



Original article

**Dyslipidemia in patients with Multiple Sclerosis and its correlation with disease parameters**

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**Abstract**

**Background:** Much interest was directed towards studying vascular complications in patients with multiple sclerosis (MS). However, the mechanisms of these complications are not well-understood. **Objective:** our work aimed to evaluate the risk of dyslipidemia in patients with MS and to correlate this risk with disease parameters. **Methods:** A case-control study included 50 patients with MS diagnosis and 50 age- and sex-matched healthy controls. The incidence of dyslipidemia was assessed in all participants by measuring serum lipid parameters in patients and controls. **Results:** Serum total cholesterol and triglycerides levels were significantly higher in MS, compared with controls, while HDL-cholesterol levels were significantly lower in MS patients, compared with controls. No significant correlation was found between serum lipids and disease duration or disability. **Conclusion:** MS patients had significantly higher serum levels of total cholesterol and triglycerides and significantly lower serum level of HDL-cholesterol.

## **1. Introduction:**

Multiple sclerosis (MS) is a chronic autoimmune neurological disease with recurrent episodes of inflammation, demyelination of the CNS and axonal degeneration. (1) It is considered important significant cause of neurological disability in young people, which affects women two times more than men. (2) The clinical course of MS varies; more than 80% of patients develop attacks of disability followed by periods of partial or complete recovery, while about 15% of patients have a progressive course without remissions. (3)

MS patients were reported to have a higher mortality rate than the general population which may be caused by many factors including the higher incidence of cardiovascular diseases among this category of patients. (4) There is established evidence that MS was associated with an increased risk for stroke and myocardial infarction, especially in the first years after diagnosis. (5)

Many CV risk factors were found to be relatively common among MS patients. One of the most prevalent CV risk factors was dyslipidemia. The relationship between dyslipidemia and MS is not well-understood yet. Multiple case-control studies reported higher total and LDL-cholesterol in MS patients than controls (6). Many hypotheses, that might explain the association between dyslipidemia and MS, have been suggested.

The association between inflammation and alterations in lipid metabolism is well-

characterized. The pro-inflammatory state, characterized by an immune-cell mediated release of cytokines, can cause a rise in triglyceride-rich serum lipoproteins secondary to increases in production and reduced hepatic clearance (7). This association between chronic inflammation and impaired lipid metabolism has previously been reported in other inflammatory autoimmune diseases like SLE (8).

Another hypothesis about lipid dysregulation in MS is that it may occur as a secondary by-product of myelin destruction in the central nervous system (9). Also, genetic susceptibility associated with MS may drive changes in lipid and amino acid composition of the serum, although at present none of the polymorphisms associated with MS have been involved directly in lipid metabolism (10). Furthermore, Penesova and colleagues have described decreased insulin sensitivity and postprandial hyperinsulinemia in MS patients (11). Reduced insulin sensitivity is typically associated with lipoprotein abnormalities (12). Also, the impact of the various disease-modifying drugs (DMDs) on the lipoprotein profile of MS patients cannot be neglected. The results of many studies suggest that treatments with fingolimod and dimethyl fumarate (DMF) are associated with increased serum levels of HDL, HDL/LDL, and HDL/TC ratios in MS patients (13). Also, the usage of corticosteroids, the

standard treatment for relapses, has been known to induce dyslipidemia (14). Despite the importance of research in this field, assessment of vascular function wasn't extensively performed in those patients and little data is available about the variable risk of dyslipidemia in MS patients. So, this work aimed at assessment of serum lipids of MS patients, compared to healthy controls, and to correlate them with disease duration and severity. This might aid in early detection of MS patients at risk of dyslipidemia, and consequently improving their vascular health.

## **2. Patients and Methods:**

### **Study design and study population:**

A case-control study that included 50 patients diagnosed with relapsing-remitting multiple sclerosis and 50 age- and sex-matched controls. MS patients were recruited in the period from January to October 2020. A written informed consent, as taken from all patients and controls, or their relatives. The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the ethical committee.

