



Association of Body Mass Index With Progression and Prediction of Multiple Sclerosis

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Abstract

Background/Aim: Multiple sclerosis is a disease whose aetiology involves multifactorial interactions among genetic and environmental factors. Obesity is one of the most important environmental factors conducive to the onset and progression of the disease. The aim of the study was to determine the value of body mass index (BMI) in a population of patients with multiple sclerosis compared to the general population, in order to assess the relation between the BMI and physical disability in patients with multiple sclerosis and the influence of the BMI on the course and progression of the disease.

Methods: A cross-sectional study was performed in 100 patients suffering from multiple sclerosis (experimental group) and 50 healthy people (control group). In order to determine the degree of physical disability, the Expanded Disability Status Scale (EDSS) was used. Clinical and demographic data and values of the BMI in both studied groups were collected. Statistical analysis included the descriptive statistics, t-test, chi-square test, analysis of variance, correlation and regression analysis.

Results: Mean body weight and BMI were significantly higher in the control group ($p < 0.05$). There was no significant correlation between EDSS and BMI ($p = 0.574$). There was a correlation between the course of MS and the fact whether BMI was abnormal or normal ($p = 0.031$).

Conclusion: BMI is an environmental factor that significantly correlates with the progression and prediction of multiple sclerosis, but not to the degree of physical disability.

Key words: multiple sclerosis, BMI, progression, prediction, physical disability.

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Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) that often occurs in a population of young adults, predominantly female.¹ Pathophysiological mechanisms of this disorder include a degenerative and an inflammatory component that covers both grey and white matter of the CNS. These mechanisms are basis for a very heterogeneous relapsing or progressive clinical course of MS, where longer duration of the disease leads

to physical and cognitive disability. A reliable long-term individualised prognosis has not yet been possible and represents a subject to intensive research.² The aetiology of MS involves multifactorial interactions among genetic and environmental factors. Genetic predisposition is only a part of the risk of MS, while lifestyle and environmental factors are key participants in the development of the disease.³ Proven risk factors for the development of the disease are

female gender, smoking, low level of vitamin D, dietary habits, Epstein Barr virus infection and obesity in childhood and adolescence.^{4,5}

According to the previous studies, there is an obvious connection between the disability in MS and obesity. Increased level of disability decreases the level of physical activity and the frequency of overweight or obese status is higher and *vice versa*.⁶ This may be associated with loss of mobility, but also with other disorders that accompany MS such as depression, pain, fatigue, loss of social contacts and associated chronic diseases.⁷ However, this interdependence also exists at the molecular level. Since obesity is associated with latent inflammatory reactivity, it leads to the release of inflammatory cytokines that influence the immune response and is associated with a possible risk for the development of MS.⁸ Adipose tissue secretes hormones that affect the functioning of the immune system, including leptin and interleukin-6, known inhibitors of T-cell activity. Elevated leptin levels in obese people are inversely proportional to the function of T cells in individuals with MS. Another potential mechanism is related to the fact that obese people have lower levels of serum 25-hydroxy vitamin D correlates with leads to an increased risk for MS.^{7,8} Inflammasome is a protein complex that participates in the inflammatory response and it is found in the adipose tissue. Recent studies have shown its significant role in the pathogenesis of autoimmune and inflammatory diseases and demonstrated that elevated levels of these proteins leads to the progression of these diseases, which is particularly applicable to diabetes, atherosclerosis and MS.⁹⁻¹¹

So far, in several studies the body composition has been studied as a factor influencing the onset and progression of MS, which was mostly related to the body mass index (BMI), total body fat and lean body mass.^{12,13} In well-designed studies, in populations of Sweden and the United States of America (USA), the interactions between HLA genotype and BMI of 20-year-old people were investigated, where it was shown that obesity was associated with an increased risk of MS compared to people with normal weight body.¹⁴

The influence of obesity on MS was confirmed by a large longitudinal study, which included nurses in the USA (Nurses Health Study and

Nurses Health Study II). The results of this study showed that obesity at the age of 18 years was related to a doubled risk of developing MS, compared to the individuals with normal BMI, while such a correlation was not found in the adult population.¹⁵ Munger et al¹⁶ in a long-term cohort study also examined children from 7-13 years of age and the results showed that obesity in this age carries a higher risk for the development of MS.

