TIMOČKI MEDICINSKI GLASNIK

TIMOK MEDICAL GAZETTE

Glasilo zaječarske podružnice Srpskog lekarskog društva **Izlazi od 1976.**
The Bulletin of the Zajecar branch of the Serbian Medical Association **has been published since 1976.**

Godina 2023 *Vol. 48 Broj 1*
Year 2023 *Vol. 48 No. 1*

YU ISSN 0350-2899

B. Dinić, Zaječar,2000

www.tmg.org.rs *tmglasnik@gmail.com*

TIMOČKI MEDICINSKI GLASNIK

TIMOK MEDICAL GAZETTE

Glasilo zaječarske podružnice Srpskog lekarskog društva **Izlazi od 1976.**
The Bulletin of the Zajecar branch of the Serbian Medical Association **has been published since 1976.**

VLASNIK I IZDAVAČ/OWNER AND PUBLISHER

Srpsko lekarsko društvo, podružnica Zaječar/
Serbian Medical Society, Branch of Zaječar
web adresa/web address: www.sldzajecar.org.rs

ADRESA REDAKCIJE/EDITORIAL OFFICE
Timočki medicinski glasnik
Zdravstveni centar Zaječar
Pedijatrijska služba
Rasadnička bb, 19000 Zaječar

ADRESA ELEKTRONSKE POŠTE/E-MAIL
tmglasnik@gmail.com
dusanbastac@gmail.com

WEB ADRESA/WEB ADDRESS
www.tmg.org.rs

Časopis izlazi četiri puta godišnje./The Journal is published four times per year.

TEKUĆI RAČUN/ CURRENT ACCOUNT
Srpsko lekarsko društvo, podružnica Zaječar 205-167929-22

ŠTAMPA/PRINTED BY
Spasa, Knjaževac

TIRAŽ/CIRCULATION 500 primeraka/500 copies

CIP - Каталогизација у публикацији
Народна библиотека Србије, Београд

61
TIMOČKI medicinski glasnik /
glavni i odgovorni urednik Prim Dr Sc med Dušan Bastać; - God. 1, br. 1 (1976)-
- Zaječar : Srpsko lekarsko društvo, podružnica Zaječar, 1976- (Knjaževac : Spasa). - 30 cm

Dostupno i na: http://www.tmg.org.rs. - Tromesečno
ISSN 0350-2899 = Timočki medicinski glasnik
COBISS.SR-ID 5508610

RECENZENTI TIMOČKOG MEDICINSKOG GLASNIKA 2006-2020

Bastać Dušan
Beleslin Branko
Biočanin Vladimir
Bjelaković Goran
Bogavac Mirjana
Bulat Petar
Čovičković Šternić Nadežda
Ćuk Vladimir
Cvejić Vesna
Cvetković Zorica
Čvorović Vojkan
Čvorović Ljiljana
Dikić Đorđević Ana
Dimitrijević Milovan
Đorđević Nataša
Đorđević Vidojko
Golubović Zoran
Ignjatović Mile
Ilić Vekoslav
Jakovljević Vladimir
Jelenković Bratimirka
Joksimović Zoran
Jozić Tanja
Kocić Gordana
Krstić Zoran
Manojlović Snežana
Martinović Žarko
Micić Dragan
Milenković Branislava
Mitrović Predrag
Mitrović Slobodan
Mladenović Zorica
Nikolić Maja
Nikolić Slobodan
Panajotović Ljubomir
Pejčić Tatjana
Pešić Srđan
Radojčić Ljiljana
Ranković Žarko
Romić Predrag
Runić Slobodan
Saravolac Siniša
Šijački Ana
Spalević Ljiljana
Srzentić Snežana
Stančić Ivica
Suvajdžić Vuković Nada
Tirmenštajn-Janković Biserka
Todorović Jelisaveta
Trbojević Božo
Vasiljević Mladenko
Veljković Radovan
Vučetić Dušan
Žigić Dane
Živić Saša
Živković Zorica
Živojinović Vesna

C O N T E N T S

ORIGINAL PAPERS

REVIEW ARTICLE

CASE REPORT

THE EFFECT OF THE METABOLIC SYNDROME ON THE INCIDENCE AND DEGREE OF LEFT VENTRICULAR MYOCARDIAL HYPERTROPHY IN HYPERTENSIVE PATIENTS

Igor Đorđijoski (1), Maja Mladenović (1), Anastasija Raščanin (2), Mila Bastać (3), Zoran Joksimović (2), Dušan Bastać (2)

