PROFESSIONAL ARTICLES
STRUČNI ČLANCI

University of Novi Sad, Faculty of Medicine Novi Sad
Department of Pathophysiology and Laboratory Medicine[1]
Clinical Center of Vojvodina, Novi Sad
Center of Laboratory Medicine[2]
Clinic of Neurology[3]

Professional article
Stručni članak
UDK 616.832-004.2:616-008.9
https://doi.org/10.2298/MPNS2208237S

TRIGLYCERIDE GLUCOSE INDEX IN PATIENTS WITH MULTIPLE SCLEROSIS

INDEKS TRIGLICERIDA I GLUKOZE KOD PACIJENATA SA MULTIPLOM SKLEROZOM

Maša SLADOJEVIĆ[1, 2], Tanja ŠAŠIĆ OSTOJIĆ[1, 2], Stanislava NIKOLIĆ[1, 2], Željko ŽIVANOVIĆ[1, 3], Branislava ILINČIĆ[1, 2] and Velibor ČABARKAPA[1, 2]

Summary

Introduction. Multiple sclerosis is a chronic, inflammatory disease of the central nervous system characterized by areas with inflammatory changes associated with demyelination. Cholesterol is a significant structural component of the central nervous system incorporated into the myelin sheath. The aim of study was to examine values of lipid status parameters in patients with multiple sclerosis and the correlation between these parameters and the triglyceride glucose index. **Material and Methods.** A retrospective study included 28 patients with multiple sclerosis. Medical records of the Clinic of Neurology and databases of the Center of Laboratory Medicine, Clinical Center of Vojvodina were analyzed**.** Based on the obtained data of the glycemic index and lipid profile, triglyceride glucose index was calculated. **Results.** Borderline elevated values of total cholesterol and low-density cholesterol (5.25 ± 1.08 mmol/L; 3.90 ± 4.54) were found in patients with multiple sclerosis. Linear correlation analysis showed a statistically positive correlation between triglyceride glucose index and total cholesterol (r = 0.572; p = 0.01), low-density cholesterol (r = 0.256; p = 0.05) and low-density cholesterol to high-density cholesterol ratio (r = 0.502); p = 0.01). No statistically significant correlation between triglyceride glucose index and high-density cholesterol was observed. **Conclusion.** The examined group with multiple sclerosis had borderline elevated values of total cholesterol and low-density cholesterol. There is a significant correlation between the triglyceride glucose index and values of total cholesterol, low-density cholesterol, as well as the low-density cholesterol to high-density cholesterol ratio.

Key words: Multiple Sclerosis; Triglycerides; Blood Glucose; Lipids; Glycemic Index; Insulin Resistance; Cholesterol, LDL; Cholesterol, HDL

Sažetak

Uvod. Multipla skleroza je hronično, inflamatorno oboljenje centralnog nervnog sistema koje karakterišu izolovana područja zapaljenjskih promena udruženih sa demijelinizacijom. Unutar centralnog nervnog sistema, holesterol je većinski inkorporiran u mijelinski omotač, te predstavlja značajnu strukturnu komponentu. Cilj rada bilo je ispitivanje vrednosti parametara lipidskog statusa kod pacijenata obolelih od multiple skleroze i stepena povezanosti navedenih parametara sa indeksom triglicerida i glukoze. **Materijal i metode.** Retrospektivna studija obuhvatila je 28 pacijenata obolelih od multiple skleroze. Uvidom u medicinsku dokumentaciju Klinike za neurologiju i baze podataka Centra za laboratorijsku medicinu Kliničkog centra Vojvodine preuzete su izmerene vrednosti glikemije u bazalnim uslovima, vrednosti parametara lipidskog statusa i izračunata je vrednost indeksa triglicerida i glukoze. **Rezultati.** Kod obolelih od multiple skleroze uočavaju se granično povišene vrednosti ukupnog holesterola i holesterola niske gustine (5,25 ± 1,08 mmol/l; 3,90 ± 4,54). Linearnom korelacionom analizom triglicerida i glukoze utvrđena je statistički pozitivna korelacija indeksa sa vrednostima ukupnog holesterola (r = 0,572; p = 0,01), holesterola niske gustine (r = 0,256; p = 0,05), i vrednostima odnosa holesterola niske i visoke gustine (r = 0,502; p = 0,01). Nije uočena statistički značajna korelacija indeksa triglicerida i glukoze sa vrednostima holesterola visoke gustine. **Zaključak.** Ispitivana grupa imala je granično povišene vrednosti ukupnog i holesterola niske gustine. Postoji značajna korelacija indeksa triglicerida i glukoze sa vrednostima ukupnog, holesterola niske gustine, kao i sa vrednostima odnosa holesterola niske i visoke gustine.

