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Egypt J Neurol Psychiatry Neurosurg (2021) 57:114
https://doi.org/10.1186/s41983-021-00369-2

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

RESEARCH Open Access

Serum levels of leptin and adiponectin in patients with multiple sclerosis

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Abstract

Background: The role of adipokines such as leptin and adiponectin in regulating the immunity has been documented, however data concerning their consequence on multiple sclerosis (MS) Egyptian patients are deficient. The aim of this study is to demonstrate the serum levels of leptin and adiponectin in MS patients and to assess their association with disease disability and severity. A case–control study including 60 subjects (30 MS patients and 30 age, sex and body mass index-matched healthy controls) was performed.

Results: Serum leptin level was significantly higher among MS patients than controls ($P<0.001$) while adiponectin was not significantly elevated in MS patients ($P=0.24$). There was a significant positive correlation between leptin levels with MS disability (Expanded Disability Status Scale) ($r=0.678$; $P<0.001$), severity (Multiple Sclerosis Severity Score) ($r=0.631$; $P<0.001$) and progression (progression index) ($r=0.461$; $P=0.01$). There was no statistically significant correlation between adiponectin with disease disability, severity or progression.

Conclusions: MS patients had significantly higher serum leptin levels and insignificant adiponectin levels compared to controls. Leptin has a potential role in multiple sclerosis disability and severity. However, adiponectin is not useful as a biomarker of MS disease, disability and severity.

Keywords: Multiple Sclerosis, Leptin, Adiponectin, Disability, EDSS, MSSS

Background

The role of adipokines in regulating the immunity has been documented, however data concerning their consequence on multiple sclerosis (MS) are deficient. A few recent studies demonstrated that adipose tissue as producer of adipocytokines including leptin and adiponectin may play an important role in MS pathogenesis [1–3]. While leptin has pro-inflammatory activity, adiponectin has been consistently shown to be an important anti-inflammatory factor [4, 5].

Leptin plays a role in the regulation of innate and adaptive immunity as well as inflammatory responses. In innate immunity, it activates proliferation of monocytes, enhances phagocytosis activity of macrophages and production of pro-inflammatory cytokines, IL-6, IL-12. In acquired immunity, leptin stimulates proliferation of naïve T cells and promotes memory T cells differentiation and production of Th1 and tumor-necrosis factor (TNF). Leptin release supports the differentiation of pro-inflammatory T helper1 (Th1) cells, producing pro-inflammatory cytokines such as interferon (INF)-γ and IL-2. Leptin also suppresses the production of Th2 cytokines, IL-4 and IL-10 and thus modulates immune response towards a pro-inflammatory profile [6].

Adiponectin has been consistently shown to be an important anti-inflammatory factor [4, 5, 7]. It inhibits the activation and proliferation of T and B lymphocytes and phagocytic activity of macrophages, as well as synthesis of pro-inflammatory cytokines as (IL-17, INF-γ) and induces production of anti-inflammatory cytokines such as IL-10 and IL-1 [7, 8].

Biomarkers that can predict disability progression, monitor disease activity, and assess treatment response

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are integral in assessment regarding MS treatment [9]. Only a few biomarkers are available in MS clinical practice. The aim of our study is to demonstrate the levels of leptin and adiponectin in MS patients and to assess their association with disease disability and severity.

Methods

The case–control study included a total of 60 subjects; 30 MS patients and 30 age, sex and body mass index-matched healthy volunteers as controls. MS patients with clinically definite multiple sclerosis were recruited from the department and outpatients MS clinic of Neurology Department from February 2018 to July 2019. The research protocol was approved by the Ethical Committee (ZU-IRB# 4164/22-11-2017). Written informed consent was obtained from all patients or written assent from a relative.

We included MS patients fulfilling the 2017 MacDonald's criteria [10]. All types of MS were included and patients were taken during relapse and in remission. Exclusion criteria were as follows: age less than 18 years, patients receiving steroids in the past 30 days, suspected evidence for inflammatory or degenerative disorders of the central and peripheral nervous system, clinically isolated syndrome (CIS) patients, history of cardiovascular disease, hypertension, diabetes mellitus type I and II patients and current smoking, hepatic or renal patients, malignancy and acute or chronic infection, history of antipsychotics, carbamazepine, valproate and Vitamin D supplement or Omega 3 fatty acids intake, as they may affect serum leptin and adiponectin levels.

