ORIGINAL ARTICLE

Plasma chemerin levels in patients with multiple sclerosis

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Abstract

OBJECTIVES: Chemerin, a novel adipokine produced by adipose tissue and liver, is associated with markers of metabolic syndrome, and additionally, acting as chemoattractant for cells of immune system it may regulate immune cell properties.
MATERIAL AND METHODS: In order to evaluate plasma chemerin concentration in multiple sclerosis (MS) individuals we investigated 39 MS patients (among them 23 subjects were lean and 16 were overweight or obese) and 42 controls with tension headaches (29 of them were lean and 13 were overweight or obese). All patients had a brain MRI scan with gadolinium contrast as well as an assessment of the presence of oligoclonal bands in cerebrospinal fluid (CSF) and estimation of the CSF IgG index. The neurologic status was evaluated with use of the Expanded Disability Status Scale. Chemerin levels in plasma were measured using ELISA kit. Lipid profile, glucose and insulin levels, CRP and selected cytokine concentrations were also determined.
RESULTS: Plasma chemerin concentrations in overweight/obese MS subjects were higher when comparing to lean MS individuals and the controls, both from lean and overweight/obese subgroups. Significant difference was found between the results of overweight/obese MS and lean controls.
CONCLUSIONS: An increase of chemerin levels in patients with multiple sclerosis is associated with overweight and obesity.

INTRODUCTION

Chemerin is a newly discovered adipokine also known as tazarotene–induced gene 2 (TIG2) or retinoic acid receptor responder 2 (RARRES2). Pro-chemerin is an inactive form containing 163 amino acids, and is activated by inflammatory and coagulation serine proteases to active form containing 146 amino acids which is present in the circulation (Zabel *et al.* 2005). Chemerin is a natural ligand of orphan receptor ChemR23 (Wittamer *et al.* 2003).

Chemerin possesses leukocyte chemoattractant properties through its receptor ChemR23, chemokine–like receptor 1 ($CMKLR_1$). It has been demonstrated that ChemR23 is expressed

by immature myeloid and plasmacytoid dendritic cells, monocytes/ macrophages, and natural killer (NK) cells (Parolini *et al.* 2007). Moreover, chemerin is also able to induce endothelial angiogenesis (Kaur *et al.* 2010) in the mechanism of activation ERK1 and 2 of the MAPK pathway (Zabel *et al.* 2006; Bozaoglu *et al.* 2010). Previous studies revealed that chemerin binds with high affinity with two other receptors GPR1 (Barnea *et al.* 2008) and C-C chemokine receptor-like 2 (CCLR2) (Zabel *et al.* 2008).

The main expression of GPR1 was discovered in the liver, intestine, kidney and adipose tissue; while CCLR2 is expressed in the lung, endothelial cells and liver endothelium (Monnier *et al.* 2012). Graham and co-workers demonstrated that chemokine-like receptor-1 ($CMKLR_1$) may participate in the inflammatory mechanism of experimental autoimmune encephalomyelitis (EAE) which is an experimental model of human multiple sclerosis (Graham *et al.* 2009). Those authors suggested that chemerin promotes inflammatory responses during EAE.

Multiple sclerosis (MS) is regarded as a chronic neuroinflammatory disease of the central nervous system. Generally, autoimmune processes lead to demyelination and neurodegeneration (Rostami & Ciric 2013). To our knowledge, the role of chemerin in metabolic dysfunction and induction of inflammatory response in the course of multiple sclerosis in humans is not thoroughly investigated. Thus, we aimed in this study to evaluate chemerin concentrations in plasma of patients with multiple sclerosis.

MATERIAL AND METHODS

The material consisted of 39 individuals (28 women, 11 men) aged between 19 and 59 years (mean age 34.7±8.29) with newly diagnosed multiple sclerosis (MS) and control group (C) that comprised of 42 subjects (36 women, 6 men) aged between 18 and 51 years (mean age 32.29±8.09) with tension headaches in whom MS was excluded during the diagnostic procedure. The groups under the study were matched for age. Individuals with severe cardiac, hepatic and renal failure, and neoplastic disease were excluded from the study.

The diagnosis of MS was established according to the Diagnostic Criteria for Multiple Sclerosis (2010 Revisions to the "McDonald Criteria") (Polman *et al.* 2010).