Ključne reči: multipla skleroza; trigliceridi; glikemija; lipidi; glikemijski indeks; insulinska rezistencija; LDL holesterol; HDL holesterol

Introduction

Demyelinating diseases are disorders of the central and peripheral nervous system which are characterized by damage to the myelin sheath of neurons. Various causes, such as infectious, toxic, metabolic and autoimmune processes may lead to the damage of the myelin sheath. The most common

Corresponding Author: Asist. dr Maša Sladojević, Medicinski fakultet Novi Sad, KCV-Centar za laboratorijsku medicinu, 21000 Novi Sad, Hajduk Veljkova 1-7, E-mail: masa.todorovic@mf.uns.ac.rs

Abbreviations

CNS	– central nervous system
MS	– multiple sclerosis
HDL	– high-density cholesterol
LDL	– low-density cholesterol
TyG	– triglyceride glucose
HOMA-IR	– homeostasis model assessment of insulin resistance

demyelinating disease of the central nervous system (CNS) is multiple sclerosis (MS) [1].

Today, it is believed that MS is an autoimmune disease that occurs in genetically predisposed individuals, i.e. individuals who possess an altered major histocompatibility complex on chromosome 6 [1]. The development of the disease in genetically predisposed individuals is associated with a certain "trigger" (viral infection, psychological stress, toxins, physical trauma...). The transendothelial migration of activated lymphocytes from the blood into the brain tissue is the main cause of inflammatory lesions of CNS. As a result of the activation of the immune system in the nervous tissue there is an abundant intrathecal synthesis of class G immunoglobulins by individual clones of activated lymphocytes [1].

Generally, MS is diagnosed between the age of 20 and 40 years (~70%) twice as often in women than in men [2]. The disease has a variable course, and on the one hand the predominant clinical presentation is benign MS which implies the existence of minimal disability, while on the other hand, the rapid progression of the disease may lead to severe disability or death. Multiple sclerosis greatly impairs the quality of life, and a large number of patients are confined to a wheelchair. About 15% of patients in the final stages of the disease require full supervision and care. About 50% of MS patients die from complications that occur during the course of disease [2].

Cholesterol is an important structural component of the CNS. Approximately 25% of total cholesterol in the body is found in the CNS [3], mostly as a structural component of the myelin sheath, while smaller amounts of cholesterol originate from the plasma membranes of astrocytes and neurons. In addition to its structural role, cholesterol plays a significant role in maintaining the morphology of neurons, as well as synaptic transmission. Multiple sclerosis is characterized by the destruction of myelin, as well as changes in lipid metabolism within the CNS. Lipids, especially lipoproteins, are involved in the regulation of nerve functions in the CNS by different metabolic mechanisms. High-density lipoproteins (HDL) and low-density lipoproteins (LDL) play a key role in the transport of cholesterol and lipids in plasma, primarily HDL particles have immunomodulatory and antioxidant effects on endothelial cells [4]. The pathophysiological mechanisms of changes in plasma lipid levels in MS patients have not yet been fully clarified. Some studies point primarily to the significant role of the autonomic nervous system on lipolysis and lipoprotein metabolism [5]. It is thought that lipolysis caused by increased sympathetic activity may be one of the potential pathophysiological mechanisms leading to dyslipidemia in patients with MS. The aim in this study is to determine the parameters of lipid status in patients with MS and to examine the association between these parameters and the triglyceride glucose (TyG) index as an indicator of insulin resistance.