Thirty age, sex and body mass index (BMI)-matched healthy volunteers as controls were recruited from other clinics of the hospitals. Control group was subjected to same exclusion criteria.

The demographic and clinical characteristics as well as the BMIs for all participants were recorded. Every patient underwent extensive detailed medical and neurological history taking including MS disease onset and disease duration. Calculation of annual relapse rate (ARR) was done using the formula: ARR = number of relapse/duration of disease. Disability evaluation was performed according to Expanded Disability Status Scale (EDSS) [11]. Severity was assessed using Multiple Sclerosis Severity Score (MSSS), which is an algorithm that relates EDSS scores to distribution of disability in patients with comparable disease duration [12]. Disease progression was assessed by progression index (PI). The PI was defined as the current EDSS score divided by disease duration expressed in years [12].

Laboratory investigations

Complete blood count (CBC), liver function tests (LFT), kidney function tests (KFT), random blood glucose (RBG) and lipid profiles including total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

Measurement of serum leptin and adiponectin concentrations was done using enzyme linked immune-sorbent assay (ELISA) technique kit (INOVA, No. 18 Keyuan Road, DaXing Industry Zone, Beijing, China). Venous blood samples of patients were obtained before administration of steroids. After collection of blood sample from all subjects, it was allowed to clot at room temperature for 20 min then blood containing tubes were centrifuged for 15 min at 2000–3000 rpm. Serum was separated from the blood, aliquoted, and stored at -20∘C until use.

Radiological investigations

Magnetic resonance imaging (MRI) of brain and/or spinal cord was done at the time of recruitment to all patients. A standardized protocol of MRI comprising T2-weighted, fluid-attenuated inversion recovery (FLAIR), pregadolinium and postgadolinium (Gd) enhancing T1 images were obtained using 1.5 Tesla superconducting MR imager (Achieva, Philips Medical System).

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. Quantitative variables were expressed as mean ± standard deviation (SD), whereas qualitative variables were expressed as frequencies and percentages. The following tests were used to test differences for significance. Difference and association of qualitative variable by Chi-square test (χ^2) or Fisher exact test as deemed appropriate. Differences between quantitative independent groups were done using Student's t test, and multiple by ANOVA or Kruskal–Wallis. Pearson's correlation was performed to examine the association between leptin and adiponectin with continuous independent variables. P value was set at ≤ 0.05 for significant results.

Results

Sixty subjects, 30 patients (21 female and 9 male) and 30 controls (20 female and 10 male) were included in this study. Their mean age (± SD) was 31.03 ± 6.31 for MS patients and 31.4 ± 7.5 for controls. There were 24 patients (80%) diagnosed as RRMS, 3 patients (10%) had a diagnosis of SPMS and 3 patients (10%) were PPMS. With regard to the type of treatment, 12 (40%) patients

were treatment naïve, 15 patients (50%) received interferon beta 1a, two patients (6.7%) received fingolimod and only one (3.3%) patient received cyclophosphamide.

Data showed that there was no statistical significant difference between MS patients and controls with regard to age, sex, and BMI. Demographic data and clinical characteristic of MS patients and controls are summarized in Table 1 including age, sex, type of MS, age of onset, disease duration, disease activity, disability, severity and progression index of MS. There was statistically significant difference with regard to leptin level between MS patients and controls. However, there was no significant difference in serum adiponectin levels between MS patients and controls (Table 1).

With regard to different types of MS, serum leptin levels were significantly higher in SPMS than other types. However, there was no significant difference in serum adiponectin levels among different types of MS (Table 2).

Higher serum leptin and adiponectin levels were observed in females MS patients but without statistical significance. There was no statistically significant difference in serum levels of leptin and adiponectin between patients in remission and in relapse. Moreover, there was no significant difference with regard to either low or high ARR or treatment for leptin and adiponectin levels (Table 3).

Table 2 Serum leptin and adiponectin levels in different types of MS

MS type	Leptin (pg/ml) Mean ± SD	Adiponectin (ng/ml) Mean ± SD
RRMS	11,135.08 ± 6453.45	4335 ± 1411
SPMS	30,257.69 ± 14,434.56 *	4862 ± 765
PPMS	30,301.28 ± 12,708.60	4063 ± 187
F	13.99	0.29
P	< 0.001*	0.74

RRMS relapsing remitting MS, *SPMS* secondary progressive MS, *PPMS* primary progressive MS, *SD* standard deviation, *F* analysis of variance (ANOVA), *Significant

There was statistically significant positive correlation with regard to serum leptin levels with MS disability (EDSS), severity (MSSS) and progression (PI). Moreover, a significant positive correlation was found between serum leptin and cholesterol, LDL as well as TGL. There was a significant negative correlation between serum leptin levels with disease onset and HDL (Table 4).

