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ORIGINAL ARRTICLE

Impact of Obesity on Disease Modifying Therapies (DMTS) Response and IL-17 mRNA in Patients with Multiple Sclerosis in Relation to Its Phenotypic Features

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ABSTRACT

Background: Obesity induces neuroinflammatory effects on the central nervous system (CNS) through dysregulation of energy metabolism, inflammation, and immune responses. Obesity is associated with poor clinical response of multiple sclerosis (MS) to immune mediator drugs. We aimed to assess IL-17 serum and mRNA levels in MS patients and to explore the association of obesity with DMT response and IL-17 serum and mRNA levels in patients with MS.

Methods: we examined 40 patients with MS, the diagnosis was according to the latest 2017 McDoland criteria, and 40 subjects as a control group. IL-17 mRNA and serum levels of IL-17 were determined by ELISA.

Results: 40 patients with MS were included, of whom 15 (37.5%) were obese, and 25(62.5%) patients were lean. IL-17 mRNA level was significantly higher in the obese MS group (3.4±1.24) compared to the lean MS group (2.5±1.11) and control group (0.9±0.09), P <0 .001. Also, IL-17 level was significantly high in the obese group (46.75±12.2) compared to the lean group (36.23±9.2) and the control group (23.1±5.7), P <0 .001. MS patients treated with fingolimod had statistically significant lower levels of IL-17 mRNA and serum IL-17 compared to patients treated with Interferon beta-1a and b. These markers were associated with BMI, number of relapses in the last 2 years, Expanded Disability Status Scale (EDSS), ESR, and hs-CRP.

Conclusions: IL-17 serum and mRNA levels were upregulated in MS patients, particularly obese patients. MS patients treated with fingolimod had statistically significant lower levels of IL-17 mRNA and serum IL-17 compared to other patients.

Keywords: Multiple sclerosis; Disease-modifying therapies; Fingolimod; Interleukin-17; disease-modifying therapies

INTRODUCTION

Multiple sclerosis (MS) is a neuroinflammatory disease, characterized by demyelination and neurodegeneration [1]. The severity and phenotypic features of MS could contribute to different factors [2]. Some authors have linked obesity with autoimmune disease as adipose tissue secretes pro-inflammatory factors that could contribute to autoimmunity [3]. Previous reports have demonstrated that obesity induces inflammatory effects on the CNS through the initiation of neuro-inflammatory effects, mediated by induction of the NF-κB pathway, impaired insulin signaling, mitochondrial dysfunction, excess of reactive

oxygen species, and dyslipidemia [4], this leads to significant dysregulation of energy metabolism, inflammation, and immune responses [5].

It has been established that Th17 cells share in CNS autoimmunity in particular MS pathogenesis. Th1 cells secrete IFN-γ, TNF-β and interleukin-17 (IL-17), [6]. Based on the previous hypothesis, MS development is susceptible to adipokines released from adipose tissue. Interestingly, serum IL-17 is upregulated in obesity [7]. Additionally, some authors detected lower production of the Th17 cells producing IL-17 which participates in the pathogenesis of MS [8].

Accumulating evidence demonstrates that treatment of MS is changeable due to many factors such as the complexity of MS pathogenesis, adverse effects, and efficacy of disease-modifying therapies (DMTs) There are more than 13 drugs approved for the treatment of MS; one of the most common oral therapies for MS is fingolimod which is used in the relapsing phenotype of MS [9]..

Given the crucial role of obesity as a chronic low-grade inflammation in MS development and progression. Emerging evidence revealed that obesity is associated with poor clinical response to DMT, and this could be due to variations in pharmacokinetics among obese patients [11]. Till now the study that investigated the influence of obesity on the clinical response of MS patients is scarce worldwide. To the best of our knowledge, this is the first Egyptian to evaluate the influence of obesity on DMT response and IL-17 serum and mRNA levels in patients with MS about its phenotypic features.

METHODS

We conducted 40 healthy controls and 40 patients with MS. Among patients with MS [12], 15 patients were obese, and 25 patients were lean. the calculation of disease severity by the Expanded Disability Status Scale (EDSS) at the initial assessment visit [13]. The flowchart of the study is described in Figure 1. Routine diagnostic analyses were carried out according to Zagazig University Hospital.

Routine diagnostic analyses were carried out according to Zagazig University Hospital. Written informed consent was obtained from all participants and the study was approved by the research ethical committee of the Faculty of Medicine, Zagazig University. (Ethics number. 10898), this study has been carried out by the Code of Ethics of the World Medical Association (Declaration of Helsinki) for students involving humans.

