ORIGINAL ARTICLE

Vascular comorbidities in patients with multiple sclerosis and their impact on physical disability

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ABSTRACT

Aim Given the impact of vascular comorbidities (VC) on the diagnosis, treatment, and outcome of multiple sclerosis (MS), we examined the incidence and correlation of VC and risk factors for vascular disease in people with MS (PwMS) compared to the general population, and the impact on the physical disability of patients.

Methods Cross-sectional study involved 100 patients with MS and 50 healthy people from the general population, matched by sex and age. The values of demographic, biochemical, and anthropometric parameters, the presence of VC and risk factors for vascular diseases in both groups, and clinical parameters in PwMS were analysed. Statistical analysis included methods of descriptive statistics, $\chi 2$ test, Student's t-test, analysis of variance, correlation and regression analysis.

Results Groups differed by a higher frequency of transient ischemic attack in the control group (p=0.024), and the treatment of hypertension (p=0.038) and smoking frequency (p=0.044) in the MS group. Normal triglycerides levels were statistically significantly more prevalent in the MS group (p=0.000). Total body weight and BMI were statistically significantly higher in the control group (p=0.000). The increase in Expanded Disability Status Scale (EDSS) score was associated with higher levels of total (p=0.001) and low-density lipoprotein (LDL) cholesterol (p=0.003), and activated partial thromboplastin time APTT (p=0.002).

Conclusion In PwMS it is necessary to pay attention to the higher frequency of smoking than in general population, and the impact of total cholesterol, LDL and APTT levels as significant parameters that affect physical disability.

Key words: cholesterol, hypertension, smoking, vascular diseases

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Original submission:
27 April 2022;
Revised submission:
10 May 2022;
Accepted:
21 June 2022
doi: 10.17392/1499-22

Med Glas (Zenica) 2022; 19(2): 166-172

INTRODUCTION

Comorbidities can be defined as the total burden of factors that affect health disorders independent on the observed underlying disease but taking into account habits and certain lifestyle elements (1). The main goal of comorbidities research is to improve overall human health. In the population of patients with multiple sclerosis (MS) we must take into account the frequency of comorbidities and their treatment, MS treatment, lifestyle factors, socioeconomic status, and health-related interactions on quality of life (2). Comorbidities in MS are associated with an increase in disability, with the course of the disease, and they have an impact on the choice and application of therapy, hospitalization, mortality, and the overall quality of life of patients and their families (3). Although there is a significant number of studies assessing comorbid conditions in people with MS (PwMS), vascular comorbidities studies are less common, especially in regions outside of North America and Northern and Western Europe, where the findings are also quite inconsistent (4).

Despite previous research (5), to date there are no uniform conclusions about the frequency of vascular comorbidities (VC) in the MS population compared to the general population, and their possible impact on clinical parameters in MS; they differ greatly depending on the population, sample size, study design, and data collection methods (4). There are no studies on vascular comorbidities in MS population in Bosnia and Herzegovina including Republic of Srpska.

The aim of this study was to investigate the prevalence of VC and risk factors for vascular disease in the MS patients compared to the general population, their mutual correlation, and the impact on their physical disability.

PATIENTS AND METHODS

Patients and study design

The study was designed as a cross-sectional study and included 100 patients diagnosed with definitive MS, and 50 healthy people from the general population, matched with the MS group by gender and age, and those who were not blood- related to the MS patients, who did not have an inflammatory disease of the central nervous system nor a cerebrovascular disease (CVD), and did not use statins. Exclusion criteria for MS group were the use of statins and corticosteroids in chronic therapy, and relapse in the last month.

The research was conducted at the Centre for MS, University Clinical Centre of the Republic of Srpska (UKCRS), Banja Luka for a period of two years, from May 2012 to May 2014.

Respondents confirmed their voluntary consent to participate in the research with their signatures, with the prior approval of the Ethics Committee of the UKCRS for conducting research.

Methods

All subjects had blood samples taken on an empty stomach, and total cholesterol, low density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride levels, glycemia, haematocrit, fibrinogen, and activated partial thromboplastin time (APTT) were measured. Reference values were according to the UKCRS Banja Luka. Body weight (BW) and body height (BH) were used to calculate body mass index (BMI), blood pressure values were measured, and target values were defined according to the recommendations of the American College of Cardiology / American Heart Association (ACC/AHA) (6).