With regard to adiponectin, there was no significant correlation between adiponectin with disease onset, disease disability (EDSS), severity (MSSS) and progression (PI). However, there was significant positive correlation

Table 1 Demographic and clinical data of the MS patients and controls

	MS patients (*N* = 30)	Controls (*N* = 30)	Test of significance	*P*
Age (years): Mean ± SD	31.03 ± 6.31	31.4 ± 7.5	0.36	0.71
Gender: N (%)			0.08	0.78
Male	9 (30%)	10 (33.3%)		
Female	21 (70%)	20 (66.7%)		
BMI (kg/m^2) Mean ± SD	28.4 ± 7.2	26.7 ± 6.5	0.95	0.5
Serum leptin (pg/ml) Mean ± SD	14,963.96 ± 10,917.97	6389.61 ± 3473.51	20.7	< 0.001*
Serum adiponectin (ng/ml) Mean ± SD	4352 ± 1275	3995 ± 1088	1.17	0.24
MS types: N (%)				
RRMS	24 (80.0%)	NA		
SPMS	3 (10%)			
PPMS	3 (10%)			
Patients in relapse N (%)	12 (40%)	NA		
Onset of disease (years): Mean ± SD	27 ± 7.6	NA		
Duration of disease (years) Mean ± SD	3.7 ± 3.5	NA		
Total relapse number Mean ± SD	3.23 ± 1.63	NA		
ARR: Mean ± SD	1.08 ± 0.89	NA		
EDSS: Mean ± SD	2.17 ± 1.87	NA		
MSSS: Mean ± SD	3.84 ± 2.6	NA		
PI: mean ± SD	0.83 ± 0.9	NA		

MS multiple sclerosis, *RRMS* relapsing remitting MS, *SPMS* secondary progressive MS, *PPMS* primary progressive MS, *SD* standard deviation, *EDSS* Expanded Disability Score, *MSSS* Multiple Sclerosis Severity Score, *PI* progression index, *NA* not applicable, *Significant

Table 3 Difference between serum leptin and adiponectin levels with regard to parameters

Parameters	Leptin (pg/ml)			Adiponectin (ng/ml)		
	Mean ± SD	*t*- test	*P*	Mean ± SD	*t*- test	*P*
Gender						
Male	12,558.4 ± 9061.6	0.193	0.064	4324.8 ± 1224.3	0.437	0.669
Female	20,576.89 ± 13,273.8			4560.25 ± 1404.8		
Remission	15,977.6 ± 12,234.2	0.463	0.648	4264.2 ± 954.9	0.542	0.592
Relapse	14,077 ± 9946.9			4510.36 ± 1501.3		
ARR						
> 1	16,417.64 ± 11,689	1.015	0.32	4517.7 ± 1290.43	0.699	0.492
< 1	12,453.1 ± 9423.2			4184.3 ± 1239.6		
Treatment						
No	18,140.7 ± 13,017.6	0.201	0.051	4083.5.5 ± 1218.1	0.83	0.415
Yes	10,198.8 ± 3329.75			4463.35 ± 1171.65		

ARR annual relapse rate

Table 4 Correlation between serum leptin levels and adiponectin with parameters

Parameter	Leptin (pg/ml)		Adiponectin (ng/ml)	
	r	*P*	*r*	*P*
MSSS	0.631	< 0.001*	0.09	> 0.05
EDSS	0.678	< 0.001*	0.03	> 0.05
PI	0.461	< 0.01*	0.22	> 0.05
Disease duration (years)	0.113	0.552	− 0.16	> 0.05
Disease onset (years)	− 0.53	< 0.001*	0.03	> 0.05
ARR	0.15	0.428	0.198	< 0.05
BMI (kg/m^2)	0.206	0.275	0.13	> 0.05
Systolic BL. Pr	0.315	0.09	0.23	> 0.05
Blood glucose	0.1	0.957	0.36	< 0.001*
Cholesterol (mg/dl)	0.394	0.031*	0.06	> 0.05
TGL (mg/dl)	0.4	0.028*	0.07	> 0.05
LDL (mg/dl)	0.425	0.019*	0.029	> 0.05
HDL (mg/dl)	− 0.395	0.031*	− 0.05	> 0.05

EDSS Expanded Disability Score, *MSSS* Multiple Sclerosis Severity Score, *PI* progression index, *r* correlation coefficient, *BMI* body mass index, *TGL* triglycerides, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *ARR* annual relapse rate, *Significant

between adiponectin levels and blood glucose level (Table 4).