All individuals had a brain MRI scan with gadolinium contrast as well as an assessment of cerebrospinal fluid to demonstrate the presence of oligoclonal bands and estimate the CSF IgG index. The neurologic status was evaluated with use of the Expanded Disability Status Scale (EDSS). After basic anthropometric measurements that included weight, height and calculation of body mass index (BMI = weight/height^2), all patients and the controls were assigned to the subgroups according to BMI. Based on the widely accepted normal weight definition those individuals with BMI <25 kg/m^2 were concerned as lean, and those with BMI ≥25 kg/m^2 were assigned to overweight/obese subgroup.

The blood samples were collected after 6 hours of fasting for adipokines and biochemical analyses. Tubes containing EDTA and aprotinine (protease inhibitor) were used for chemerin, cytokine and insulin assessment. The tubes were centrifuged at 4 °C and collected plasma samples were stored at –70 °C until assays were performed.

Chemerin levels were measured using a commercial ELISA kit (BioVendor, Heidelberg, Germany). The sensitivity of this assay was less than 0.1 ng/ml. Intra-assay and inter-assay precisions were 7% and 8.3%, respectively.

Insulin was determined using immunoradiometric assay (DIA Source Immunoassay SA Nivelles, Belgium). The detection limit was 1 μgIU/ml. Intra-assay and inter-assay coefficients of variation were 2% and 6%, respectively.

Plasma IL6 and IL10 concentrations were estimated by ELISA commercial kits (Endogen). The sensitivities for IL6 and IL 10 were <1 pg/ml, and <3 pg/ml, respectively

Serum lipid profiles and glucose and CRP (C-reactive protein) levels were determined using standard laboratory procedures. CRP <5 mg/l were concerned as within normal range.

Insulin resistance was estimated using homeostasis model assessment method (HOMA-IR). HOMA-IR= glucose mmol/l × Insulin μU/ml / 22.5.

The study was approved by the Ethical Commission of the Centre of Postgraduate Medical Education in Warsaw. Informed consent was obtained from all study participants.

Statistical analysis

Statistical analyses were performed using Statistica 10 (Stat Soft Inc., Tulsa, OK, USA). Data are presented as mean ± standard deviation of the mean (SD). The normality of distribution among the groups was investigated using the Shapiro-Wilk test and the Kolmogorow-Smirnoff test. Non parametric data were compared between the groups using the Mann-Whitney U test.

The significance of correlations between two variables was determined by the Spearman rank correlations coefficient.

All values of less than 0.05 were accepted as statistically significant.

RESULTS

Chemerin concentrations in plasma were significantly higher in overweight/obese individuals with MS comparing to lean controls ($p<0.05$). We also noticed a non-significant tendency to increase of chemerin level in overweight/obese patients in both in MS and control groups when compared to lean subjects with the MS and those of the controls, respectively. No marked rise

of chemerin was also observed in overweight/obese MS individuals in comparison to overweight/obese controls (Figure 1). All clinical and biochemical data are presented in Table 1.

Insulin levels were higher in overweight/obese groups as compared with lean subgroups of MS and the controls, respectively but the differences were not significant. Analysis of lipid profiles revealed that triglyceride levels in overweight/obese controls were significant higher comparing to lean persons of MS group and the controls ($p<0.05$; $p<0.001$ respectively). HDL concentrations in overweight/obese MS group were significantly decreased as compared with lean MS individuals and the controls ($p<0.001$; $p<0.001$ respectively).

We also noticed the following significant differences in IL 6 concentrations. IL6 levels in overweight/obese MS patients were markedly higher in comparison with those results of lean MS ($p<0.001$). Moreover, we observed in overweight/obese controls that IL6 levels were significantly increased when compared to levels of lean MS ($p<0.001$), lean controls ($p<0.05$) and overweight/obese MS subjects ($p<0.01$).

Furthermore, assessment of IL10 concentration in MS patients revealed lower values in overweight/obese subgroup as compared to lean MS ($p<0.05$).

CRP levels in overweight/obese controls were higher as compared to lean MS ($p<0.05$) and lean controls ($p<0.01$). However, they were still within normal range.

A number of significant correlations were identified in the study.