Demographic data were recorded for both groups: age, gender, level of education, occupation, employment. For PwMS clinical data were recorded: duration of the disease, age at onset of the disease, clinical form of MS, and degree of neurological deficit using the Expanded Disability Status Scale (EDSS) (7). Based on the quotient of EDSS scores and the duration of the disease, the disease progression index was calculated.

For all participants in the study, data related to the presence of VC were taken: transient ischemic attack, stroke, hypertension, treatment of hypertension, ischemic heart disease, atrial fibrillation, other CVD, ischemic peripheral vascular disease, venous thrombosis, diabetes, insulin-dependent diabetes mellitus (DM), hyperlipidaemia, smoking, alcoholism, family history of stroke, and family history of CVD.

Statistical analysis

A statistical analysis included methods of descriptive statistics (mean, standard deviation, mode, median, skewness / kurtosis), $\chi 2$ test, Student's t-test, analysis of variance (ANOVA), correlation

(Pearson's and Spearman's correlation test) and regression analysis. Results were presented as mean±SD. A $p<0.05$ was considered as statistically significant. To determine a statistical correlation between biochemical parameters and the affiliation to the examined groups, the □2 test was used.

For each category, the values were classified into two modalities: pathological and normal. All examined parameters can be observed from a different angle because these are numerical characteristics. It is important to determine whether the mean values of each of them differ between the MS and the control group. For this purpose, statistical testing with two independent samples was used. To determine the correlation (degree and direction), of the examined variables (cholesterol, HDL, LDL, glycemia, fibrinogen, APTT, disease progression index) in the MS group, Pearson's correlation coefficient was used. Spearman's correlation coefficient to analyse the relationship between EDSS as a measure of physical disability and other parameters, and BMI and other observed parameters was used.

RESULTS

The analysed sample in our study consisted of an experimental group, consisting of 100 patients with MS, and a control group with 50 healthy people, matched according to gender and age (±2) years.

The mean age of patients at the beginning of the study was 41.9±10.1 years in the MS group; the youngest patient 20 and the oldest 64 years of age. In the control group, the average age was 42.1±12.3, with the youngest 18 and the oldest 63 years of age.

Out of a total of 100 patients with MS, 25 (25%) were males and 75 (75%) females, and in the control group 14 (28%) and 36 (72%), respectively.

The number of years of education in the MS group was 12.5±2.5 years, and in the control group 11.4±2.6 years, with less variability in the MS group.

The occupation was interdependent between the groups (p= 0.032). High education was more frequent in the MS group, 26 (26%), than in the control group, nine (18%).

Unemployment was more frequent in both groups, and did not differ significantly by groups (p=0.423).

The mean age at the onset of MS was 33.6±11.18 years. The disease duration is a rather unstable quantity (standard deviation is relatively high compared to the mean value), so the obtained average value cannot be taken as a representative measure (8.5950±7.651). In regard to the course of MS, most of our patients, 72 (72%) had relapsing-remitting MS, 27 (27%) had secondary progressive MS, and one (1%) had primary progressive MS.

The mean EDSS score was 3.7±2.1; 59 (59%) patients had EDSS scores in the range of 1-4, while 38 (38%) had EDSS >4, and three (3%) of patients had EDSS 0.

The mean value of the disease progression index was 0.9±1.

The analysis of the presence of VC and nonbiochemical risk factors for CVD in the group of patients with MS and the control group, showed that only three characteristics depended on the affiliation to MS or the control group: transient ischemic attack (p = 0.024), treatment of hypertension (p= 0.038), and smoking (p= 0.044). No statistical significance was observed in the analysis of other observed parameters (stroke, hypertension, ischemic heart disease, atrial fibrillation, other cardiovascular disease, ischemic peripheral vascular disease, venous thrombosis, diabetes, insulin dependents diabetes, hyperlipidaemia).

In the control group four (8%) had transient ischemic attack (TIA), while in the MS group one (1%) patient. In the control group, eight (75%) patients were treated for hypertension, while in the MS group 18 (95%). A total of 71 (71%) of MS patients were smokers and 14 (28%) in the control group (Table 1).

Mean values of systolic and diastolic pressure differed significantly by group (p=0.001): 114.5 (±12.01) and 122.4 (±16.23) and (p = 0.025): 75.55 (±7.85) and 78.80 (±9.18), respectively, in MS and control group, respectively. The duration of hypertension did not differ significantly by group, 9.5 and 10, respectively (p>0.05).

The share of smokers by groups differed statistically significantly (p=0.044). There was no statistically significant difference in the number of cigarettes smoked per day: in MS group 15.17 (± 8.10) and in control 16.12 (±6.77), nor in the duration of smoking, MS group 18.47 (±10.54) and control 23.16 (± 10.18) years.