**Inclusion criteria:** Patients diagnosed as having relapsing-remitting multiple sclerosis (RRMS) according to the International Panel on Diagnosis of Multiple Sclerosis "McDonald's criteria 2017". (15) Patients were assessed in the remission state (at least one month after the last relapse). The age range for the patients, included in the study, was between 15 and 45 years.

**Exclusion criteria:** The following patients were excluded from the study: hypertensive or diabetic patients, patients with known cardiovascular disease, patients with associated autoimmune disease, and patients with known pulmonary, hepatic, renal or hematological disease. Pregnant patients were also excluded from the study.

### **The included participants were subjected to the following**

1. **History taking from MS patients regarding:** the total number of relapses, disease duration and the prescribed disease-modifying drugs (DMDs).
2. **Clinical assessment of all participants including:** blood pressure, heart rate, height, weight, body mass index (BMI) and body surface area.
3. **Assessment of neurological disability for MS patients using Expanded Disability Status Scale (EDSS):** The evaluated functional systems were pyramidal, cerebellar, cerebral, sensory and visual. The score of this scale ranges from zero (average) to 10 (death). (16)
4. **Radiological assessment using magnetic resonance imaging (MRI) on the brain and spinal cord:** to detect size and site of MS plaques in addition to lesion load and to exclude other structural brain or spinal cord lesions.
5. **Laboratory Work:** Fasting peripheral blood samples were collected from all patients and controls. The

samples were immediately centrifuged at 3000g for 15 min and measured by the spectrophotometer device for cholesterol, triglycerides and HDL-C. LDL-C was calculated indirectly by the Friedewald formula (17):

$$\text{LDL-C (mg/dl)} = \text{Total cholesterol} - \text{HDL-C} - (\text{triglycerides}/5).$$

### **Statistical analysis:**

Statistical analysis was performed with SPSS software version 20 (IBM Statistics 20). Continuous variables were expressed as mean and standard deviation (SD). Categorical variables were reported as numbers and percentages. Independent samples test-test was used to compare between MS patients and controls in continuous variables, while chi-square test was used to compare MS patients and controls in categorical variables. Pearson's correlation was used to describe the association between continuous variables. P-values  $\leq 0.05$  (2-sided) were considered statistically significant.

### **3. Results:**

The current study was conducted at Beni-Suef university hospital from February to October 2020. 100 participants were divided into two groups; Group 1: 50 patients with a definite diagnosis with MS and group 2: 50 age- and sex- matched healthy controls.

The baseline characteristics of patients and controls were demonstrated in table 1. The MS patients and controls didn't differ in age, sex, BMI, BSA, SBP, DBP, HR, or smoking status.

The neurological and radiological characteristics of MS patients, in addition to the current DMDs, were demonstrated in table 2.

Regarding the lipid profile of MS patients and controls, Ms Patients had significantly higher serum levels of T-cholesterol (165.8 VS 151.5, P-value $< 0.001$ ), triglycerides (140 VS 120, P-value= 0.025), compared with controls. Compared with controls, they also had insignificantly higher serum levels of low-density and very-low-density lipoprotein cholesterol. On the other hand, serum level of HDL-cholesterol was significantly lower in MS patients, compared with controls (46 VS 49.7, P-value= 0.007) (table 3). There was no statistically significant correlation between T-cholesterol, triglycerides, or LDL-cholesterol in MS patients and either disease duration or disability, except for a significant positive correlation between HDL-C and disease duration (Table 4 & 5).

To study the effect of DMDs on lipid profile in MS patients, we compared MS patients who were on DMDs (n=22) to those who didn't receive DMDs (n=28), but there was no statistically significant difference between the two groups.