Total RNA was separated from the PBMCs with TRIzol reagent (Invitrogen, California, USA) matching with the manufacturer's instructions. The primer sequences are shown in. β-Actin was used as a reference gene to quantitatively analyze the genes of interest in the study. The primers were as follows.

Gene	Forward primer (5'- -3')	Reverse primer (5'- -3')
IL-17A	5'-AACCTGAACATCCATAACCGG-3'	5'-ACTTTGCCTCCCAGATCAC-3'
GAPDH	5'-AGCCACATCGCTCAGACACC-3'	5'-GCGCCCAATACGACCAAATCC-3'

Statistical analysis:

Statistical analysis was executed with SPSS software (version 22.0; IBM Corp.). Categorical variables were described by counts and percentages, and continuous and ordinal variables by mean and standard deviation. We used the following tests to analyze the results, t-test, Pearson correlation, linear regression test, and the receiver operating characteristic (ROC) curve analysis. p-value < 0.05 was considered significant.

RESULTS

We enrolled 40 patients with MS and according to BMI, they classified 25 lean patients and 15 obese patients. Interestingly, case and control groups were matched concerning age and sex to prevent any effect of age and sex on gene expression. anthropometric and laboratory variables are reported in Table 1. We investigated obesity indices such as body mass index (BMI) and Waist/Hip Ratio and as expected there were significant differences between studied groups, p <0.001*. As indicators of inflammation, we examined erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, neutrophil count, and hs-c-reactive protein (CRP) and we found significantly higher values in obese MS patients compared to other groups. Concerning MS clinical and phenotypic features; there was a statistically significant increase of disease duration/year, number of relapses in the last 2 years, poor response to DMT, expanded disability status scale (EDSS), IgG index, and oligoclonal band (OCB), p <0. 001. On the other hand, there were non-significant differences regards other investigated variables, p>0.05.

To analyze the association of current DMT drugs with obesity indices and MS phenotypic features, we compared the MS patients treated with Interferon beta-1a (n=13) with patients treated with Interferon beta-1b(n=10) and Fingolimod (n=17) in Table 2. We detected a statistically significant difference between these patients regards; BMI,

Waist/Hip ratio, number of relapses, EDSS, and clinical response to the DMT, ESR, and hs-CRP For further in-depth analysis we detected that MS patients treated with fingolimod had statistically significant lower BMI, Waist/Hip ratio, number of relapses, EDSS, ESR, and hs-CRP compared to patients treated with Interferon beta-1b, p <0.001* .While, the clinical response to the fingolimod including 10 lean and 5 obese patients was statistically significantly higher than patients treated with Interferon beta-1a including 5 lean and 1obese and patients treated with Interferon beta-1b including 3 lean and 2 obese p <0.05*

To assess the relative expression of IL-17 mRNA in the studied groups, we analyzed our results, and we detected significantly higher values in the obese MS group (3.4±1.24) compared to the lean MS group (2.5±1.11) and control group (0.9±0.09). Figure 2A, P <0 .001.

Concerning IL-17(pg/ml) in the studied groups, we detected significantly higher values in the obese MS group (46.75±12.2) to the lean MS group (36.23±9.2) and control group (23.1±5.7). Figure 2B, P <0 .001.

To evaluate the association between each DMT with MS patients both lean and obese patients, in figure 3 we detected the difference between obese and lean MS groups regarding the number of patients as the number and percentage of lean patients treated with fingolimod (10,40%), patients treated with Interferon beta-1a (8,32%) and patients treated with Interferon beta-1b (7,28%), p>0.05. Concerning obese MS patients, patients treated with fingolimod (7,46.7%), patients treated with Interferon beta-1a (5,33.3%), and patients treated with Interferon beta-1b (3,20%), p>0.05.

To investigate the association between current DMT drugs and IL-17 mRNA we applied ANOVA test and we found MS patients treated with Fingolimod had statistically significant lower levels of IL-17 mRNA and serum IL-17(2.76 ±1.95, 36.6±9.12, respectively), compared to patients treated with Interferon beta-1b(4.4±1.72, 45.8±9.56, respectively), As well as patients treated with Interferon beta-1a(3.7±1.54, 40.3±6.42, respectively), table 2, P <0 .001.

We have demonstrated that by applying Pearson correlation, BMI, number of relapses in the last 2 years, EDSS, ESR, and hs-CRP were significantly positively correlated with IL-17 mRNA and serum IL-17 values among other examined variables as described in Table 3, P <0 .001.