(1) ZAJEČAR HEALTH CENTER, ZAJEČAR; (2) OFFICE OF INTERNAL MEDICINE "DR BASTAĆ", ZAJEČAR; MEDSCAN TADIĆ DIAGNOSIS, ZAJEČAR (3)

Summary : **INTRODUCTION.** Metabolic syndrome (MetS) is characterized by the simultaneous presence of obesity, hypertension, dyslipidemia and hyperglycemia in an individual, which leads to an increased risk of cardiovascular disease (CVD). Left ventricular hypertrophy (LVH) is thickening of the heart muscle wall - hypertrophy of cardiomyocytes in concentric and/or elongation of cardiomyocytes and hyperplasia of connective tissue in eccentric hypertrophy with the participation of hemodynamic and non-hemodynamic factors (genetics, stress, other external factors). MetS, which essentially includesinsulin resistance, hyperinsulinemia, and hyperglycemia, alters myocardial metabolism and promotes myocardial inflammation, fibrosis, hypertrophy, and left ventricular remodeling. **OBJECTIVE:** To determine the impact of MetS, that is, obesity to the incidence and degree of severity of LVH in hypertensive patients with metabolic syndrome in comparison with the control group - hypertensive patients without metabolic syndrome.
PATIENTS AND METHODS: Consecutive patients of the Office of Internal Medicine "Dr. Bastać" were examined, a total of 55 patients with hypertension, who were divided into two groups: the first group with MetS, 22 people, average age 56±8.5 years with BMI>30kg /m ^{2} and waist circumference more than 80 cm for women and >94 cm for men, the second control group without MetS-33 people, average age 52±14 years, with BMI<30kg/m ^{2}. Echocardiography was done for all subjects on a Power Vision 6000 Toshiba echo camera with standard echocardiographic measurements in the M, B and Doppler technique, and the mass of the left ventricular myocardium was determined for them using the Devereux formula.
RESULTS: The prevalence of LVH in group 1 with metabolic syndrome (MetS) was 64%, while in the control group without (MetS) it was 36%. There was a statistically significantly higher number of patients with LVH in hypertension with MetS compared to hypertensive patients of the control group without MetS (X2, p=0.027). In the group of hypertensive patients with MetS, the degree of severity of myocardial hypertrophy, that is, the myocardial mass , was statistically significantly higher compared to the control group (respectively 302±84g versus 224±89g, p=0.0002). Arterial pressure values were higher for both systolic and diastolic blood pressure 168/106 mmHg in hypertensive patients with MetS, but did not reach statistical significance in relation to blood pressure values in hypertensive patients without MetS (156/95 mmHg, p=0.16).
CONCLUSION. Patients with metabolic syndrome and hypertension have a statistically significantly higher prevalence of left ventricular myocardial hypertrophy and a highly statistically significant degree of left ventricular hypertrophy compared to the control group of hypertensive individuals without MetS.
Given that mean values of arterial pressure do not differ between groups, it can be concluded that non-hemodynamic factors for the development of LVH have an important role in the induction of a more severe degree of LVH in hypertensive patients with metabolic syndrome.
Key words: left ventricular hypertrophy, metabolic syndrome, arterial hypertension, obesity, hyperglycemia, diabetes mellitus

INTRODUCTION

Metabolic syndrome (MetS) is a cluster of several disorders and includes abdominal obesity, dyslipidemia of HDL and LDL cholesterol, elevated triglycerides, elevated blood pressure, glucose intolerance or type 2 diabetes [1]. The term cardiometabolic syndrome has been used increasingly. According to the NCEP-ATPIII -2001 classification and harmonized definition [1] metabolic syndrome exists if three of the five risk factors are positive:

1. Abdominal obesity-waist circumference in men ≥ 94 cm (previously >102 cm), and in women ≥80 cm (previously >88 cm)
2. triglycerides higher than 1.9 mmol / L (> 1.7 mmol/L)
3. HDL cholesterol lower than 1.1 mmol / L (1 , 2 ; 1,4)
4. glycemia higher than 5.6 mmol / L
5. blood pressure >130/85 mmHg or higher

MetS is characterized by the simultaneous presence of obesity, hypertension, dyslipidemia, and hyperglycemia in an individual, which leads to an increased risk of cardiovascular disease (CVD). It affects nearly 35% of the US adult population, and its prevalence increases with age. Elevated blood pressure is an almost regular component of the metabolic syndrome; however, optimal antihypertensive therapy has not yet been defined [2].

Abdominal obesity, glucose intolerance, hypertension and diabetes synergistically interact and lead to left ventricular remodeling. These facts may explain the significantly increased risk of heart failure with preserved ejection fraction and cardiovascular disease when these factors are grouped together [3].