A large multinational EnvIMS study that included populations in Italy and Norway has shown that an increased body weight, in particular at the age of 20-25, poses a risk for the MS in Norwegian population, which partly also applies to the Italian population, but without reaching statistical significance. These results are compatible with low levels of vitamin D and a chronic inflammatory condition in the obese, which may originate from the differences in protective exposure to the sun.¹⁷ These data are significant, because in other studies lower levels of vitamin D metabolites in obese human subjects were observed and, among other things, this is why overweight status in infancy may be a risk factor for MS.¹⁸⁻²¹ Most recent studies confirmed the impact of obesity on the occurrence of MS in paediatric patients as well as on a weaker response to the drugs of the first-line therapy in the obese patients.²² It is also important to know that certain genetic structure is a common predictor for the elevated BMI before the onset of MS as well as for the occurrence of the disease.²³

Why are these findings important? The survey data show that in the period from 2009 to 2010, 16.9 % of children and adolescents in the USA were obese. Although genetic and some other causes that lead to the disease cannot be affected, it is important to influence the environmental factors that are suitable for modification.²⁴

The aim of this study was to determine the value of BMI in the population of people with MS compared to the general population, to estimate the association of BMI and the degree of physical disability in patients with MS and to estimate the possible influence of BMI on the course and the progression of the disease.

Methods

This cross-sectional study was conducted at the Clinic of Neurology, University Clinical Centre of the Republic of Srpska, Banja Luka. The sample consisted of 100 MS patients and 50 healthy people (control group) from general population, matched according to sex and age and who were not blood-related to the MS patients, who did not have an inflammatory disease of the CNS nor a cerebrovascular disease and did not use statins (control group). The duration of the study was twelve months.

The research was performed upon prior approval of the Ethics Committee of the University Clinical Centre of the Republic of Srpska, Banja Luka. For this study a general questionnaire, consisting of questions related to the demographic and clinical characteristics of patients and the questionnaire for risk factors for vascular diseases in patients with MS, which was created for the scientific purposes at the Institute of Epidemiology, Faculty of Medicine, University of Belgrade were used. In order to determine the degree of physical disability, the Expanded Disability Status Scale (EDSS) was used.²⁵ BMI was defined as the body weight (BW) in kilograms divided by the surface area measured in square meters.²⁶ BMI was determined in both groups of participants and based on its value participants were classified in following groups: reduced BMI (less than 18.5 kg/m²), normal BMI (18.5-24.9 kg/m²) and people with increased BMI (more than 25 kg/m² - overweight status and over 29.9 kg/m² - obesity).

Statistical analyses included methods of descriptive statistics, χ^2 test, Student t-test, variance analysis, correlations and regression analysis.

Results

From a total of 100 patients with MS, 25 % were male and 75 % female. The average age of participants at the beginning of the study was 41.9 \pm 10.1 years in the MS group, while participants from the control group were slightly older (average age 42.1 \pm 12.3 years). The distribution of patients according to the clinical form of the disease is shown in Figure 1.

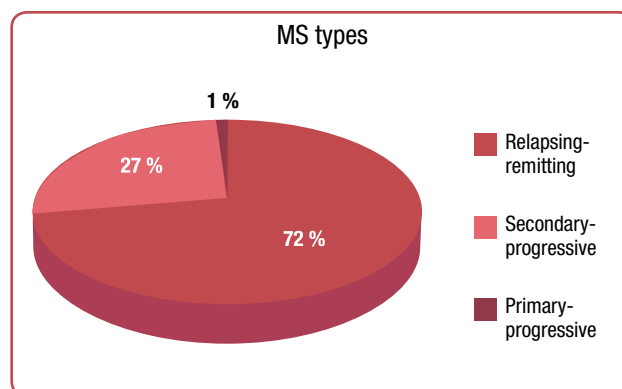


Figure 1. Distribution of clinical types of MS in the group of patients (n=100)

The average value of the EDSS score in the group of patients was 3.7. Based on the quotient of these values and the duration of the disease, the mean value of the index of disease progression was obtained, which in this patient group was 0.9.