In the whole control group, the following significant positive correlations were observed between chemerin as a first parameter and BMI (r=0.37, $p<0.05$), CRP (r=0.40, $p<0.01$), insulin (r=0.60, $p<0.001$) and HOMA-IR (r=0.61, $p<0.001$).

However, in the whole group of MS individuals the significant correlation was found only between chemerin and total cholesterol (r=0.338, $p<0.05$).

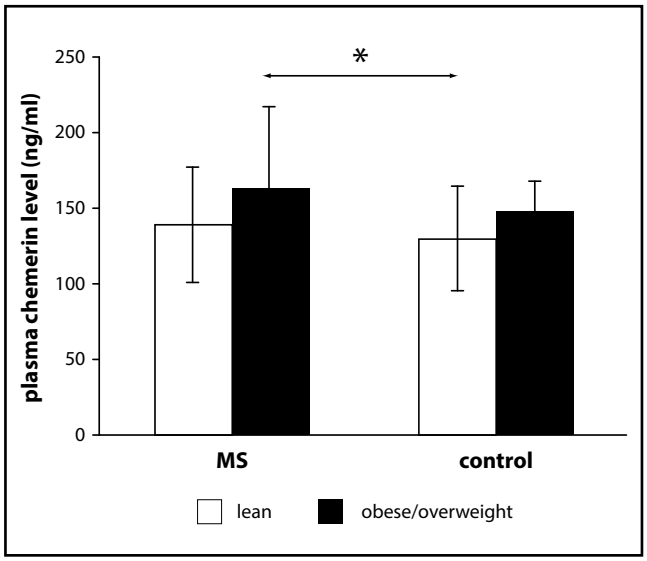

Fig. 1. Plasma chemerin concentrations in MS and control group. Results are mean ± SD. *$p<0.05$.

Tab. 1. Anthropometric and biochemical data of patients with multiple sclerosis and subjects of control group.

	Patients with MS (n=39)		Control group (n=42)	
	Lean (n=23)	Overweight/Obese (n=16)	Lean (n=29)	Overweight/Obese (n=13)
Men/women	3/20	8/8	4/25	2/11
Age (years)	32.05±6.90	37.53±8.90	30.79±7.98[a]	35.62±7.60
BMI (kg/m^2)	21.32±1.18[b,c]	28.71±4.32	22.09±2.06[b,c]	29.36±4.67
Glucose (mg/dl)	91.10±10.78	92.92±15.72	94.66±12.12	98.60±20.90
Insulin (uU/ml)	15.66±9	26.84±26.22	16.55±15.92	27.30±37.02
HOMA-IR	3.62±2.19	6.37±6.81	3.92±4.01	2.81±1.46
Cholesterol (mg/dl)	190.01±35.47	189.50±46.10	172.15±32.38	188.22±36.73
HDL (mg/dl)	70.99±18.15[d,e]	54.38±13.47	61.14±17.72	51.29±16.21
LDL (mg/dl)	104.63±30.96	119.06±38.30	95.64±25.14	108±32.12
TG (mg/dl)	95.43±55.34[f]	106.24±47.46	81.14±37.65[e]	136.97±64.85
CRP (mg/l)	1.13±1.22[f]	1.31±0.97	0.95±0.91[e]	2.07±1.59
IL-6 (pg/ml)	1.25±0.73[c,d]	2.07±0.87[f]	1.56±0.82[e]	2.63±0.97
IL-10 (pg/ml)	4.32±3.29[a]	1.76±1.34	2.24±1.56	2.34±1.27

[a] $p<0.05$, as compared to overweight/obese MS patients; [b] $p<0.001$, as compared to overweight/obese MS patients; [c] $p<0.001$, as compared to control group of overweight/obese individuals; [d] $p<0.01$, as compared to overweight/obese MS patients; [e] $p<0.01$, as compared to overweight/obese individuals of control group; [f] $p<0.05$, as compared to overweight/obese individuals of control group; Values expressed as mean ± SD.