Discussion

Our study demonstrated that MS patients had statistically significant increase of serum leptin levels compared to control. These finding was supported by the results of a meta-analysis including nine studies from different countries and regions [13]. The incorporated analysis showed that patients with MS had significantly higher levels of leptin when compared with healthy controls indicating that increased leptin levels may be a factor related to MS. Hietaharju et al. [14] investigated the levels of leptin in the serum and CSF of twins being discordant for MS. They found no difference in the levels of serum leptin between twins with MS and their healthy co-twins. However, higher concentrations of adipocytokines were observed in the CSF of twins with MS, suggesting an in situ synthesis of leptin within the central nervous system and/or an increased transport of leptin through blood–brain barrier subsequent to high systemic levels.

In this study, there was no statistically significant difference between serum adiponectin levels in patients and controls. Previous results of adiponectin were conflicting as some studies reported enhanced levels of serum adiponectin in MS patients [14, 15], other studies observed low levels of adiponectin in MS [2, 16]. Unaltered level of adiponectin has also been reported in MS [17]. Previous studies suggested that adiponectin might potentially serve as a biomarker in both the pathogenesis and progression of MS [18, 19]. This discrepancy is probably due to the small number of patients or the recruitment of patients on steroids management [2] and disease-modifying therapies (DMTs) [16].

Although there was a high level of serum leptin and adiponectin in females, this was not significant in our study. Our result is in agreement with Eftekhari et al. [20] who found that leptin in females was insignificantly higher than in males. Other studies found that leptin was significantly higher in females [21–23]. The gender dimorphism in leptin levels (higher in females) is well established in normal subjects and has also been previously observed in MS patients [24, 25].

In this study, a significant elevation in serum leptin levels was found in SPMS compared to other types of MS. This is in agreement with the result of Messina et al. [26], they reported that the difference between SPMS and healthy controls remained statistically significant even after controlling for BMI, but the difference between RRMS and controls was no longer statistically significant. A possible explanation could be due to a correlation between leptin levels and adipose tissue mass at the beginning of disease, but with disease progression and age the increased levels of leptin are no longer dependent on adipose tissue and may be produced by other cells including monocytes [27].

With regard to adiponectin, in agreement with Signoriello et al. [19] we found no significant difference in serum adiponectin levels in different types of MS. Natarajan et al. [5] conducted a 2 year prospective follow-up study and assessed different types of adipokines including leptin and adiponectin in different types of MS and estimated no significant difference in leptin and adiponectin levels in different MS types. However, other studies observed lower adiponectin in RRMS [2] and benign MS patients [18].

In agreement with Wu et al. [28] and Wannamethee et al. [29], we found that serum leptin levels were inversely correlated with HDL. In contrast, other studies reported no correlation between serum leptin levels and HDL [30, 31]. This significant correlation could underline the role of disturbed lipid profile in immune dysfunction or it could be a result of myelin damage. Further studies with larger number of patients are needed to establish this association.

With regard to disease onset, we found strong negative correlation between serum leptin levels and disease onset. This is in agreement with Biström et al. [32]; they stated that high leptin concentration was associated with elevated MS risk among patients younger than 20 years. No significant correlation was found between serum leptin levels and disease duration in this study and this is in agreement with the results of previous studies [25, 33, 34].

In the present study, serum levels of leptin and adiponectin were insignificantly different among patients in remission or relapses. Although data about this point are limited, Kvistad et al. [35] reported no difference between MS patients with and without relapses in baseline serum leptin and adiponectin. However, previous studies observed that serum leptin levels increased several weeks before relapse and declined in the clinically active phase of the disease [33] or reported higher levels during remission [21, 34]. Moreover, our results revealed no significant correlation between serum leptin and adiponectin levels with ARR, and this is in agreement with other studies observed no significant correlation between baseline leptin levels and ARR [35, 36].