Table 1. Analysis of vascular comorbidities (VC) and nonbiochemical risk factors for VC in multiple sclerosis (MS) and control group

Variable	Group	No (%) of patients	p
Transient ischemic attack	MS	1 (1)	0.024
	Control	4 (8)	
Stroke	MS	1 (1)	0.216
	Control	2 (4)	
Hypertension	MS	19 (19)	0.573
	Control	12 (24)	
Treatment of hypertension	MS	18 (36)	0.038
	Control	8 (16)	
Ischemic heart disease	MS	4 (4)	0.466
	Control	5 (10)	
Atrial fibrillation	MS	3 (3)	0.720
	Control	1 (2)	
Other cardiovascular diseases	MS	21 (21)	0.691
	Control	12 (24)	
Ischemic peripheral vascular disease	MS	4 (4)	0.584
	Control	3 (6)	
Venous thrombosis	MS	2 (2)	0.748
	Control	2 (4)	
Diabetes	MS	3 (3)	0.072
	Control	6 (12)	
Insulin dependent diabetes	MS	1 (1)	0.187
	Control	4 (8)	
Hyperlipidaemia	MS	36 (36)	0.371
	Control	22 (44)	
Smoking	MS	71 (71)	0.044
	Control	14 (28)	
Alcohol	MS	12 (12)	1.000
	Control	6 (12)	
Family history of stroke	MS	21 (21)	0.491
	Control	12 (24)	
Family history of stroke of CVD	MS	48 (48)	0.248
	Control	22 (44)	

CVD, cerebrovascular disease;

Statistical significance between groups was found for the triglycerides (p= 0.001) and APTT (p= 0.050) (Table 2).

Table 2. Analysis of the biochemical risk factors for vascular comorbidities (VC) in multiple sclerosis (MS) and control group

Variable	Group	Mean(±SD)	p
Total cholesterol	MS	5.1903 (1.1504)	0.241
	Control	5.4340 (1.28104)	
HDL	MS	1.3620 (0.32622)	0.856
	Control	1.3760 (0.62354)	
LDL	MS	3.3900 (0.93533)	0.211
	Control	3.5900 (0.88853)	
Triglycerides	MS	1.2710 (0.51489)	0.001
	Control	2.1880 (2.79764)	
Glycemia	MS	5.0905 (0.88753)	0.076
	Control	5.5408 (2.19192)	
Haematocrit	MS	.4218 (0.04491)	0.958
	Control	.4222 (0.04316)	
Fibrinogen	MS	3.3900 (0.98016)	0.108
	Control	3.6900 (1.23641)	
APTT	MS	24.9130 (2.50473)	0.050
	Control	25.7420 (2.26446)	

SD, standard deviation; LDL, low density lipoprotein; HDL, high density lipoprotein; APTT, activated partial thromboplastin time

A normal level of triglycerides was noticed in control group in 29 (58%), while in the MS group the level was significantly higher, in 86 (86%) patients. No statistical significance was observed in the analysis of other parameters that had normal values (cholesterol, HDL, LDL, fasting glycemia, haematocrit, fibrinogen, APTT) (Table 2).

The difference between the groups was statistically significant for the body weight BW and BMI (p=0.000), but not for body height (p= 0.563) (Table 3).

Table 3. Analysis of characteristics related to determination of body mass index (BMI) in multiple sclerosis (MS) patients and control group

Variable	Group	Mean (±SD)	p
Body weight (kg)	MS	67.1060 (13.1973)	0.000
	Control	76.1380 (16.3600)	
Body height (cm)	MS	171.3300 (8.8968)	0.563
	Control	170.4200 (9.4439)	
BMI	MS	22.7540 (3.0814)	0.000
	Control	26.0700 (4.3719)	

Correlation analysis of the cholesterol, HDL, LDL, glycemia, fibrinogen, APTT, disease progression index, in the MS group showed the coefficient had low absolute values. The exception was direct and very high correlation between LDL and cholesterol (r=0.867). None of the analysed variables had a statistically significant correlation with the disease progression index (p>0.05). The ratio of EDSS-cholesterol (r=0.330; p=0.001), EDSS-LDL (r=0.296; p=0.003) and EDSS-APTT (r= -0.305; p=0.002) had statistical significance. The correlation coefficient was also statistically significant for the variables BMI-fibrinogen (r=0.329; p=0.001), BMI-triglycerides (r=0.249; p=0.012), and BMI-APTT (r= -0. 243; p=0.015) (data have not shown).