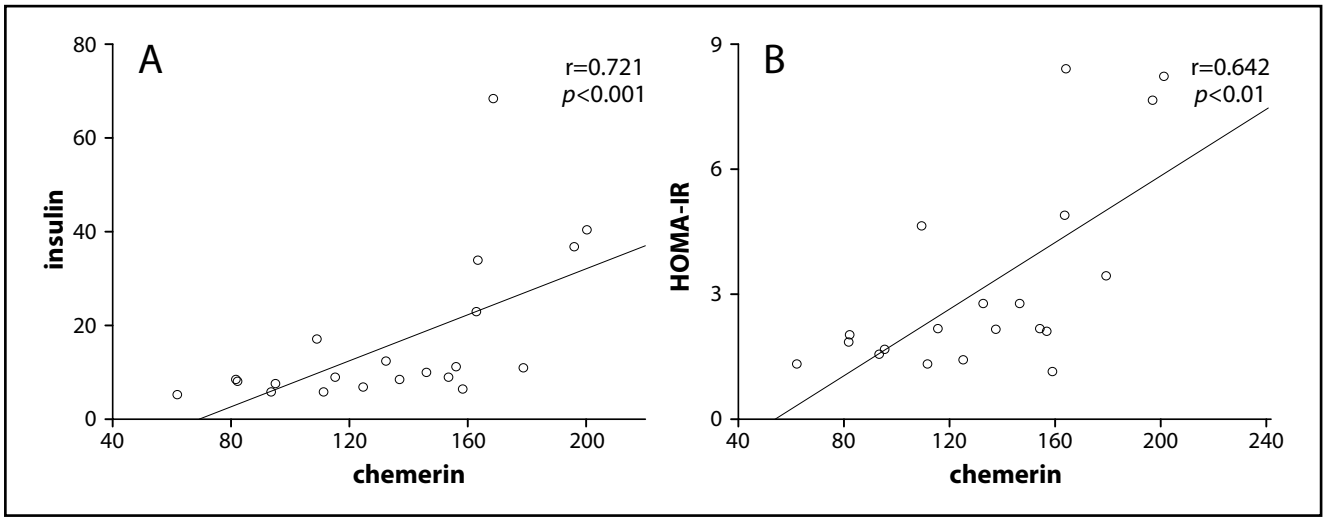

Fig. 2. Correlation between plasma chemerin concentrations and insulin (A), HOMA-IR (B) in lean patients of control group.

After dividing both investigated groups, MS and the controls, into two subpopulations based on BMI basis to lean and overweight/obese subgroups, significant positive correlation was seen between chemerin and insulin, and HOMA-IR (r=0.721, $p<0.001$, r=0.642, $p<0.01$ respectively) in lean controls (Figure 2).

We observed a significant positive correlation between chemerin and HDL in overweight/ obese MS group (r=0.505, $p<0.05$) (Figure 3).

DISCUSSION

It has been commonly accepted that obesity is associated with inflammation. On the other hand, adipokines may modulate immune functions (de Heredia *et al.* 2012). Adipose tissue is able to produce many cytokines and adipokines. Amongst them there is leptin which promotes Th_1 responses and leads to a reduction of regulatory T-cell activity (Matarese *et al.* 2008). Moreover, an increase of the release of proinflammatory cytokines which promote Th_1 response and decrease the number of regulatory T cells may result in activation of CD4+cells that target central nervous system (CNS) auto-antigens (Hedström *et al.* 2014). Hedström and co-workers reported a presence of interaction between human leukocyte antigen (HLA) geno type and body mass index (BMI). They suggested that inflammatory and immunologic mechanisms in obesity may potentially explain the association between adolescent obesity and increase risk of multiple sclerosis (Hedström *et al.* 2014).

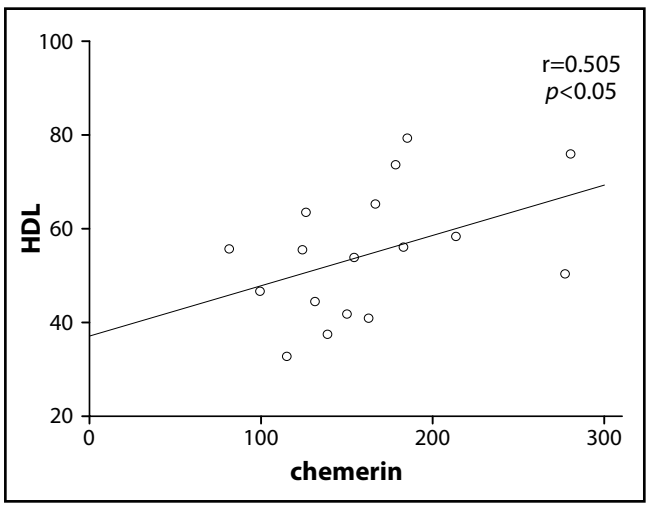

Fig. 3. Correlation between plasma chemerin concentrations and HDL in overweight/obese patients with MS.