Material and Methods

This retrospective study was conducted at the Clinical Center of Vojvodina after obtaining the approval of the Ethics Committee of this institution.

The study included 28 medical history data of patients with the diagnosis of MS. Patients with acute infections, thyroid dysfunction, liver disease, and malignancy were excluded from the study.

In all the respondents, plasma glucose was determined by a standard enzyme-specific glucose oxidase and phenol aminophenazone peroxidase method using a biochemical analyzer Abbott Architect c 8000. The reference values for glucose are 3.9 - 6.1 mmol/L.

Serum concentrations of total cholesterol, HLD-cholesterol and triglycerides were determined automatically, using the biochemical analyzer Abbott Architect 4,000 and commercial sets. Recommended reference values for total cholesterol do not exceed 5.19 mmol/L, border risk values are 5.20 - 6.19 mmol/L, and high-risk values are ≥ 6.20 mmol/L; for triglyceride do not exceed 1.70 mmol/L, border-risk values are 1.70 - 2.29 mmol/L, and high-risk values are ≥ 2.30 mmol/L; desirable values for HDL-cholesterol are above 1.60 mmol/L for both sexes, the border risk values are 1.00 - 1.60 mmol/L, and high risk values are ≤ 1.00 mmol/L.

The LDL-cholesterol was determined indirectly by the Friedewald formula. Recommended reference values for LDL-cholesterol do not exceed 3.40 mmol/L, border risk values are 3.40 - 4.09 mmol/L, and high-risk values are ≥ 4.10 mmol/L [1].

In all patients the TyG index was calculated using the formula:

$$\text{TyG index} = \frac{\ln(\text{triglycerides (mg/dL)} \times \text{glucose (mg/dL)})}{2}$$

Complete statistical analysis was done using the Excel Data Analysis (Microsoft Corp, Redmond, WA) statistical software. The results are shown in tables.

Results

This retrospective study included 28 patients with MS.

Borderline elevated values of total cholesterol and LDL-cholesterol were found in patients with MS: 5.25 ± 1.08 mmol/L; 3.90 ± 4.54 mmol/L, respectively, while the TyG index values were 4.49 ± 0.32 mmol/L. The values of other tested parameters did not differ from the reference values **(Table 1)**.

Linear correlation analysis showed a statistically significant positive correlation between the TyG index and the values of total cholesterol ($r = 0.572$; $p < 0.01$),

Table 1. Characteristics of the respondents
Tabela 1. *Karakteristike ispitanika*

	MS/*MS*
Gender/*Pol*	M/*M* =10 F/*Ž* = 18
Years/*Godine*	45.1 ± 9.6
Glucose (mmol/L)/*Glukoza (mmol/L)*	5.02 ± 0.74
Cholesterol (mmol/L)/*Holesterol (mmol/L)*	5.25 ± 1.08
Triglycerides (mmol/L)/*Triglicerdi (mmol/L)*	1.22 ± 0.79
HDL cholesterol (mmol/L)/*HDL holesterol (mmol/L)*	1.54 ± 0.36
LDL cholesterol (mmol/L)/*LDL holesterol (mmol/L*)	3.90 ± 4.54
LDL/*HDL*	2.19 ± 0.84
TyG index/*TyG indeks*	4.49 ± 0.32

Legend: HDL - high-density cholesterol; LDL - low-density cholesterol; LDL/HDL - low to high density cholesterol ratio; TyG index - triglyceride glucose index
Legenda: HDL - holesterol visoke gustine, LDL - holesterol niske gustine; LDL/HDL – odnos holesterola niske i visoke gustine; TyG indeks - indeks triglicerida i glukoze

Table 2. Linear correlation analysis
Tabela 2. *Linearna korelaciona analiza*

n = 28	TyG index/*TyG indeks*	
	r	p
Total cholesterol/*Ukupni holesterol*	0.572	0.01
LDL cholesterol/*LDL holesterol*	0.256	0.05
LDL/*HDL*	0.502	0.01
HDL cholesterol/*HDL holesterol*	- 0.191	0.102

Legend: HDL - high-density cholesterol; LDL - low-density cholesterol; LDL/HDL - low to high density cholesterol ratio; TyG index - triglyceride glucose index; r - correlation coefficient; p - statistical significance
Legenda: HDL – holesterol visoke gustine, LDL – holesterol niske gustine; LDL/HDL – odnos holesterola niske i visoke gustine; TyG indeks – indeks triglicerida i glukoze; r – koeficijent korelacije; p – statistička značajnost

LDL-cholesterol ($r = 0.256$; $p < 0.05$), and the LDL/HDL ratio ($r = 0.502$; $p < 0.01$). There was no statistically significant correlation between the TyG index and HDL-cholesterol values.