Left ventricular hypertrophy (LVH) is thickening of the wall of the heart muscle - hypertrophy of cardiomyocytes and hyperplasia of connective tissue, the consequence of which is a decrease in the volume of the ventricles in concentric hypertrophy, which is typical for hypertension with the participation of non-hemodynamic factors (genetics, stress, other external factors) as well. [4]. The consequences of concentric hypertrophy are: left ventricular diastolic dysfunction with preserved left ventricular ejection fraction, reduction of longitudinal systolic function, electrical instability (arrhythmias) and subendocardial microvascular ischemia (Figure 1). Eccentric and dilatational hypertrophy (elongation of cardiomyocytes via sarcomere replication) increases chamber volume and is typical for athletes but also occurs in obesity and volume overload. A more severe degree of myocardial hypertrophy (Figure 2) increases overall cardiovascular risk and mortality (congestive heart failure, sudden cardiac death). LVH is an independent prognostic factor and lethal marker of hypertension

Figure 1. taken from https://remixeducation.in/case-of-ischemic-heart-disease-hid/

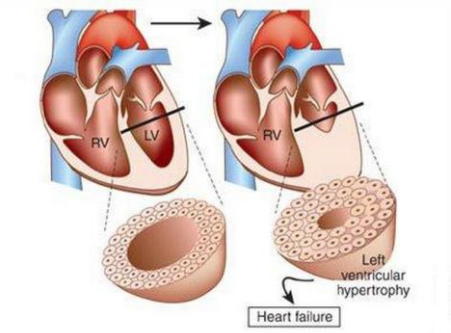
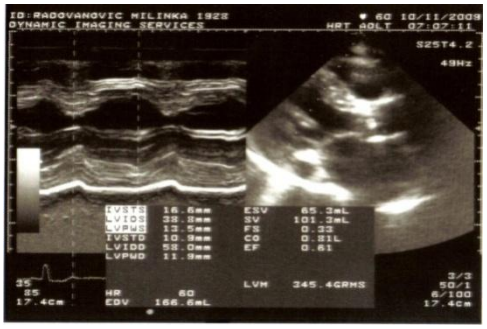


Figure.2. Echocardiographic image of a patient with extreme LVH of 345 g



Metabolic syndrome, which essentially includes insulin resistance, hyperinsulinemia, and hyperglycemia, alters myocardial metabolism and promotes myocardial inflammation, fibrosis, and left ventricular remodeling [5-8]. The ejection fraction of the left ventricle is most often preserved in metabolic syndrome and diabetes because the altered metabolic milieu leads to remodeling of the heart cavities, left ventricular hypertrophy and diastolic dysfunction, but also to subtle impairment of systolic function, which is detected through longitudinal global strain echocardiography [5-9]. For these reasons, the development of left ventricular hypertrophy doubles the risk for heart failure with preserved ejection fraction.

OBJECTIVE:

Determination of the impact of obesity to the incidence and degree of severity of myocardial hypertrophy in hypertensive patients with metabolic syndrome in comparison with the control group - hypertensive patients without metabolic syndrome .

PATIENTS AND METHODS

Consecutive patients of the Office of internal medicine "Dr. Bastać" were examined, a total of 55 patients with hypertension, who were divided into two groups :

- with metabolic syndrome N=22 (40%) patients , 10 male and 12 female, average age 56 ± 8.5 years with BMI>30kg/m ^{2} and waist circumference higher than 80 cm for females and > 94cm for men
- control group without metabolic syndrome 33 (60%) 11 male and 22 female, average age 52 ± 14 years, with BMI<30 kg / m ^{2}

Body mass index (BMI in kg/m^2) in the control group is 24.9±3 kg/m^2 , and in the examined group 32.5±2.5 kg/m^2 , a highly statistically significant difference is evident in body weight (p<0.001)

The number of cardiovascular risk factors that make up metabolic syndrome in the individual .

distribution was in the study group with metabolic syndrome - study group (N = 22 pts)

- 5 factors - 5 patients (22%)
- 4 factors - 8 patients (36%)
- 3 factors - 9 patients (42%)

It was not possible to observe other factors, e.g. parameters of systemic inflammation (hsCRP, interleukins, etc.) and measurement of insulin resistance (HOMA index, insulinemia during the OGTT test, etc.).

All patients had standard biochemical results, including serum concentrations of lipid fractions and blood glucose.