The results of the linear regression test to investigate the independent factors that were associated with IL 17 mRNA and serum IL-17 in the prediction of MS. Concerning serum IL-17, the independent factors that were associated with it were BMI, EDSS, ESR, and hs-CRP, table 4, P <0 .001.Although,only BMI was the independent factor associated with IL 17 mRNA among other investigated variables, table 4, P <0 .001

To examine the efficiency of IL-17(pg/ml) and IL-17 mRNA levels for differentiation of patients with MS among participants. We applied ROC curve analysis and the results revealed that AUC of IL-17 and IL-17 mRNA =[0.934 (C.I=0.863-1.000), 0.919 (C.I=0.852-0.986), respectively] . Interestingly, the IL-17 sensitivity was 92.5%, and the specificity was 95% at a cutoff of 27.6. Intriguingly the IL-17 mRNA sensitivity was 95%, and the specificity was 98.5% at a cutoff of 0.980 (Fig. 4A), P <0 .001.

To analyze the effectiveness of IL-17(pg/ml) and IL-17 mRNA levels in distinguishing obese MS from lean MS, ROC curve outcomes showing that AUC of IL-17 and IL-17 mRNA =[0.645 (C.I=0.364-0.926), 0.752 (C.I=0.504-1.000), respectively]. Interestingly, the IL-17 sensitivity was 83.3%, and the specificity was 63.1% at a cutoff of 36.4. Intriguingly the IL-17 mRNA sensitivity was 80%, and the specificity was 60.1% at a cutoff of 1.26 (Fig. 4B), P <0 .001.

Table 1: Clinical MS phenotypic features, laboratory as well as radiological characteristics of studied groups.

Characteristics	Control group, n=40	Lean MS Group, n=25	Obese MS Group, n=15	P
Age (years)	31.4±6.4	29.7±5.3	32.3±6.4	0.188
Sex (Male/female)	7/33	9/16	6/9	0.130
BMI	22.3±1.1	22.4±1.3	39.4±3.9$^{\$, \&}$	<0.001*
Waist/Hip Ratio	0.65±0.07	0.68±0.09	1.9±0.36$^{\$, \&}$	<0.001*
Disease duration/year	NA	5.18±1.7	6.4±1.5$^{\&}$	<0.001*
Number of relapses in the last 2 years	NA	0.68±0.09	1.9±0.36$^{\&}$	<0.001*

Characteristics	Control group, n=40	Lean MS Group, n=25	Obese MS Group, n=15	P
Clinical response to the DMT n ,%	NA	18(72%)	8(53.3%)	<0.001*
Phenotypes of MS patients **RRMS** **SPMS**	NA	20 (80%) 5 (20%)	13 (86.7%) 2 (13.3%)	0.467
Clinical picture of MS **Sensory** **Motor** **Cerebellar** **Speech** **Visual**	NA	 11(44%) 9(36%) 3(12%) 3(12%) 1(4%)	 10(66.7%) 10(66.7%) 3(20%) 1(6.7%) 1(6.7%)	 0.165 0.060 0.400 0.515 0.615
ESR (mm/h)	13.5±5.3	44.5±10.3$^{£}$	73.5±13.78$^{\$, \&}$	<0.001*
EDSS	NA	1.6±0.9	3.5±0.57$^{\&}$	<0.001*
WBC count (cell × 10^3/µl)	5.59±1.1	6.5±1.53$^{£}$	6.7±1.6$^{\$, \&}$	<0.001*
Neutrophil count (cell × 10^3/µl)	3.19±1.5	4.6±1.6$^{£}$	4.5±1.6$^{\$, \&}$	<0.001*
hs-CRP (µg/ml)	1.3±0.61	5.39±1.4$^{£}$	13.3±4.53$^{\$, \&}$	<0.001*
IgG index	NA	0.69±0.7$^{£}$	2.61±0.6$^{\&}$	<0.001*
OCB (count)	NA	6.1±3.88$^{£}$	14.5±5.97 $^{\&}$	<0.001*
MRI findings				
Presence of T1 black holes	NA	5(20%)	4(26.6%)	0.626
Sites of lesion **Juxtacortical** **Periventricular** **Infratentorial**	NA	20(80%) 21(84%) 7(28%) 19(76%) 7(28%)	10(66.7%) 9(60%) 8(53.3%) 11(73.3%) 4(26.7%)	0.350 0.986 0.114 0.850 0.927
Activity Enhancement **New T2 lesions**	NA	9(36%) 7(28%)	6(40%) 5(33.3%)	0.800 0.7219

MS; Multiple sclerosis, **RRMS**; relapsing-remitting multiple sclerosis, **SPMS**; secondary-progressive multiple sclerosis, **EDSS**; Expanded Disability Status Scale, **OCB**; oligoclonal band, **IgG index**; immunoglobulin G index n * P < 0.001. £ Significant P values (P < 0.05) when comparing the control group with lean MS.$ Significant P values (P < 0.05) when comparing the control group with obese MS. &Statistically significant P values (P < 0.05) when comparing lean and obese MS.

