß and TNF-α (Leeper et al., 2009).

Regarding the role of adipocytokines in autoimmune and inflammatory diseases, very little research reported their role in MS. The aim of the present study was to investigate the concentrations of plasma CTRP-3, CTRP-9, adiponectin and apelin in MS patients compared to healthy subjects. The relationship between these adipokines and levels of TNF-α and hs-CRP as an inflammatory factors was also studied.

2. Materials and methods

2.1. Subjects

Totally, 50 women, including 26 relapsing–remitting MS patients and 24 healthy individuals, who were matched for age were enrolled in this study. The MS patients were recruited from the neurology clinic of a tertiary referral hospital. The diagnosis of MS was made based on the 2010 revised McDonald's criteria (Polman et al., 2011) by a neurologist. Patients with newly diagnosed relapsing remitting MS and/or patients who have not received any immunosuppressive or immunomodulatory drugs for at least three months, with an Expanded Disability Status Scale (EDSS) score = 2.0 or less at the time of diagnosis, age between 20 and 45 years were included. The exclusion criteria were: cardiovascular disease, hypertension, diabetes mellitus, thyroid disease, smoking, hepatic or renal disease, cancer and infection or use of any medication (based on the patient information). The control group was selected from the same geographical areas of the patients. The study was approved by the local ethics committee of Iran University of Medical Sciences and all subjects completed the consent form.

3. Biochemical measurements

Venous blood was collected between 9:00 and 11:00 a.m. for the assessment of plasma levels of adiponectin, CTRP3, CTRP9, apelin, TNF-α, and hs-CRP and centrifuged for 15 min at $1600 \times g$. Plasma was separated from the blood, aliquoted, and stored at $-80\,°C$ until assayed. The concentration of adipokines was measured in plasma with ELISA immunoenzymatic test (adiponetin- Biovendor Laboratory Medicine Inc., Modrice, Czech Republic, apelin- Abnova, Taiwan, CTRP3 and CTRP9- Cusabio, China). The intra and inter-assay coefficients of variation were: 5.9% and 7% for adiponectin, < 10% and 15% for apelin, and < 8% and 10% for CTRP3 and CTRP9.

Levels of TNF-α and hs-CRP in plasma samples were also measured by ELISA kits (IBL, Germany). The intra and inter-assay coefficients of variation for TNF-α and hs-CRP were 6.0%, 7.4%, 6.9% and 6.3%, respectively.

3.1. Statistical analysis

All data were analyzed with SPSS software version 16.0 (SPSS, Inc.

Table 1
Demographic, anthropometric and clinical characteristics of study population.

Characteristics	Participants		
	MS ($n = 26$)	Controls ($n = 24$)	P value
Age (years)	31.4 ± 6.5	34.83 ± 7.7	0.25
Height (cm)	1.6 ± 0.06	1.6 ± 0.05	0.63
Weight (kg)	62.96 ± 5.3	64.67 ± 5.1	0.25
BMI (kg/m^2)	24.06 ± 1.8	24.4 ± 1.3	0.25
Age of onset (Years)	30 ± 5	–	–
Disease duration (Years)	0.08 (0.5)	–	–
Number of relapses	1.52 ± 1	–	–
EDSS	1.28 ± 0.4	–	–

BMI: Body Mass Index; EDSS: Expanded Disability Status Scale. Values are expressed as mean ± SD or median (interquartile range).

Chicago, IL) and reported as the mean ± standard deviation (SD) or the median (interquartile range). The differences between the patients and the control groups analyzed by Mann-Whitney U test for non-parametric data and Student's t-test for parametric data. The Pearson's (parametric) and Spearman's (non-parametric) correlation tests were used to evaluate the correlations between biochemical parameters. Spearman correlation was used to evaluate the correlation between adipokine levels with clinical characteristics of MS patients. $P < .05$ was considered statistically significant.