Echocardiography was done for all subjects on a Power Vision 6000 Toshiba echo camera with standard echocardiographic measurements in the M, B and Doppler technique, and the mass of the left ventricular myocardium was determined for them using the Devereux formula [10]:

$$\mathbf{LVM(g)= ((EDD+IVSd+PWd)^3 - EDD^3) \times 1.05 - 13.4}$$

Also, myocardial mass is indexed to the body surface and myocardial mass index-LVMI (g/m^2) is obtained.

The echocardiographic criterion for normal myocardial mass is up to 224g for men and 162g for women, on average less than 193g for both sexes. Normal myocardial mass index is less than 95 g/m^2 for women, less than 115 g/m^2 for men, on average less than 105 g/m^2.

Statistical processing was done through descriptive processing, for attributive characteristics using chi-squared test, and for numerical ones the Student's T test, both by means of the Mikrostat program.

RESULTS

Individual distribution - prevalence of left ventricular hypertrophy (LVH) in groups (for women LVMI >95 g/m^2 and for men LVMI >115 g/m$^{2)}$ is shown in Chart 1

CHART 1a. Prevalence of LVH in the group with metabolic syndrome and hypertension

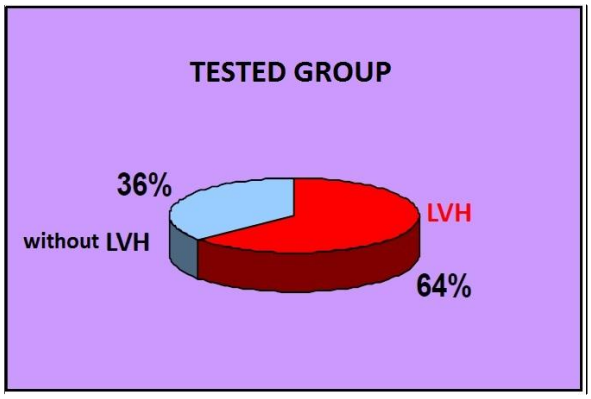
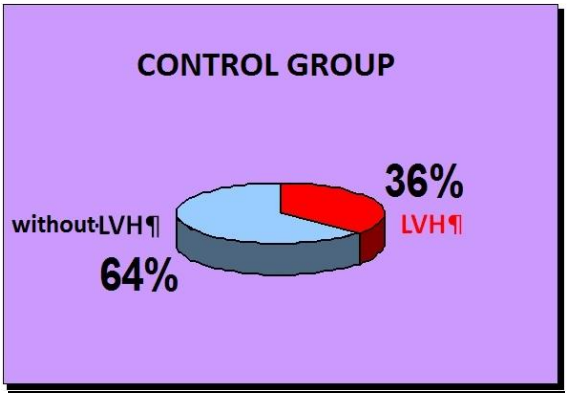


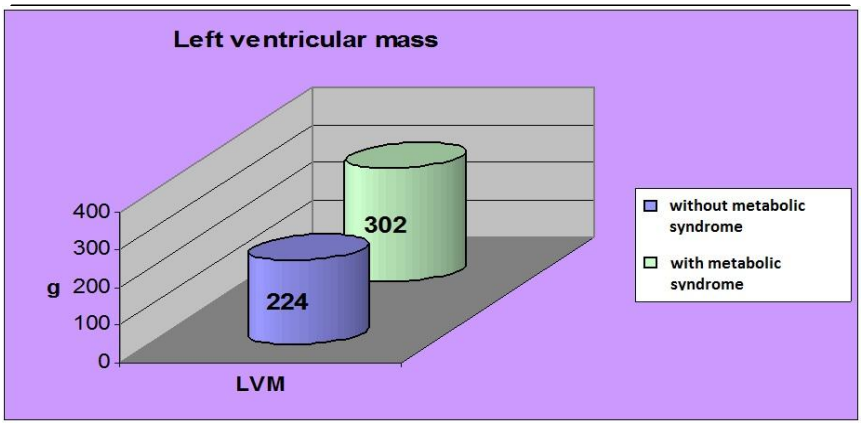
CHART 1b. Prevalence of LVH in the group with hypertension without metabolic syndrome



In the examined group 64% had LVH (Chart 1a), while in the control group 36 % had it (Chart 1b). There is a statistically significantly higher number of patients with LVH in hypertension with metabolic syndrome compared to hypertensive patients of the control group without metabolic syndrome (X^2 , p = 0.027)