An increase of HLA class II genes has been found in macrophages of adipose tissue (Lumeng *et al.* 2007). Indeed, a number of macrophages in adipose tissue correlated with adiposity (Weisberg *et al.* 2003). The existence of interaction between obesity and HLA genotype may support the hypothesis that obesity increases the risk of developing MS.

Furthermore, in obesity, an imbalance in anti-inflammatory M_2 polarization to a proinflammatory M_1 polarization was demonstrated (Lumeng *et al.* 2007). It should be highlighted that imbalance of M_2/M_1 promotes relapsing EAE (experimental autoimmune encephalomyelitis) that serves as a model of MS (Mikita *et al.* 2011).

Besides, an association of obesity with several inflammatory diseases such as autoimmune thyroiditis, diabetes, psoriasis and multiple sclerosis has been reported (Onkamo *et al.* 1999; Warren *et al.* 2008). A relationship between obesity in early life and increased MS risk has been also suggested (Munger *et al.* 2009; Hedström *et al.* 2012; Langer-Gould *et al.* 2013).

Chemerin is a newly discovered adipokine that possesses not only metabolic but also immunological properties. Interestingly, chemerin except its metabolic properties is a chemoattractant for immune cells such

as macrophages and thereby may regulate immune cells function (Bozaoglu *et al.* 2007; Ernst & Sinal 2010). It has been known that chemerin secretion is augmented by chronic inflammation and adipocyte hypertrophy (Sell *et al.* 2009; Kralisch *et al.* 2009; Bauer *et al.* 2011). Proinflammatory cytokines may also regulate vascular expression of chemerin receptor, CMKLR1 as it has been reported by Mattu and colleagues (Mattu *et al.* 2013).

In this paper we demonstrated for the first time that plasma chemerin levels are elevated in overweight/obese patients with multiple sclerosis. Previously published data indicated that chemerin was associated with obesity, diabetes mellitus, insulin resistance, hypertension and fatty liver disease (Bozaoglu *et al.* 2007; Bozaoglu *et al.* 2009; Sell *et al.* 2009; Ernst & Sinal 2010; Yamawaki *et al.* 2012; Chu *et al.* 2012; Bremer & Jialal 2013). Besides, the results concerning an association between chemerin and metabolic and inflammatory markers remain controversial. Some authors showed that chemerin correlated with selected markers of metabolic status including BMI, WHR (waist to hip ratio), systolic blood pressure and serum triglycerides, as well as with inflammatory markers (Weigert *et al.* 2010). However, Bauer and coworkers (2012) observed that chemerin levels was higher in obesity and positively correlated with cholesterol but did not correlate with markers of insulin sensitivity.

It is widely accepted that obesity is connected with metabolic syndrome. Moreover, it has been known that dysfunction of adipose tissue observed in metabolic syndrome leads to insulin resistance and low-grade inflammation (Bremer & Jailal 2013). Several studies have supported the relationship between metabolic syndrome and inflammation (Hotamisligil 2006; Monteiro & Azevedo 2010). It has been shown that chemerin is associated with inflammatory markers in metabolic syndrome in patients with obesity, diabetes and hypertension (Roman *et al.* 2012; Gu *et al.* 2013). Some authors observed that chemerin correlates positively with indicators of inflammation such as TNF-alpha, interleukin 6 and C-reactive protein (Weigert *et al.* 2010; Jialal *et al.* 2013). In contrast to those findings, in our study we did not observe significant correlations between chemerin and insulin resistance (HOMA-IR) as well as with proinflammatory and anti-inflammatory markers and cytokines (CRP, IL6 and IL10) in the group of patients with multiple sclerosis. A significant correlation was only found between chemerin and HDL in overweight/obese MS group.

Finally, our results indicate that chemerin is altered in multiple sclerosis individuals being overweight or obese. To find a significance and exact mechanism of this finding, further intensive research is needed.

CONCLUSION

An increase of chemerin levels in patients with multiple sclerosis is associated with overweight and obesity.

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