4. Results

Demographic, anthropometric and clinical characteristics of the study population are presented in Table 1. The patients and control groups did not have a significant difference in age, height, weight, and body mass index. Plasma level of TNF-α as inflammatory mediators was significantly higher in MS patients compared to the control group ($p = .000$). Plasma level of apelin was significantly lower in MS patients compared with healthy subjects ($p = .000$) while adiponectin was significantly higher in MS patients compared to healthy subjects ($p = .01$). Plasma CTRP3, CTRP9 and hs-CRP levels were not significantly different between the two examined groups ($p > .05$) (Table 2). There was no significant correlation between the studied adipokines and inflammatory mediators.

Table 3 shows correlations of studied adipokines with clinical characteristics in MS patients. The plasma levels of apelin were significantly and positively correlated with EDSS scores ($p = .04$, $R = -0.4$) and number of relapses ($p = .02$, $R = -0.4$) in MS patients. There was a positive correlation between CTRP9 levels and disease duration ($p = .01$, $R = 0.5$). None of the other biochemical parameters showed a significant correlation with clinical characteristics.

Table 2
Plasma levels of adipokines and inflammatory mediators in study population.

Characteristics	Participants		
	MS (n = 26)	Controls (n = 24)	P value
CTRP-3 (ng/mL)	0.30 ± 0.04	0.32 ± 0.04	0.14
CTRP-9 (ng/mL)	0.81 (0.64–0.95)	0.77 (0.64–1)	0.8
Adiponectin (µg/mL)	32.97 ± 1.8	26.7 ± 1.4	0.01
Apelin (ng/mL)	107 (82.3–137.9)	172 (133.7–320.21)	0.000
TNF-α (pg/mL)	28.63 ± 3.7	10.27 ± 1.3	0.000
hs-CRP (µg/mL)	1.5 (1.1–2.3)	1.6 (0.57–2.2)	0.5

TNF-α: tumor necrosis factor-alpha; hs-CRP: high sensitivity C-reactive protein. Parameters with normal distribution are presented as mean ± standard deviation. Parameters without normal distribution are presented as median (interquartile range).

Table 3
Correlations of adipokines and inflammatory mediators with clinical characteristics in MS patients.

P values	CTRP3	CTRP9	adiponectin	Apelin	TNF-α	Hs-CRP
Age of onset	0.5	0.5	0.5	0.7	0.09	0.1
Disease duration	0.7	*0.01*	0.05	0.7	0.06	0.4
Number of relapses	0.8	0.13	0.7	*0.02*	0.3	0.8
EDSS	1	0.2	0.4	*0.04*	0.8	0.6
R values	CTRP3	CTRP9	adiponectin	Apelin	TNF-α	Hs-CRP
Age of onset	−0.13	−0.14	−0.12	−0.06	0.34	0.2
Disease duration	0.08	*0.5*	−0.3	−0.08	0.37	0.14
Number of relapses	0.05	0.29	−0.05	*−0.4*	−0.18	−0.04
EDSS	0.0	0.2	−0.17	*−0.4*	−0.03	−0.08

Coefficients (R) and p values are calculated by the Pearson and spearman correlation test. EDSS: expanded disability status scale; TNF-α: tumor necrosis factor-alpha; hs-CRP: high sensitivity C-reactive protein.
p-value < .05 was considered significant. Significant values were denoted with bold and italic characters.

5. Discussion

The result of this study showed that the levels of circulating apelin decrease in MS patients, which was accompanied by a significant increase in TNF-α and adiponectin concentration.

Several studies have investigated adiponectin levels in MS patients, with inconsistent results. Our observation consistent with Hietaharju et al. and Palavra et al., which demonstrated that elevated levels of adiponectin in serum and CSF of MS patients (Hietaharju et al., 2010; Palavra et al., 2013). Although some reports have revealed that the level of adiponectin are reduced in MS patients compared to normal subjects (Kraszula et al., 2019; Musabak et al., 2011). The reason for these contradictory results may be due to the fact that in some studies, patients received medication which might have affected serum adiponectin levels (Sukumaran et al., 2012). In our study, patients were newly diagnosed and/or did not receive any immunosuppressive or immunomodulatory medications. In this regard, studies have shown that adiponectin levels increase in other inflammatory/autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes (Bjornstad et al., 2017; Diaz-Rizo et al., 2017; Dikbas et al., 2016; Dini et al., 2017; Garcia and Sood, 2012; Tan et al., 2009; Toussirot et al., 2010).