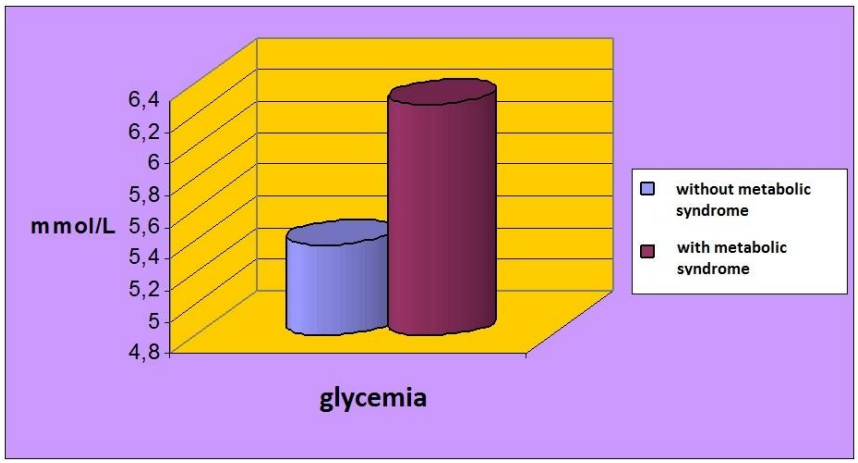
In the group of hypertensive patients with metabolic syndrome, the degree of severity of myocardial hypertrophy ie. myocardial mass is statistically significantly higher compared to the control group (respectively 302±84g versus 224±89g , p=0.0002) (Graph 2.)

Graph. 2. The degree of severity of hypertrophy - left ventricular myocardial mass in grams (g) in relation to the presence of metabolic syndrome



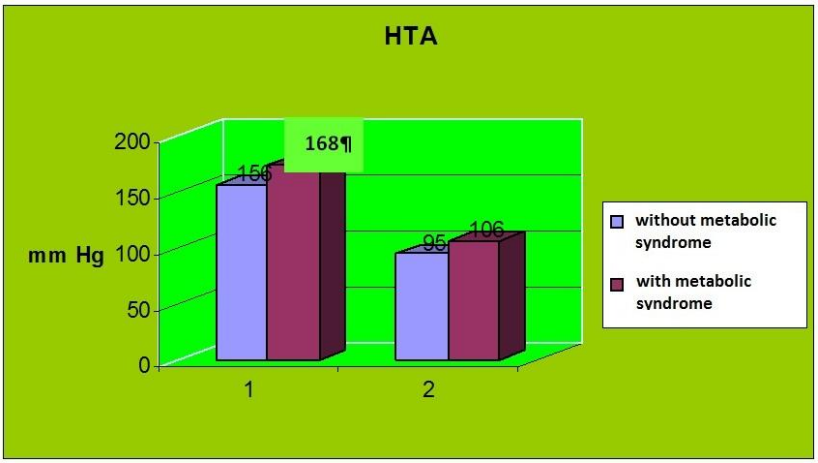
Glycemia values are slightly elevated in hypertensive patients with metabolic syndrome, on average 6.1 mmol/L, and in hypertensive patients without metabolic syndrome, they are normal at 5.5 mmol / L. (p<0.05) (Graph 3.)

Graph.3. Glycemia values in hypertensive patients with and without metabolic syndrome



Arterial pressure values were higher for both systolic and diastolic blood pressure 168/106 mmHg in hypertensive patients with metabolic syndrome, but did not reach statistical significance in relation to blood pressure values in hypertensive patients without metabolic syndrome (156/95 mmHg, p=0.16) (Chart 4).

Graph 4. Arterial pressure values in hypertensive patients with and without metabolic syndrome



DISCUSSION

The prevalence of left ventricular hypertrophy (LVH) in the examined group with metabolic syndrome (MetS) was quite high (64%), almost twice as high as the prevalence of the control group with isolated hypertension (36%). In the Second Strong heart study, De Simone et al. out of 1648 patients, they found 406 (25%) patients with LVH [11], which is a much lower number. We explain this difference by the fact that it is difficult to compare the given data, due to different patient selection factors, as well as genetic predisposition for hypertrophy. It is evident that the prevalence of hypertrophy is higher in our group because there were more severe patients with more metabolic syndrome factors. In patients without MetS with hypertension, our result of the prevalence of myocardial hypertrophy is 36%, while in the 2nd Strong Heart there were only 13% of subjects with LVH, which can be explained by the fact that they were without hypertension and that it was physiological hypertrophy or incipient hypertrophic cardiomyopathy [12]

Von Jensen et al. [3] in a population cohort study of 5741 participants of the Framingham study published in 2020, state that the prevalence of LVH is increased in subjects with associated hypertension, obesity and diabetes. Also, MetS and diabetes affect the reduction of left ventricular ejection fraction

(LVEF), which is not the case when there is hypertension with MetS without diabetes.