DISCUSSION

Since vascular comorbidities have been found to affect outcomes in PwMS, there has been growing concern about the presence of these conditions in this group of patients, compared to the general population. In our research presence of hyperlipidaemia, as well as the levels of cholesterol and its fractions (observed as pathological or normal), did not differ between the MS and the control group**.** We obtained the same results by analysing the average values of cholesterol and its fractions in both groups. However, normal triglyceride levels were more prevalent in the MS group than in the general population. Studies on

this topic in other regions have shown different results, from those where the level of cholesterol and its fractions was higher in the general population, to those where the opposite result was obtained (8,9).

The best-designed studies showed normal or discretely elevated values of total and LDL cholesterol, and decreased HDL values in the MS population compared to the general population (10,11). The correlation between the analysed biochemical (cholesterol, HDL, LDL, glycemia, haematocrit, fibrinogen, APTT), and anthropometric parameters (BMI, BW, BH) in the MS group found a statistically significant association between LDL and total cholesterol, and BMI and triglycerides. A positive correlation was found between the EDSS score and total cholesterol levels, and the EDSS score and LDL. Almost identical conclusions have been shown in several studies on this topic (12-14).

Analyses of anthropometric measurements showed that BMI values, as well as BW, were statistically significantly higher in the control group, in contrast to BH where the significance was not shown. Our results are in line with the best-designed studies conducted on this topic in other countries (15,16). Several studies of BMI values in MS patients showed BMI values within those in the general population (17,18), but other research showed that over 50% of patients with MS are overweight (19-21).

Studies in the different MS population have shown that the impact of smoking on the development of comorbidities, in correlation with genetic factors, leads to the onset and progression of MS (22,23). The analysis of our results showed the proportion of smokers in the MS group had been higher than in the control group, which is consistent with most studies in other countries (24,25).

In our study, there was no association between EDSS score and smoking, while most other studies showed such an association (26). By analysing the presence of insulin-independent and dependent diabetes we found that there was no dependence concerning the study groups in our country, which is consistent with most other studies (27), but there are some researches where the frequency was higher in the MS population (28). We also found, that there was no statistically significant difference between the levels of fasting glycemia (normal or pathological), nor between the average values of fasting glycemia, between the two study groups. These mean values in both groups were within normal values, as shown by studies in other MS populations (29). A study by Moss et al., in contrast to our results, showed that in MS patients the prevalence of elevated fasting glucose concentrations, as well as impaired glucose tolerance, was statistically significantly higher in the MS group (28).

Of the observed CVDs (TIA, stroke) in our study, a higher frequency of TIA was observed in the control group. Previous studies on the prevalence of stroke in the MS population showed inconsistent results, but the best-designed studies, characterized by a high degree of reliability, showed a slightly higher mortality rate from CVD in people with MS, as well as an increased prevalence of CVD in MS compared to the general population (30). A lower prevalence of CVD (including TIA) in MS patients compared to the general population was also observed in a study by Persson et al. (31).

In our study the presence of hypertension did not differ by group, but the number of patients treated for hypertension was statistically significantly higher in the MS group. It should be noted that the duration of hypertension does not differ much by group, nor was it statistically significant. It is difficult to draw a single conclusion from previous research: data range from low (32), above normal (13), to a higher prevalence of hypertension in the population of MS patients compared to the general population (30). There are a few studies that have analysed the values of systolic and diastolic pressure in the MS population. In our study, the mean values of systolic and diastolic pressure, observed individually, were statistically significantly higher in the control group. In the study of Stampanoni et al. lower blood pressure values were also shown in the MS than in the control group (33). A statistically significant difference in APTT levels in favour of the control group was found in our study. The correlation analysis obtained a statistically significant association between BMI and fibrinogen levels, which could correspond to the results of previous research on the state of latent chronic inflammation in people with elevated BMI, and where, as noted on several occasions, there are elevated levels of fibrinogen (34).

Given the aim of our study, we observed statistically a significant correlation between the EDSS score as a measure of physical disabilitythe and APTT. This correlation in terms of the impact of coagulation factors on cerebral hypoperfusion, and thus the impact on physical disability, has been shown in other studies (35).

The limitation of this study is the research period. However, given the specificity of the examined scientific field and the fact that other research centres in Bosnia and Herzegovina have not conducted research on this topic in the previous period, we decided to disclose our results.