Discussion

Multiple sclerosis is a chronic, inflammatory disease of the CNS characterized by numerous isolated areas with inflammatory changes (plaques) associated with demyelination. Considering that MS is a disease that contributes to early disability, disclosure of the diagnosis at the right time is necessary. The diagnosis of MS is based on several factors, clinical symptoms, magnetic neuroimaging, and blood and cerebrospinal fluid laboratory testing.

Laboratory tests have a very important place in the diagnosis of MS, primarily the cerebrospinal fluid analysis. The cerebrospinal fluid analysis of the lumbar puncture includes macroscopic examination, cytological examination, biochemical tests, as well as electrophoretic techniques and examination of the degree of intrathecal synthesis of immunoglobulins. Oligoclonal bands in the cerebrospinal fluid indicate the intrathecal synthesis of immunoglobulins and it is found in approximately 90% of patients with MS [6].

The diagnosis of MS is based on a combination of clinical and paraclinical criteria. Diagnostic algorithms that are used today are recommended by the International Commission for the Diagnosis of MS (revised McDonald Criteria) [7–9].

In this study, elevated values of certain lipid parameters (total cholesterol and LDL-cholesterol) were observed in patients with MS. Similar results were reported by other studies [10, 11], clearly showing elevated levels of total cholesterol in MS patients compared to the healthy population. Also, some studies indicate a significant correlation of high plasma cholesterol levels with cognitive impairment and significant clinical disability in MS [12], which indicates the importance of determining this parameter of lipid metabolism.

In this study, mean triglyceride values were within the reference range, which is in accordance with other studies, indicating no significant deviations of the triglyceride values in the group of subjects with MS [11, 13]. However, the results of the study by Weinstock et al. showed significantly higher triglyceride values in patients with MS [14].

Changes in energy metabolism in MS patients have not been fully clarified. Certain studies point to the possibility of the sympathetic nervous system, the hypothalamus, affecting the energy metabolism

[14]. Autonomic dysfunction, primarily increased sympathetic activity, in combination with reduced physical activity, may be considered as a significant pathophysiological mechanism for early dysregulation of glucose metabolism [15]. Recent studies also indicate an important role of the hypothalamus in triglyceride metabolism primarily through the innervation of the liver, white and brown adipose tissue mainly through the sympathetic innervation of the autonomic nervous system. Some neurons, such as neuropeptide Y and neurons which express melanocortin as well as some hormones may affect the sympathetic response of the hypothalamus to target organs and thus affect the peripheral metabolism of triglycerides [16].

In this study, the TyG index was calculated in the group of subjects with MS in order to assess insulin resistance. According to the study results, the mean TyG index was 4.49 ± 0.32 mmol/L, which is in agreement with other studies examining insulin resistance in patients with MS [17]. According to the literature data, the TyG index was in the range of 4 - 8. Given the relatively wide range of normal values, finer changes in energy metabolism could be monitored by this parameter as a surrogate index of insulin resistance [18].

Certain studies showed a significant correlation between the TyG index and the homeostasis model assessment of insulin resistance (HOMA-IR) index, and pointed to the fact that this index could be used in the assessment of insulin resistance in routine clinical practice, considering that it only includes data from basic laboratory analyses, i.e. basal blood glucose and triglyceride levels [19, 20].

Systemic chronic inflammation is considered to be one of the important pathophysiological factors in the pathogenesis of insulin resistance [21]. There are numerous studies that indicate the existence of insulin resistance, compensated by hyperinsulinemia in certain neurodegenerative diseases [22]. A study by Oliveira et al. [23] showed the existence of insulin resistance in approximately 40% of MS patients compared to the control group, based on the value of the HOMA index.