In our group of hypertensive patients with MetS, the degree of severity of myocardial hypertrophy, i.e. myocardial mass is statistically significantly higher compared to the control group (respectively 302±84g versus 224±89g, p=0.0002). On average, the contribution of the metabolic syndrome gives a higher myocardial mass by 26% than in hypertension without the metabolic syndrome, while this increase in the Von Jensen study of 36% is comparable because it was done on a very large sample [3]. In both, differences are highly statistically significant for the impact of metabolic syndrome on the increase in myocardial mass.

Arterial pressure values were higher for both systolic and diastolic blood pressure 168/106 mmHg in hypertensive patients with MetS, but did not reach statistical significance in relation to blood pressure values in hypertensive patients without MetS (156/95 mmHg, p=0.16). Given that the mean values of arterial pressure do not differ between groups, it is concluded that non-hemodynamic factors for the development of myocardial hypertrophy: abdominal obesity, hyperglycemia, insulin resistance and dyslipidemia associated with hypertension synergistically affect cardiac remodeling in terms of a more severe degree of left myocardial hypertrophy chambers. Similar conclusions are drawn on a large sample by von Jensen et al. [3]. These findings may explain the significantly increased risk of heart failure and cardiovascular disease when these factors are grouped together and play an important role in the induction of a more severe degree of myocardial hypertrophy in hypertensive patients with metabolic syndrome.

Metabolic syndrome (MetS) is associated with an increased prevalence of electrocardiographically and echocardiographically determined (LVH) and is a powerful predictor of cardiovascular outcome [11]. LVH is a strong predictor of composite fatal and nonfatal cardiovascular events over 8 years of follow-up, either in the presence or in the absence of the metabolic syndrome, and accounts for a significant portion of the high CV risk associated with MetS [11].

In the study by von Jeinsen B. et al. [3], 5741 participants of the Framingham study were examined who underwent echocardiographic measurements of left ventricular mass (LVM), ejection fraction (LVEF) and global longitudinal strain (GLS) through multivariable regression analysis. Statistically significant differences were obtained between BMI category, hypertension and diabetes with LVH, LVEF and GLS ($p < 0.01$). Obesity, hypertension and diabetes status were individually and jointly associated with greater severity of left ventricular hypertrophy (LVM) and worse GLS ($p<0.01$ for all). Obesity, hypertension and diabetes synergistically affect cardiac remodeling. These findings may explain the significantly increased risk of heart failure and cardiovascular disease when these factors are grouped together in the metabolic syndrome [3].

Determining the etiology of left ventricular hypertrophy (LVH) can be a challenge due to the similarity of various manifestations in clinical presentation and morphological characteristics [12,13]. Patients with LVH remain asymptomatic for several years, but disease progression will lead to the development of systolic or diastolic dysfunction and end-stage heart failure. Distinguishing individuals with treatable causes of LVH is important for the prevention of cardiovascular events and mortality. An athlete's heart with physiological LVH does not require treatment [13] The most common causes of hypertrophy, usually concentric type, include etiologies due to pressure overload, such as systemic hypertension, less common aortic valve stenosis and very rarely infiltrative heart diseases such as amyloidosis, Fabry disease and sarcoidosis. Volume overload is common in aortic and mitral insufficiency and extreme obesity [12,13].

Concentric myocardial hypertrophy occurs as a compensatory mechanism for pressure overload in hypertension [14-16]. Myocyte hypertrophy is associated with interstitial fibrosis, changes in cardiomyocyte metabolism, myocyte apoptosis, and microvascular dysfunction. These myocardial changes in hypertension are manifested as pathological remodeling of the left atrium and left ventricle accompanied by diastolic dysfunction, LVH and subtle myocardial systolic dysfunction, while LVEF is initially preserved [14-17]. Thus, obesity, diabetes mellitus and arterial hypertension cause LVH, but it is still not entirely clear how their joint presence can affect cardiac structure, function and ventricular geometry [17-35].

Finally, the results of epidemiological studies in the last 30 years have shown that visceral adipose tissue, precisely measured by CT or MRI, is an independent marker of the risk of cardiovascular and metabolic morbidity and

mortality [36]. Emerging evidence also suggests that ectopic fat deposition, including hepatic and epicardial fat, may contribute to increased atherosclerosis and cardiometabolic risk.

CONCLUSION

Patients with metabolic syndrome and hypertension have a statistically significantly higher prevalence of myocardial hypertrophy compared to the control group of hypertensive individuals without metabolic syndrome. The degree of myocardial hypertrophy of the left ventricle is statistically significantly higher compared to hypertensive patients without metabolic syndrome .