Experimental studies have shown that adiponectin has anti-inflammatory properties and can suppress inflammation and also macrophage activity (Ouchi and Walsh, 2007; Zhang et al., 2017). Thus a high concentration of adiponectin in MS patients may be a mechanism for controlling the inflammatory or immunological processes that occur in this disease. In this regards, it has been shown that adiponectin plays a protective role against inflammatory and autoimmune diseases by inhibiting the differentiation of pathogenic Th17 cells (Zhang et al., 2017). On the other hand, the increase in adiponectin may be due to resistance to adiponectin induced by autoimmune disease (Parker et al., 2011).

Alternatively, some reports show that adiponectin has pro-inflammatory effects and increase in a number of autoimmune and inflammatory disease (Fantuzzi, 2008; Fantuzzi, 2013). It also reported that adiponectin activates dendritic cells, enhances the production of pro-inflammatory cytokines and induces Th1 and Th17 responses (Jung et al., 2012). Adiponectin has a direct pro-inflammatory effects in chondrocytes and its expression increase locally in the inflamed joints of rheumatoid arthritis patients (Choi et al., 2009; Conde et al., 2012; Frommer et al., 2010). So, it is possible that the increase of adiponectin, which may have pro-inflammatory properties, plays an important role in the pathogenesis of MS. Further research is required to investigate the exact molecular mechanism of adiponectin in inflammatory and autoimmune diseases.

CTRP3 and CTRP9 are also two newly-discovered adipokines from the CTRP family. Recent data indicate that CTRP3 is an anti-inflammatory adipokine that reduces inflammation through inhibition of Toll-like receptor (TLR) and nuclear factor κB (NF-κB) signaling pathways and also reduces the secretion of IL-6 and TNF-α in monocytes and adipocytes (Kopp et al., 2010; Weigert et al., 2005). CTRP9 also has anti-inflammatory and protective effects against oxidative (Cheng et al., 2016; Jung et al., 2016; Li et al., 2016) and ischemia–reperfusion damage (Bai et al., 2016; Kambara et al., 2012). The role of CTRP3 and CTRP9 in the pathogenesis of MS has not been studied. Our result showed that plasma CTRP3 and CTRP9 levels in MS patients were not significant differences with the control subjects. This finding suggests that CTRP3 and CTRP9 may not be associated with the pathogenesis of MS, although more studies are needed in this regard.

Apelin is another anti-inflammatory adipokine, which is expressed with its receptor APJ in neurons and oligodendrocytes of the central nervous system. Apelin significantly downregulates the expression of TNF-α, monocyte chemoattractant protein (MCP)-1, IL-6, and macrophage inflammatory protein (MIP)-1α in macrophage cell culture that lead less activation of extracellular matrix-digesting enzymes (Leeper et al., 2009). Moreover, apolin 13 protects against cerebral ischemia/reperfusion (I/R) injury through inhibition of inflammation (Duan et al., 2019). We found for the first time the plasma level of apelin decrease in MS patients. Serum levels of apelin have been shown to be lower in Alzheimer, rheumatoid arthritis and psoriasis patients (Capo et al., 2018; Di Franco et al., 2012; Eren et al., 2012). These findings indicate that apelin may be involved in the pathogenesis of inflammatory and autoimmune disease. Besides, the negative correlation between the levels of apelin with EDSS scores and the number of relapses in MS patients further implying that apelin may participate in the course and disability development.

6. Conclusions

In conclusion, the data of the present study showed that relapsing remitting MS was associated with higher adiponectin and lower apelin plasma levels, while there were no associations with CTRP9 and CTRP3. Our findings provide further evidence that adipokines may play a role in the immunopathogenesis of MS and can be considered in future studies because of their immunoregulatory actions.

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