To quantify the insulin resistance, several indices are used today, primarily the HOMA index [24], but other indices are also used, such as TyG index, which assesses insulin resistance based on basal blood glucose and triglyceride levels. The TyG index provides assessment of insulin resistance without determination of basal insulin and it can be considered a quick and simple test for establishing the existence of insulin resistance [25].

The pathophysiological mechanisms of insulin resistance in patients with MS have not been fully explained. Some authors point to the dysregulation of the autonomic nervous system as a potential cause of metabolic disorders, i.e. the development of insulin resistance while on the other hand the resulting hyperinsulinemia additionally activates the sympathetic nervous system [26]. In addition, physical inactivity, reducing the content of mitochondria, reduces the sensitivity of cells to insulin, and according to some authors, it is an important factor of insulin resistance in these patients [27]. Also, insulin resistance with proatherogenic lipid profile is considered to be a contributing factor in the occurrence and development of atherosclerosis [28].

The results we obtained showed borderline elevated values of total cholesterol and LDL-cholesterol in patients with MS. There was a significant correlation between the TyG index and values of total cholesterol, LDL-cholesterol, and the LDL/HDL ratio. In relation to all of the above, in patients with MS, it would be useful to determine the lipid status parameters, as well as indicators of insulin resistance, as an additional diagnostic tool in monitoring the progression of the underlying disease.

Conclusion

Borderline elevated values of total cholesterol and low-density cholesterol were found in patients with multiple sclerosis. There is a significant correlation between the triglyceride glucose index and the values of total cholesterol, low-density cholesterol, as well as the low-density cholesterol to high-density cholesterol ratio.

References

1. Reich DS, Lucchinetti CF, Calabresi PA. Multiple sclerosis. N Eng J Med. 2018;378(2):169-80.

2. Ascherio A. Environmental factors in multiple sclerosis. Expert Rev Neurother. 2013;13(12 Suppl):3-9.

3. Dietschy JM, Turley SD. Thematic review series: brain lipids. Cholesterol metabolism in the central nervous system during early development and in the mature animals. J Lipid Res. 2004;45(8):1375-97.

4. Weinstock-Guttman B, Živadinov R, Mahfooz N, Carl E, Drake A, Schneider J, et al. Serum lipid profiles are associated with disability and MRI outcomes in multiple sclerosis. J Neuroinflammation. 2011;8:127.

5. Bartness TJ, Sherestha YB, Vaughan CH, Schwartz GJ, Song CK. Sensory and sympathetic nervous system control of white adipose tissue lipolysis. Mol Cell Endocrinol. 2010;318(1-2):34-43.

6. Bourahoui A, De Seze J, Guttierez R, Onraed B, Hennache B, Ferriby D, et al. CSF isoelectrofocusing in a large cohort of MS and other neurological diseases. Eur J Neurol. 2004;11(8):525-9.

7. Čovičković Šternić N, editor. Nacionalni vodič dobre kliniče prakse za dijagnostikovanje i lečenje multiple skleroze. Beograd: Ministrastvo zdravlja Republike Srbije; 2013.

8. Deisenhammer F, Zetterberg H, Fitzner B, Zettl UK. The cerebrospinal fluid in multiple sclerosis. Front Immunol. 2019;10:726.

9. Simonsen CS, Flemmen HØ, Lauritzen T, Berg-Hansen P, Moen SM, Celius EG. The diagnostic value of IgG index versus oligoclonal bands in cerebrospinal fluid of patients with multiple sclerosis. Mult Scler J Exp Transl Clin. 2020;6(1): 2055217319901291.

10. Noori H, Gheini MR, Rezaeimanesh N, Saeedi R, Rezaei Aliabadi H, Sahraian MA, et al. The correlation between dyslipidemia and cognitive impairment in multiple sclerosis patients. Mult Scler Relat Disord. 2019;36:101415.