Given that mean values of arterial pressure do not differ between groups, it is concluded that non-hemodynamic factors for the development of myocardial hypertrophy play an important role in the induction of a more severe degree of myocardial hypertrophy in hypertensive patients with metabolic syndrome. Abdominal obesity, hyperglycemia and insulin resistance associated with hypertension synergistically affect heart remodeling in terms of a more severe degree of left ventricular hypertrophy than in hypertension without metabolic syndrome. These results may partly explain the significantly increased risk of heart failure and cardiovascular disease when the metabolic syndrome, including obesity, prediabetes or diabetes, dyslipidemia and hypertension factors are grouped together.

LITERATURE:

1. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI,at al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-5. doi: 10.1161/CIRCULATIONAHA.109.192644. Epub 2009 Oct 5. PMID: 19805654.
2. Katsimardou A., Imprialos K., Stavropoulos K., Sachinidis A., Doumas M., Athyros V. Hypertension in Metabolic Syndrome: Novel Insights. Curr Hypertens Rev. 2020;16(1):12-18. doi: 10.2174/1573402115666190415161813.
3. Jeinsen BV, Vasan RS, McManus DD, Mitchell GF, Cheng S, Xanthakis V. Joint influences of obesity, diabetes, and hypertension on indices of ventricular remodeling: Findings from the community-based Framingham Heart Study. PLoS One. 2020;15(12):e0243199. doi: 10.1371/journal.pone.0243199. PMID: 33301464; PMCID: PMC7728232.
4. Bastac D. et al. Differences in Left-Ventricular geometric Remodeling induced by Hypertension and Obesity .. *Int J Obes* 2001;25 (Suppl 3): S31–S32. https://doi.org/10.1038/sj.ijo.0801878 .
5. Lorenzo-Almoros A, Tuñón J, Orejas M, Cortés M, Egido J, Lorenzo Ó. Diagnostic approaches for diabetic cardiomyopathy. *Cardiovasc Diabetol*. 2017;16(28):1–11. 10.1186/s12933-017-0506-x
6. Varma U, Koutsifeli P, Benson VL, Mellor KM, Delbridge LMD. Molecular mechanisms of cardiac pathology in diabetes—Experimental insights. *BBA—Mol Basis Dis.* 2018;1864(5PtB):1949-1959. doi: 10.1016/j.bbadis.2017.10.035.
7. Marwick TH, Ritchie R, Shaw JE, Kaye D. Implications of Underlying Mechanisms for the Recognition and Managment of Diabetic Cardiomyopathy. *J Am Coll Cardiol*. 2018;71(3):339–51. 10.1016/j.jacc.2017.11.019
8. Hölscher ME, Bode C, Bugger H. Diabetic Cardiomyopathy: Does the Type of Diabetes Matter? *Int J Mol Sci.* 2016;16:1–11. 10.3390/ijms17122136
9. Bastać D., Raščanin A., Bastać M. Da li će globalni longitudinalni strejn kao superiorni parametar sistolne funkcije potpuno zameniti ejekcionu frakciju leve komore u proceni hipertenzivne hipertrofije? Srce i krvni sudovi (Heart and Blood Vessels Journal of the Cardiology Society of Serbia) 2019;38(3):124. Dostupno na: http://uksrb.rs/uploads/sazetci%20XXII%20INT%20sks%2003%202019%2038%203.pdf
10. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. Am J Cardiol. 1986; 57(6):450–8. https://doi.org/10.1016/0002-9149(86)90771-x PMID: 2936235
11. De Simone G, Devereux RB, Chinali M, Roman MJ, Lee ET at al. Metabolic syndrome and left ventricular hypertrophy in the prediction of cardiovascular events:The Strong Heart Study. Nutr Metab Cardiovasc Dis. 2009;19(2):98–104. doi:10.1016/j.numecd.2008.04.001.
12. Bastać D. *Komparativna studija hipertrofije miokarda izazvane hipertireozom, esencijalnom hipertenzijom i gojaznošću,* doktorska disertacija,. Medicinski fakultet Univerziteta u Beogradu. Beograd 1998].
13. Sayin BY and Oto A. Left Ventricular Hypertrophy: Etiology-Based Therapeutic Options.Cardiol Ther. 2022;11(2):203–230. Published online 2022 Mar 30. doi: 10.1007/s40119-022-00260-y PMCID: PMC9135932 PMID: 35353354
14. Raman S V. The Hypertensive Heart. An Integrated Understanding Informed by Imaging. *J Am Coll Cardiol*. 2010;55(2):91–6. 10.1016/j.jacc.2009.07.059
15. Messerli FH, Rimoldi SF, Bangalore S. The Transition From Hypertension to Heart Failure: Contemporary Update. *JACC Hear Fail*. 2017;5(8):543–51. 10.1016/j.jchf.2017.04.012
16. Díez J, Frohlich ED. A translational approach to hypertensive heart disease. *Hypertension*. 2010;55:1–8. 10.1161/HYPERTENSIONAHA.109.141887