Table 2: Association of current DMT drugs with obesity indices, MS phenotypic features and laboratory characteristics of studied groups.

Variables	Interferon beta-1a N=13	Interferon beta-1b N=10	Fingolimod N=17	P value
BMI	30.9±4.5	35.3±3.5$^{£}$	30.4±2.8	<0.001*
Waist/Hip Ratio	0.74±0.28	1.19±0.073$^{£}$	0.65±0.24 $^{\&}$	<0.001*
Number of relapses in the last 2 years	1.2±0.34	1.5±0.28	0.8±0.21$^{\$, \&}$	<0.001*
EDSS	1.7±1.018	3.02±1.152$^{£}$	1.31±1.05$^{\&}$	<0.001*
Duration of treatment (years)	6.5±1.581	5.76±1.36	5.05±2.07	0.128

Variables	Interferon beta-1a N=13	Interferon beta-1b N=10	Fingolimod N=17	P value
Clinical response to the DMT n, % **Lean** **Obese**	6(46.1%) 5(38.4%) 1(7.7%)	5(50%) 3(30%) 2(20%)	15(88.2%) $^{\$, \&}$ 10(58.8%) 5(29.4%)	<0.05*
ESR (mm/h)	56±27.31	63±18.42	39±11.15$^{\$, \&}$	<0.001*
hs-CRP (µg/ml)	15.63±6.31	11.63±6.3	8.34±2.47$^{\$, \&}$	<0.001*
IL-17 mRNA	3.7±1.54	4.4±1.72	2.76 ±1.95$^{\$, \&}$	<0.001*
IL-17(pg/ml)	40.3±6.42	45.8±9.56	36.6±9.12$^{\$, \&}$	<0.001*

Table 3: Pearson correlation coefficient between circulatory IL-17 serum and mRNA levels with other investigated variables among obese MS patients.

Variable		IL-17, pg/ml	IL-17 mRNA
BMI	***r***	0.559	0.449
	P	<0.001*	<0.001*
Disease duration/year	***r***	0.128	0.127
	P	0.431	0.433
Number of relapses in the last 2 years	***r***	0.322	0.384
	P	<0.001*	<0.001*
EDSS	***r***	0.539	0.541
	P	<0.001*	<0.001*
WBC count	***r***	0.222	0.164
	P	0.168	0.312
Neutrophil count	***r***	0.281	0.040
	P	0.079	0.808
ESR (mm/h)	***r***	0.387	0.393
	P	<0.001*	<0.001*
hs-CRP (µg/ml)	***r***	0.740	0.606
	P	<0.001*	<0.001*

P < 0.05

Table 4: linear regression analyses to test the influence of the main independent variables against IL-17 serum and mRNA levels (dependent variable) in obese MS patients.

Model		Unstandardized Coefficients		Standardized Coefficients	t	P value	95% C.I.	
		B	S.E	Beta			Lower Bound	Upper Bound
	(Constant)	-8.553	6.523		-1.311	0.198	-21.782	4.676
Serum IL-17	BMI	4.080	0.789	0.543	5.170	<0.001*	2.479	5.680
	EDSS	0.727	0.155	0.524	4.702	<0.001*	0.413	1.040
	ESR	0.079	0.516	0.017	0.152	0.880	-0.969	1.126
	hs-CRP	-8.703	00.341	-3.323	-25.49	<0.001*	-9.378	-8.028
	(Constant)	1.130	.351		3.219	0.003	0.419	1.842
	BMI	0.235	0.092	0.547	2.570	<0.001*	0.050	0.421
IL-17 mRNA	ESR	-0.006	0.016	-0.082	-0.387	0.701	-0.039	0.027
	EDSS	-0.0006	0.016	-0.101	-0.352	0.726	-0.038	0.026
	hs-CRP	0.083	0.043	0.197	1.950	0.055	-0.002	0.169

*P < 0.05

DISCUSSION

The current research enrolled 40 healthy controls matched to 40 patients with MS. To explore the influence of obesity on MS phenotypic features and inflammatory markers as well as the clinical and laboratory response to different DMT we categorized our MS patients to obese (n=15) and lean group(n=2). We assumed obese patients had higher obesity indices, severe MS, poor response to DMT, and inflammatory markers compared to the lean group.