11. Radikova Ž, Penesova A, Vlček M, Havranova A, Sivakova M, Siarnik P, et al. LDL and HDL lipoprotein subfractions in multiple sclerosis patients with decreased insulin sensitivity. Endocr Regul. 2018;52(3):139-45.

12. Zhornitsky S, McKay KA, Metz LM, Teunissen CE, Rangachari M. Cholesterol and markers of cholesterol turnover in multiple sclerosis: relationship with disease outcome. Mult Scler Relat Disord. 2016;5:53-65.

13. Radikova Ž, Penesova A, Vlček M, Havranova A, Sivakova M, Šiarnik P, et al. Lipoprotein profiling in early multiple sclerosis patients: effect of chronic inflammation? Lipids Health Dis. 2020;19(1):49.

14. Seoane-Collazo P, Fernø J, Gonzalez F, Dièguez C, Leis R, Nogueiras R, et al. Hypothalamic-autonomic control of energy homeostasis. Endocrine. 2015;50(2):276-91.

15. Carnethon MR, Jacobs DR Jr, Sidney S, Liu K; CARDIA study. Influence of autonomic nervous system dysfuction on the development of type 2 diabetes: the CARDIA study. Diabetes Care. 2003;26(11):3035-41.

16. Geerling JJ, Boon MR, Kooijman S, Parlevliet ET, Havekes LM, Romijn JA, et al. Sympathetic nervous system control of trygliceride metabolism: novel concepts derived from recent studies. J Lipid Res. 2014;55(2):180-9.

17. Penesova A, Vlček M, Imrich R, Vernerova L, Marko A, Meskova M, et al. Hyperinsulinemia in newly diagnosed patients with multiple sclerosis. Metab Brain Dis. 2015;30(4): 895-901.

18. Placzkowska S, Pawlik-Sobecka L, Kokot I, Piwowar A. Indirect insulin resistance detection: current clinical trends and laboratory limitations. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2019;163(3):187-99.

Rad je primljen 14. X 2022.
Recenziran 7. XII 2022.
Prihvaćen za štampu 12. XII 2022.
BIBLID.0025-8105:(2022):LXXV:7-8:237-241.

19. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, Martínez-Abundis E, Ramos-Zavala MG, Hernández-González SO, et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. J Clin Endocrinol Metab. 2010;95(7):3347-51.

20. Lee EY, Yang HK, Lee J, Kang B, Yang Y, Lee SH, et al. Triglyceride glucose index, a marker of insulin resistance, is associated with coronary artery stenosis in asymptomatic subjects with type 2 diabetes. Lipids Health Dis. 2016;15(1):155.

21. Kim JH, Bachmann RA, Chen J. Interleukin-6 and insulin resistance. Vitam Horm. 2009;80:613-33.

22. Watson GS, Craft S. Insulin resistance, inflamation, and cognition in Alzheimer's disease: lessons for multiple sclerosis. J Neurol Sci. 2006;245(1-2):21-33.

23. Oliveira SR, Simao AN, Kallaur AP, de Almeida AR, Morimoto HK, Lopes J, et al. Disability in patients with multiple sclerosis: influence of insulin resistance, adiposity and oxidative stress. Nutrition. 2014;30(3):268-73.

24. Nikolić S, Ćurić N, Mijović R, Ilinčić B, Benc D. Significance and role of homeostatic model assessment in the evaluation of glucose regulation mechanisms. Med Pegl. 2017;70(5-6):155-61.

25. Unger G, Benozzi SF, Perruzza F, Pennacchiotti GL. Triglycerides and glucose index: a useful indicator of insulin resistance. Endocrinol Nutr. 2014;61(10):533-40.

26. Adamec I, Habek M. Autonomic dysfunction in multiple sclerosis. Clin Neurol Neurosurg. 2013;115 Suppl 1:S73-8.

27. Bergouignan A, Rudwill F, Simon C, Blanc S. Physical inactivity as the culprit of metabolic inflexibility: evidence from bed-rest studies. J Appl Physiol (1985). 2011;111(4):1201-10.

28. Dichi I, Simao AN. Metabolic syndrome: new targets for an old problem. Expert Opin Ther Targets. 2012;16(2):147-50.