**Table (1): General characteristics of MS patients and controls:**

		<b>Patients (n=50)</b>	<b>Controls (n=50)</b>	<b>P-value</b>
Age in years [mean (SD)]		32(8.47)	29(7.51)	0.107
Sex	Males [n(%)]	18 (36%)	16 (32%)	0.6
	Females [n(%)]	32 (64%)	34 (68%)	
BMI (kg/m <sup>2</sup> ) [mean (SD)]		26.5(6.16)	26(4.17)	0.723
BSA (m <sup>2</sup> ) [mean (SD)]		1.7(0.1)	1.7(0.2)	0.71
SBP (mmHg) [mean (SD)]		118(8.97)	116(6.66)	0.227
DBP (mmHg) [mean (SD)]		76(7.5)	74.22(6.5)	0.202
HR (beats/min) [mean (SD)]		84(13.26)	82.7(9.37)	0.55
Smoking	Smokers [n(%)]	8 (16%)	8 (16%)	1
	Non smokers [n(%)]	42 (84%)	42 (84%)	

BMI: body mass index; BSA: body surface area; DBP: diastolic blood pressure; HR: heart rate; SBP: systolic blood pressure. *P*-value >0.05 is considered statistically insignificant.

**Table (2): Neurological and radiological characteristics of MS patients**

		<b>Patients (n=50)</b>
Disease duration in years [mean (SD)]		4.29(3.61)
EDSS [mean (SD)]		3.25(1.47)
Total number of relapses [mean (SD)]		3.38(3.61)
MRI lesion load [mean (SD)]		9.72(6.66)
DMDs	No DMDs [n(%)]	28 (56%)
	Interferon beta [n(%)]	18 (36%)
	Fingolimod [n(%)]	1 (2%)
	Cyclophosphamide [n(%)]	1 (2%)
	Azathioprine [n(%)]	1 (2%)
	Rituxmab [n(%)]	1(2%)

DMDs: disease-modifying drugs; EDSS: Expanded Disability Status scale; MRI: magnetic resonance imaging.

**Table (3): Serum lipids of patients with multiple sclerosis and control subjects**

	<b>Patients (n=50) mean (SD)</b>	<b>Controls (n=50) mean (SD)</b>	<b>P-value</b>
T-Cholesterol (mg/dl)	165.86(41.13)	151.46(26.66)	0.041*
TGs (mg/dl)	139.95(57.54)	120.18(20.13)	0.025*
HDL-C (mg/dl)	46.95(6.3)	49.77(3.49)	0.007*
LDL-C (mg/dl)	90.23(39.53)	78.54(27.39)	0.089
VLDL-C (mg/dl)	28.35(11.55)	26.58(7)	0.357

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol. T-Cholesterol: total cholesterol; TG: triglycerides; VLDL: very-low-density lipoproteins. \**p*-value < 0.05 is considered statistically significant.

**Table (4): Correlation between disease duration and lipid profile**

	<b>Disease duration</b>	
	<b>(r) Coef.</b>	<b>P-value</b>
T-Cholesterol (mg/dl)	0.044	0.762
TGs (mg/dl)	-0.160	0.266
HDL-C (mg/dl)	0.365	0.009*
LDL-C (mg/dl)	0.015	0.919
VLDL-C (mg/dl)	-0.163	0.258

HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, T-Cholesterol: total cholesterol, TGs: triglycerides, VLDL: very-low-density lipoprotein cholesterol. \**P*-value < 0.05 is considered statistically significant.

**Table (5): Correlation between both EDSS and number of relapses, and serum lipids**

	<b>EDSS</b>		<b>Number of relapses</b>	
	<b>(r) Coef.</b>	<b>P-value</b>	<b>(r) Coef.</b>	<b>P-value</b>
T-Cholesterol (mg/dl)	0.222	0.122	-0.082	0.570
TGs (mg/dl)	0.006	0.965	-0.076	0.598
HDL-C (mg/dl)	0.142	0.327	0.242	0.090
LDL-C (mg/dl)	0.225	0.117	-0.108	0.455
VLDL-C (mg/dl)	0.010	0.947	-0.081	0.578

EDSS: Expanded Disability Status Scale, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, T-Cholesterol: total cholesterol, TGs: triglycerides, VLDL: very-low-density lipoprotein cholesterol. *P-value > 0.05 is considered statistically insignificant.*

#### **4. Discussion:**

Patients with MS have a lower life expectancy than the average population, but detailed data on mortality in MS are limited (18). Recent population studies showed that the median survival time from onset of disease was approximately ten years shorter for patients with MS than for the age-matched subjects, and MS was associated with an almost threefold increase in the risk of death (19). This increase in mortality might also be related to cardiovascular dysfunction (20). Many studies have shown an increased prevalence of CV risk factors in MS patients. So our work aimed to provide an assessment of the risk of dyslipidemia in those populations and correlating serum lipids with the disease duration, disability, total number of relapses, and MRI lesion load.