Table 1. Parameters of patients with multiple sclerosis (MS) and the control group

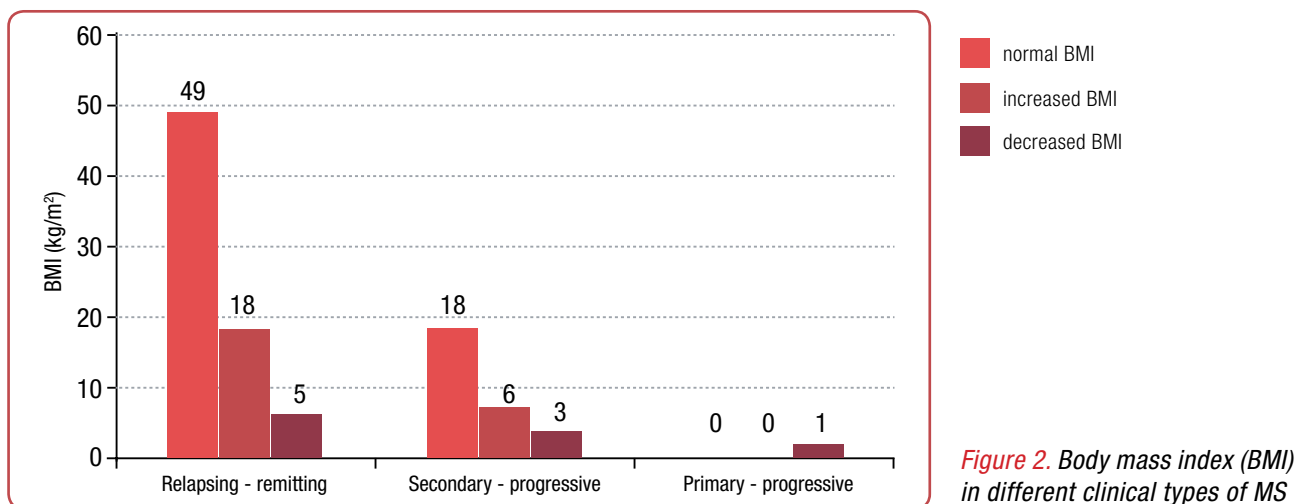
| Parameter | MS patients (n = 100) | Control group (n = 50) |
|--|-----------------------|------------------------|
| Age (years) | 41.9 \pm 10.1 | 42.1 \pm 12.3 |
| Body weight (BW, kg) | 67.1 \pm 13.2 | 76.1 \pm 16.3* |
| Body mass indeks (BMI, kg/m ²) | 22.7 \pm 3.1 | 36.0 \pm 4.4* |

* $p < 0.05$ versus the MS group

In both groups parameters necessary for calculation of the BMI–BW and body height – were registered (Table 1).

Although the MS patients and their controls were matched by age, the average BW and BMI were significantly lower in the MS group. Values of BMI fell within a normal range in the MS group, while they were increased in terms of obesity in the control group.

The group of patients with MS was analysed according to the form of the disease. In order to establish whether there is a correlation between the clinical types of the disease and the BMI (classified in the pathological and normal level), the chi-square test was used and showed a statistically significant correlation ($p = 0.031$). More specifically, there was a correlation between the clinical types of MS and the fact whether BMI has pathological or normal values. BMI was a factor that changed during the disease progression and there was a higher incidence of lower values of this parameter with the progression of the disease, ie the transition from relapsing-remitting (RR) in the secondary progressive (SP) form (Figure 2).



Among the patients with RR form, 68.1 % had a normal BMI, 25 % increased and 6.9 % decreased. In the SP group, 66.7 % of patients had a normal BMI, 22.2 % increased and 11.1 % decreased. One patient, suffering from a primary progressive (PP) form of the disease, had decreased BMI.

Using logistic regression methods (univariate analysis) the parameters that could be predictors of MS and thereby determined that the coefficient for the normal BMI was positive, ie that normal values of BMI increase odds ratio and the probability that the patient has MS were analysed.

Discussion

So far, there have been a series of studies involving the assessment of BMI in the population of patients with MS. Our results are in agreement with the hereinafter mentioned best-designed studies conducted on this topic in other environments. A highly significant difference in the values of BMI ($p < 0.05$) in the group of MS patients compared to the control group (average value of BMI in the experimental group was within the normal range, whereas it was increased in the control group) is a consequence of the lower BW of this group of patients.

The study of Markianosa et al²⁷ showed that women suffering from MS had a lower BMI compared to age- and gender-matched controls, while substantial differences were not found among male patients. Their results showed that patients suffering from MS were overweight at a younger age and later on even had a lower BMI, a fact to which attention should be paid, in the context of a po-

ssible weight loss with the disease progression in certain populations.