In conclusion, in our MS patient population it is necessary to pay attention to the higher frequency of smoking than in the general population, and the impact of total cholesterol, LDL and APTT levels as significant parameters that affect physical disability. Therefore, it is advisable to work on modifying risk factors for vascular co-morbidities in people with MS and its prevention in order to reduce their impact on the outcomes in MS.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

REFERENCES

1. Zhang T, Tremlett H, Zhu F, Kingwell E, Fisk JD, Bhan V, Campbell T, Stadnyk K, Carruthers R, Wolfson C, Warren S, Marrie RA. Effects of physical comorbidities on disability progression in multiple sclerosis. Neurology 2018; 90:e419-27.
2. Gil-González I, Martín-Rodríguez A, Conrad R, Pérez-San-Gregorio MÁ. Quality of life in adults with multiple sclerosis: a systematic review. BMJ Open 2020; 10:e041249.
3. Magyari M, Sorensen PS. Comorbidity in multiple sclerosis. Front Neurol 2020; 11:851.
4. Hauer L, Perneczky J, Sellner J. A global view of comorbidity in multiple sclerosis: a systematic review with a focus on regional differences, methodology, and clinical implications. J Neurol 2021; 268:4066-77.
5. Diržiuvienė B, Mickevičienė D. Comorbidity in multiple sclerosis: Emphasis on patient-reported outcomes. Mult Scler Relat Disord 2022; 59:103558.
6. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC Jr, Virani SS, Williams KA Sr, Yeboah J, Ziaeian B. ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019; 10:140:e596-646.
7. Kurtzke JF. Rating neurologic instrument in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 1983; 33:1444-52.
8. Fellows MK, Bhattacharya S, Bodziak ML, Jakimovski D, Hagemeier J, Browne RW, Weinstock-Guttman B, Zivadinov R, Ramanathan M. Oxysterols and apolipoproteins in multiple sclerosis: a 5-year follow-up study. J Lipid Res 2019; 60:1190-98.
9. Isshiki M, Hirayama S, Ueno T, Ito M, Furuta A, Yano K, Yamatani K, Sugihara M, Idei M, Miida T. Apolipoproteins C-II and C-III as nutritional markers unaffected by inflammation. Clin Chim Acta 2018; 481:225–30.
10. Jorissen W, Wouters E, Bogie JF, Vanmierlo T, Noben JP, Sviridov D, Hellings N, Somers V, Valcke R, Vanwijmeersch B, Stinissen P, Mulder MT, Remaley AT, Hendriks JJ. Relapsing-remitting multiple sclerosis patients display an altered lipoprotein profile with dysfunctional HDL. Sci Rep 2017; 7:43410.
11. Mukhopadhyay S, Fellows K, Browne RW, Khare P, Krishnan Radhakrishnan S, Hagemeier J, Weinstock-Guttman B, Zivadinov R, Ramanathan M. Interdependence of oxysterols with cholesterol profiles in multiple sclerosis. Mult Scler 2017; 23:792-801.
12. Murali N, Browne RW, Fellows Maxwell K, Bodziak ML, Jakimovski D, Hagemeier J, Bergsland N, Weinstock-Guttman B, Zivadinov R, Ramanathan M. Cholesterol and neurodegeneration: longitudinal changes in serum cholesterol biomarkers are associated with new lesions and gray matter atrophy in multiple sclerosis over 5 years of follow-up. Eur J Neurol 2020; 27:188-e194.
13. Rádiková Ž, Penesová A, Vlček M, Havranová A, Siváková M, Šiarnik P, Žitňanová I, Imrich R, Turčáni P, Kollár B. Lipoprotein profiling in early multiple sclerosis patients: effect of chronic inflammation? Lipids Health Dis 2020; 19:49.
14. Tettey P, Simpson S, Taylor B, Ponsonby AL, Lucas RM, Dwyer T. Kostner K; AUSLONG investigators group, van der Mei IA. An adverse lipid profile and increased levels of adiposity significantly predict clinical course after a first demyelinating event. J Neurol Neurosurg Psychiatry 2017; 88:395–401.
15. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol 2017; 13:25-36.
16. Dardiotis E, Tsouris Z, Aslanidou P. Body mass index in patients with multiple sclerosis: a meta–analysis. Neurolol Res 2019; 41:836-46.
17. Jakimovski D, Weinstock-Guttman B, Gandhi S. Dietary and lifestyle factors in multiple sclerosis progression: results from 5-year longitudinal MRI study. J Neurol 2019; 266:866-75.