The relation between multiple sclerosis and dyslipidemia is not well-understood yet. In our study, we measured complete lipid profiles in patients with Multiple sclerosis and matched control subjects. We found significantly higher serum levels of T-cholesterol (165.8 VS 151.5, P-value <0.001), triglycerides (140 VS 120, P-value= 0.25) in patients with Multiple

Sclerosis, compared with control subjects. Meanwhile, serum levels of low-density and very-low-density lipoprotein cholesterol were insignificantly higher in MS patients, compared with the control group. Also, the serum level of HDL-cholesterol was significantly lower in MS patients, compared with the control group (46 VS 49. P-value= 0.007). We did not find a significant correlation between T-cholesterol, triglycerides, or LDL-cholesterol in MS patients and disease duration or severity. Only HDL-cholesterol was found to be positively correlated with the disease duration. Triglycerides and VLDL-cholesterol were negatively correlated with the MRI lesion load.

Many studies were performed to assess the prevalence of dyslipidemia among patients with Multiple Sclerosis. Similar to our work, Soliman et al. (2020) conducted a study in the Neurology Department, Beni-Suef University in which they assessed the prevalence of insulin resistance (IR) and metabolic syndrome in patients with Multiple sclerosis. This study included 50 MS patients and 25 healthy individuals. They were subjected to neurological assessment, in

addition to assessment for metabolic syndrome and insulin resistance. They reported that MS patients had significantly higher serum levels of both LDL-cholesterol (117 VS 79, P-value= 0.001) and triglycerides (103 VS 79, P-value= 0.02), and significantly lower serum levels of HDL-cholesterol (49 VS 53, P-value= 0.01), compared to control subjects. They did not find a significant correlation between lipid profile in MS patients and disease duration or disability (21).

Moreover, Sayonara Rangel et al. (2014) assessed the prevalence of IR and dyslipidemia in 110 MS patients and 175 healthy individuals. They reported higher serum levels of lipoproteins in MS patients than controls. The authors also assessed the serum levels of inflammatory cytokines; IL-6 and IL-17. They found that MS patients had significantly higher serum levels of LDL-cholesterol (121 VS 114, P-value= 0.015) and triglycerides (189 VS 103, P-value= 0.025) in addition to significantly lower serum levels of HDL-cholesterol (50 VS 55, P-value= 0.025), compared to the control group. Still, there was no significant correlation between serum lipids and disability. They also reported a significantly higher IR level in MS patients than the control group. Serum levels of inflammatory markers; IL-6 and IL-17 were correlated with the prevalence of IR and levels of serum lipids, suggesting the involvement of the

inflammatory status of MS in the pathogenesis of impaired lipid metabolism (22). This association between inflammation and dyslipidemia is not new; it was previously reported that in patients with systemic lupus erythematosus, systemic inflammation and oxidative stress have a prominent role in the pathogenesis of impaired lipid metabolism. (8)

Furthermore, Slawta JN et al. (2002) assessed the prevalence of dyslipidemia and coronary artery disease in 123 women with Multiple sclerosis, compared to control subjects. They reported significantly higher serum levels of LDL-cholesterol and triglycerides with lower serum levels of HDL-cholesterol in MS women compared to matched controls (23).