The study of Nortvedt et al²⁸ observed a gender-mixed population (75 % female) of MS patients compared to healthy individuals, where the average values of the BMI were $23.5 \pm 3.6 \text{ kg/m}^2$, with 11 % of subjects with a BMI below 20 kg/m^2 . Low BMI values was observed in several studies in the population of MS patients compared to healthy controls, wherein there was also a significant, inverse correlation between the high BMI and the risk of developing MS.²⁹⁻³⁴

The study of Pike et al³⁵ found an average BMI of 23.9 kg/m^2 for the tested MS population from five European countries, which is within the normal range of values.³⁵ In some other studies, BMI values in patients with MS were in the range of those in the general population.^{36, 37}

A large meta-analysis of clinical trials conducted on this subject also showed a significantly lower BMI in the group of MS patients than in healthy controls and the same results were obtained for patients who had the RR form of the disease.³⁸ However, some other studies have shown conflicting results to those previously shown and also to this study's results. This may be the case because these investigations were conducted in certain regions of the world where the prevalence of obesity in the general population was higher due to the nutrition style, socio-economic conditions and less physical activity. Besides, some of these studies were performed as retrospective analyses of data from the registries dating from the 1980s, when the awareness of the need for prevention of factors affecting the cardiovascular and other diseases was significantly lower than today.¹⁰



A study in patients from the NARCOMS registry, the largest registry of MS worldwide, showed that over 50 % of patients with MS were overweight.³⁹ Similar data on the increased frequency of obesity in the population of MS patients have been shown in other several studies.⁴⁰⁻⁴⁵

In the present study, in the experimental group, a lower mean BMI value (although within a normal range) compared to the control group can be interpreted in the context of the application of immunomodulatory therapy. Namely, a significant number of patients had been treated with interferon beta-1b (34 %), whose one of the possible adverse effects is a reduction of BW.^{12, 46}

The results obtained in the present study can be explained by the fact that MS patients were under a constant medical supervision, in touch with their therapists who gave them advice on proper diet, need for physical activity and other measures of hygienic and dietetic regimens, which led to the levelling of body weight, as opposed to healthy the individuals in the control group.

Regarding the physical disability and its dependence on the value of the BMI, the results of clinical trials conducted so far were inconsistent. In the present study, there was no correlation between these two parameters, which can be interpreted by the fact that the patients from the experimental group had a higher percentage of normal values of BMI compared to the control group. However, in several studies conducted in a population of MS patients, there was a positive correlation between the degree of physical disability and the BMI.⁴⁷⁻⁴⁹

The inverse impact of the BMI on physical disability was also recorded in the research of Flauzino et al⁵⁰ In several studies as well as in the present one, it was shown that BMI may be considered as a factor that can change during the progression of the disease and that there was an increased incidence of lower values of this parameter with the progression of the disease ie with the transition from RR to SP form.³⁹

Obesity, among other factors such as gender, age, genetic profile and smoking, has a disease-modifying effect by forming its phenotypic presentation and contributes to the occurrence and progression of MS.^{51, 52} Research performed at the molecular level showed that high BMI negatively affected the course and form of MS, since the existence of obesity leads to a modulation of the

number of monocytes through the ceramide-induced DNA methylation of the antiproliferative genes.⁵³ MRI studies showed that lifestyle factors, including obesity, influenced the acceleration of cerebral atrophy, and the appearance of new lesions in patients with MS.⁵⁴

Prediction of the MS course is nowadays one of the foci of considerable research. In this study, normal BMI values were shown as a predictive factor for the onset of the MS. However, in other investigations conducted on this topic results were inconsistent. In one of them, BMI has shown a correlation with the progression of the disease and a higher frequency of relapses but was in no correlation with the prediction of the conversion from a clinically isolated syndrome to MS.⁵⁵ In other studies it was shown that in a population of MS patients during the one year follow-up there was an increase in physical disability, but there were minimal pieces of evidence that BMI was a predictive factor for this change.⁵⁶

Taiwanese researchers have shown that the BMI values below the normal range with more than four demyelinating lesions are a strong predictor for the conversion from a clinically isolated syndrome to MS.⁵⁷ It was also confirmed that the BMI values affected the prediction of cognitive disorders in patients suffering from MS.⁵⁸

Conclusion

So far, in several studies, the BMI has been studied as a factor influencing the onset of MS. Results of this study showed that BMI affected the progression and prediction of the disease, but not the degree of physical disability of patients with MS. To prevent these undesirable effects, it is very important to emphasise that this environmental factor is suitable for modification.

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Conflict of interest

None.

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