Eminent researchers suggested that obesity may prompt inflammatory mediators leading to exacerbation of autoimmune such as MS [7,14]. Consistent with these results, **Huppke et al,** detected poor response to DMT in particular first line of therapy in obese children with MS [11]. Similar results were detected by **Lutfullin et al,** they found obese patients had poorer outcome compared to lean [15].

We observed in current research significant correlations between MS and inflammatory markers. Similarly, **Haegele** and his colleagues found higher levels of inflammatory markers in MS compared to controls [16].

While other authors described a decreased number of this T-cell subset [17] and the reason for this inconsistency may be due to variation in MS phenotypes included in these studies.

We grouped our MS patients (n=40) into three groups; MS patients treated with Interferon beta-1a (n=13, 8 lean and 5 obese), patients treated with Interferon beta-1b(n=10,7 lean and 3 obese), and fingolimod (n=17 ,10 lean and 7 obese). Remarkably we found that the MS patients treated with fingolimod had statistically significant lower BMI, Waist/Hip Ratio, number of relapses, EDSS, ESR, and hs-CRP compared to other groups in particular patients treated with Interferon beta-1b..while, the clinical response to the Fingolimod was statistically significantly higher than the response to other groups in particular patients treated with Interferon beta-1b.

To evaluate the relative expression of IL-17 mRNA in the studied groups, we analyzed our results, and we detected significantly higher values in the obese MS group compared to the lean MS group and control group.

Concerning IL-17in the studied groups, we detected significantly higher values in the obese MS group than in the lean MS group and control group. The correlation between examined DMT drugs and IL-17 serum as well as IL-17 mRNA. revealed that MS patients treated with fingolimod had statistically significant lower levels of IL-17 mRNA and serum IL-17, compared to patients treated with Interferon beta-1b together with patients treated with Interferon beta-1a. A similar finding was observed in **Bălaşa et al** [19].

Sato et al, observed an increase in circulating Th17 cells after fingolimod treatment in patients with MS relapses [20]. The discrepancy between our results and this study's results could contribute to differences in the type of patients as our study patients were investigated during remission, however, the other study patients were investigated during relapse.

Our results revealed that BMI, number of relapses in the last 2 years, EDSS, ESR, and hs-CRP were significantly positively correlated with IL-17 mRNA and serum IL-17 values among other examined variables as described, P <0 .001.Furthermore, the independent factors that were associated with serum IL-17 were BMI, EDSS, ESR, and hs-CRP, P <0 .001. Though, only BMI was the independent factor associated with IL 17 mRNA among other investigated variables.

To date, the majority of evidence that suggested the association of obesity with neuroinflammation [21] is still experimental or postmortem brain examination [22]. Additionally, the mechanism by which IL-17 works is still not clearly understood. However experimental studies explored its action [23]. So, we need more human studies to assess these relations to prevent MS and other neuroinflammation. To explore the efficiency of IL-17(pg/ml) and IL-17 mRNA levels for differentiation of patients with MS among participants we detected that the IL-17 sensitivity was 92.5%, and the specificity was 95%. Whereas the IL-17 mRNA sensitivity was 95%, and the specificity was 98.5%.

To evaluate the effectiveness of IL-17(pg/ml) and IL-17 mRNA levels in distinguishing obese MS from lean MS we observed that the IL-17 sensitivity was 83.3%, and the specificity was 63.1%. Though the IL-17 mRNA sensitivity was 80%, and the specificity was 60.1%), P <0 .001.

Limitations of the study:

The results of this research have a few limitations, first the small sample size. Second, we did not investigate patients at baseline and after treatment. In the future, we will handle a large sample study and investigate patients at baseline before treatment and after treatment to enhance our results.

CONCLUSIONS

Our study results detected that the IL-17serum and mRNA levels were upregulated in MS patients, in particularly obese patients. Also, these markers were associated with BMI, number of relapses in the last 2 years, EDSS, ESR, and hs-CRP. Intriguingly, MS patients treated with fingolimod had statistically significantly lower levels of obesity indices, EDSS, number of relapses, IL-17 mRNA and serum IL-17 compared to other patients. Additionally, patients treated with fingolimod had significantly good response to treatment compared to other patients treated with Interferon beta-1b.

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