Many mechanisms are suggested to explain this relationship between Multiple Sclerosis and dyslipidemia. The association between inflammation and alterations in lipid metabolism is well-established. The pro-inflammatory state, characterized by an immune-cell mediated release of cytokines, can cause a rise in triglyceride-rich serum lipoproteins (7). The effect of chronic inflammation on lipid metabolism was previously reported in other inflammatory diseases like SLE (8). Moreover, the reported genetic susceptibility in MS may drive changes in lipid and amino acid composition of the serum (10). Also, many studies described decreased insulin sensitivity and



postprandial hyperinsulinemia in MS patients (11). Reduced insulin sensitivity is typically associated with lipoprotein abnormalities (12). In addition, inflammation-induced modifications of HDL proteins are shown to affect its function with a reduced capacity of reverse cholesterol transportation (24). Another hypothesis about lipid dysregulation in MS is that it may occur as a secondary by-product of myelin destruction in the central nervous system (9). Also, the impact of the various DMDs on the lipoprotein profile of the patients cannot be neglected (13). Also, the usage of corticosteroids, the standard treatment for MS relapses, has been known to induce dyslipidemia (14).

Disconcordant with our work, Selçuk Comoğlu et al. (2004) assessed lipid profile in 22 patients with MS and 16 healthy controls. They found that mean plasma total cholesterol levels were insignificantly higher in MS patients, compared to healthy volunteers. Mean plasma HDL-C and LDL-C levels of the MS patients were not statistically different from the mean values of the controls. However, the levels of plasma triglycerides of patients were significantly higher, compared to the levels of healthy subjects (25).

Similarly, Navarro X et al. (1988) assessed the lipid profile of 61 patients and 61 controls. They found that the mean levels of plasma total cholesterol, HDL-cholesterol, and triglycerides were in the normal range in

both MS and control groups. There were no significant differences between the two groups (26).

The association between dyslipidemia and Multiple sclerosis severity and progression is not well-understood; either it is a causal or consequential relationship. Several studies demonstrated an association between dyslipidemia and disability in MS patients. Tetty P. et al. (2014) measured lipid profile and apolipoprotein levels in 178 participants with definite MS and correlated levels of serum lipids with their baseline disability and annual change in disability. They found that nearly all lipid-related variables were positively correlated with EDSS. After adjustment for confounders, total cholesterol, apolipoprotein B (ApoB), and the apolipoprotein B to apolipoprotein A-I ratio (ApoB/ApoA-I ratio) were independently associated with a higher EDSS (27).

Also, Bianca Weinstock-Guttman et al. (2011) assessed the correlation between serum lipids and disability in Multiple Sclerosis. This study included 492 MS patients with baseline and follow-up EDSS assessments after a mean period of  $2.2 \pm 1.0$  years. They found that EDSS worsening was associated with higher baseline LDL, total cholesterol, and triglycerides, but no association was reported with HDL. They suggested that dyslipidemia may increase progression by activating inflammatory processes at the vascular endothelium (28).

This association between dyslipidemia and disease progression needs to be properly studied as it may suggest the clinical benefits of lipid-lowering agents in multiple sclerosis (29).

So, our findings are significant for the daily clinical practice, by emphasizing that this young and active population should receive the best standard of care from a multidisciplinary team, including a cardiologist. Our exploratory study needs further confirmation before being implemented by guidelines in patients with MS; however, it opens important premises for further research and innovation in the new field of neuro-cardiology.

Our study has some limitations; firstly, the cross-sectional pattern of the study; we need a longitudinal study to follow up the changes of the lipid profile of MS patients through the course of the disease. Secondly, we only studied the risk of dyslipidemia in RRMS patients. Further researches are needed to compare the cardiovascular function between the different MS variants including RRMS, primary and secondary progressive MS.

The strength of our study was that it was the first study, to the best of our knowledge, to assess the risk of the dyslipidemia among Egyptian MS patients. We also correlated the evaluated serum lipids with disease duration and disability.

## **5. Conclusion and Recommendations**

We concluded that MS patients had significantly higher serum levels of T-cholesterol and triglycerides, in addition to a significantly lower serum level of HDL-cholesterol, in comparison to controls. There was no statistically significant correlation between lipid profile and disease duration or disability, apart from a significant positive correlation between HDL-cholesterol and disease duration. No statistically significant difference in cardiac or vascular functions was found between the treated and non-treated MS patients.

The clinical benefit of treating MS patients with statins is recommended to be further evaluated. Also, the relationship between the inflammatory cytokines and dyslipidemia in MS is recommended to be studied to clarify the actual role of inflammation in the development of impaired lipid metabolism in MS.

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