With regard to disability, in agreement with Lanzillo et al. [36] this study demonstrated a statistically significant correlation between serum leptin levels and disease disability (EDSS). Natarajan et al. [5] found a positive correlation between the baseline level of leptin and EDSS scores and such associations were also observed after adjusting for combination of age, gender, and disease subtype. In contrast, other studies didn't find correlation between leptin levels and EDSS score [22, 25, 33, 35]. This discrepancy in results may be due to different inclusion criteria of different MS type, study design and laboratory measurements.

In concordance with Kvistad et al. [35], we found no correlation between serum adiponectin levels and EDSS score at baseline. Also, they found that there was no difference in serum levels between patients with EDSS progression and those without progression throughout the study [35]. Other studies were in agreement with our findings and reported no correlation between EDSS score and serum adiponectin [5, 19, 22, 25, 33, 34]. However, another study reported a significant positive correlation between serum adiponectin levels and EDSS [18].

With regard to MSSS, very few studies investigated the correlation between serum leptin levels and MSSS in multiple sclerosis patients which was statistically significant in our results. Kolić et al. [23] found no significant correlation between MSSS and plasma leptin levels but found significant correlation between LepR mRNA gene expression and MSSS. This contrast between our results may be due to different inclusion criteria as their patients were all under treatment while many of our patients were treatment naïve, also may be due to different blood sample types (serum/plasma). Regarding serum adiponectin levels, we found no significant correlation between adiponectin and MSSS or PI unlike Signoriello et al. [19] who reported that higher levels of adiponectin at baseline was significantly correlated with worse prognosis.

This work could not reveal a correlation between either serum leptin or adiponectin and treatment. This is in agreement with Kvistad et al. [35] who stated that neither of the adipokines is useful as biomarkers for treatment-response. They did however find a difference in serum levels of the adipokines before and during IFNB treatment, reflecting the anti-inflammatory effect of the drug. In their study, levels of leptin were decreased and the levels of adiponectin were elevated during treatment in comparison to the treatment-naïve period, indicating a more favorable inflammatory profile during treatment. Moreover, alteration in serum levels of adipokines was not associated with MS activity during treatment indicating that adipokines are not

beneficial biomarkers for treatment efficacy [37]. Limitations of our study include being conducted at a single-center with a small sample size.

Conclusions

Serum leptin level was significantly elevated in MS patients compared to controls. In addition, leptin levels were positively correlated with disease disability, severity and progression. This indicates that leptin has a role in multiple sclerosis disability and severity. However, there was no statistically significant difference between serum levels of adiponectin in patients and controls. As well as, serum adiponectin levels did not have a correlation with disease disability, severity, activity. Further studies with longitudinal large cohort of MS patients are needed to validate the results of this study and to assess the long-term prognosis in patients with elevated serum leptin levels. It would be beneficial to assess the effect of lowering leptin levels on disease course.

Abbreviations

MS: Multiple sclerosis; EDSS: Expanded Disability Status Scale; MSSS: Multiple Sclerosis Severity Score; PI: Progression index; IRB: Institutional Review Board; CIS: Clinically isolated syndrome; BMI: Body mass index; ARR: Annual relapse rate; CBC: Complete blood count; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; HDL: High-density lipoprotein; ELISA: Enzyme-linked immune-sorbent assay; MRI: Magnetic resonance imaging; SD: Standard deviation; ANOVA: Analysis of variance; RRMS: Relapsing remitting MS; SPMS: Secondary progressive MS; PPMS: Primary progressive MS; DMTs: Disease-modifying therapies.

Acknowledgements

Not applicable.

Authors' contributions

All authors were involved in crafting the study topic and design. RMF analyzed and interpreted the data, wrote, submitted, and prepared the final manuscript revision. DAE supervised clinical/laboratory work, interpreted results, and participated in manuscript drafting. NTS recruited the patients, carried out clinical/laboratory investigation, collected data and participated in manuscript drafting. AEK supervised clinical/laboratory work, interpreted results, and participated in manuscript drafting. All authors read and approved the final manuscript.

Funding

This study received no funding.

Availability of data and materials

The data results generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of the faculty of Medicine, Zagazig University. The reference number is 4164/22-11-2017. The purpose of the study was explained, and an informed written consent was taken before taking any data or doing any investigations. The participants were informed that their participation was voluntary and that they could withdraw from the study at any time without consequences.

Consent for publication

Is not applicable in this section.

Competing interests

The authors declare that they have no competing interests.

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Received: 27 April 2021 Accepted: 6 August 2021
Published online: 28 August 2021

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