18. Bošnjak Pašić M, Tudor KI, Mustač F, Rajič F, Pašić H, Vujević L, Šarac H, Vidrih B. Comorbidities in patients with multiple sclerosis in Croatia. Psychiatr Danub 2021; 33:475-79.
19. Ajdacic-Gross V, Steinemann N, Horváth G, Rodgers S, Kaufmann M, Xu Y, Kamm CP, Kesselring J, Manjaly ZM, Zecca C, Calabrese P, Puhan MA, von Wyl V. Onset symptom clusters in multiple sclerosis: characteristics, comorbidities, and risk factors. Front Neurol 2021; 12:693440.
20. Piluti LA, Molti RW. Body composition and disability in people with multiple sclerosis. A dual energy x-ray absorptiometry study. Mult Scler Relat Disord 2019; 29:41-47.
21. Jakimovski D, Guan Y, Ramanathan M, Weinstock-Guttman B, Zivadinov R. Lifestyle-based modifiable risk factors in multiple sclerosis: review of experimental and clinical findings. Neurodegener Dis Manag 2019; 9:149-72.
22. Hedström AK. Smoking and its interaction with genetics in MS etiology. Mult Scler 2019; 25:180-86.
23. Waubant E, Lucas R, Mowry E, Graves J, Olsson T, Alfredsson L, Langer-Gould A. Environmental and genetic risk factors for MS: an integrated review. Ann Clin Transl Neurol 2019; 6:1905-22.
24. Arneth B. Multiple Sclerosis and smoking. Am J Med 2020; 133:783-88.
25. Auer M, Bsteh G, Hegen H, Di Pauli F, Wurth S, Berger T, Deisenhammer F. Smoking is not associated with higher prevalence of JC virus in MS patients. Eur J Clin Microbiol Infect Dis 2018; 37:907-10.
26. A Bang Oturai A, Sellebjerg F, Søndergaard HB, Soelberg Sørensen P, Olsson AG, Laursen JH. Smoking is associated with increased disease activity during natalizumab treatment in multiple sclerosis. Mult Scler J 2018; 25:1298-305.
27. Passali M, Josefsen K, Frederiksen JL, Antvorskov JC. Current evidence on the efficacy of gluten-free diets in multiple sclerosis, psoriasis, type 1 diabetes and autoimmune thyroid diseases. Nutrients 2020; 12:2316.
28. Moss BP, Rensel MR, Hersh CM. Wellness and the role of comorbidities in multiple sclerosis. Neurotherapeutics 2017; 14:999-1017.
29. Berrigan LI, Fisk JD, Patten SB, Tremlett H, Wolfson C, Warren S, Fiest KM, McKay KA, Marrie RA, CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis (ECoMS). Health-related quality of life in multiple sclerosis: direct and indirect effects of comorbidity. Neurology 2016; 86:1417-24.
30. Palladino R, Marrie RA, Majeed A, Chataway J. Evaluating the risk of macrovascular events and mortality among people with multiple sclerosis in England. JAMA Neurol 2020; 77:820-28.
31. Persson R, Lee S, Yood MU, Wagner M, Minton N, Niemcryk S, Lindholm A, Evans A, Jick S. Multidatabase study of multiple sclerosis: identification, validation and description of MS patients in two countries. J Neurol 2019; 266:1095-106.
32. Jalkh G, Abi Nahed R, Macaron G, Rensel M. Safety of newer disease modifying therapies in multiple sclerosis. Vaccines 2020; 9:12.
33. Stampanoni BM, Iezzi E, Buttari F, Gilio L, Simonelli I, Carbone F, Micillo T, De Rosa V, Sica F, Furlan R, Finardi A, Fantozzi R, Storto M, Bellantonio P, Pirollo P, Di Lemme S, Musella A, Mandolesi G, Centonze D, Matarese G. Obesity worsens central inflammation and disability in multiple sclerosis. Mult Scler 2020; 26:1237-46.
34. Ziliotto N, Bernardi F, Jakimovski D, Zivadinov R. Coagulation pathways in neurological diseases: multiple sclerosis. Front Neurol 2019; 10:409.
35. Koudriavtseva T, Stefanile A, Fiorelli M, Lapucci C, Lorenzano S, Zannino S, Conti L, D'Agosto G, Pimpinelli F, Di Domenico EG, Mandoj C, Giannarelli D, Donzelli S, Blandino G, Salvetti M, Inglese M. Coagulation/complement activation and cerebral hypoperfusion in relapsing-remitting multiple sclerosis. Front Immunol 2020; 11:548604.