17. Santos M, Shah AM. Alterations in cardiac structure and function in hypertension. *Curr Hypertens Rep.* 2014;16(428):1–10.
18. Aurigemma GP, De Simone G, Fitzgibbons TP. Cardiac remodeling in obesity. *Circ Cardiovasc Imaging*. 2013;6(1):142–52.
19. Mahajan R, Lau DH, Sanders P. Impact of obesity on cardiac metabolism, fibrosis, and function. *Trends Cardiovasc Med.* 2015;25(2):119–26.
20. Alpert MA, Lavie CJ, Agrawal H, Aggarwal KB, Kumar SA. Obesity and heart failure: epidemiology, pathophysiology, clinical manifestations, and management. *Transl Res.* 2014;164(4):345–56.
21. Alpert MA, Lavie CJ, Agrawal H, Kumar A, Kumar SA. Cardiac Effects of Obesity. *J Cardiopulm Rehabil Prev.* 2016;36:1–11.
22. Lorenzo-Almoros A, Tuñón J, Orejas M, Cortés M, Egido J, Lorenzo Ó. Diagnostic approaches for diabetic cardiomyopathy. *Cardiovasc Diabetol*. 2017;16(28):1–11.
23. De Simone G, Mancusi C, Izzo R, Losi MA, Aldo Ferrara L. Obesity and hypertensive heart disease: focus on body composition and sex differences. *Diabetol Metab Syndr*. 2016;8(79):1–9.
24. Oktay AA, Lavie CJ, Milani R V., Ventura HO, Gilliland YE, Shah S, et al. Current Perspectives on Left Ventricular Geometry in Systemic Hypertension. *Prog Cardiovasc Dis*. 2016;59(3):235–46.
25. Ojji DB, Adebiyi AA, Oladapo OO, Adeleye JA, Aje A, Ogah OS, et al. Left ventricular geometric patterns in normotensive type 2 diabetic patients in nigeria: An echocardiographic study. *Prev Cardiol*. 2009;12(4):184–8.
26. Eguchi K, Kario K, Hoshide S, Ishikawa J, Morinari M, Shimada K. Type 2 diabetes is associated with left ventricular concentric remodeling in hypertensive patients. *Am J Hypertens*. 2005;18(1):23–9. 10.1016/j.amjhyper.2004.08.024
27. Milani R V., Lavie CJ, Mehra MR, Ventura HO, Kurtz JD, Messerli FH. Left ventricular geometry and survival in patients with normal left ventricular ejection fraction. *Am J Cardiol.* 2006;97(7):959–63. 10.1016/j.amjcard.2005.10.030
28. Cuspidi C, Rescaldani M, Sala C, Grassi G. Left-ventricular hypertrophy and obesity: A systematic review and meta-analysis of echocardiographic studies. *J Hypertens*. 2014;32(1):16–25. 10.1097/HJH.0b013e328364fb58
29. Cuspidi C, Sala C, Negri F, Mancia G, Morganti A. Prevalence of left-ventricular hypertrophy in hypertension: An updated review of echocardiographic studies. *J Hum Hypertens*. 2012;26(6):343–9. 10.1038/jhh.2011.104
30. Wachtell K, Bella JN, Liebson PR, Gerdts E, Dahlöf B, Aalto T, et al. Impact of different partition values on prevalences of left ventricular hypertrophy and concentric geometry in a large hypertensive population: the LIFE study. *Hypertension*. 2000;35(1 Pt 1):6–12. 10.1161/01.hyp.35.1.6
31. Alpert MA, Omran J, Mehra A, Ardhanari S. Impact of Obesity and Weight Loss on Cardiac Performance and Morphology in Adults. *Prog Cardiovasc Dis.* 2014;56(4):391–400. 10.1016/j.pcad.2013.09.003
32. Lembo M, Esposito R, Lo Iudice F, Santoro C, Izzo R, De Luca N, et al. Impact of pulse pressure on left ventricular global longitudinal strain in normotensive and newly diagnosed, untreated hypertensive patients. *J Hypertens*. 2016;1201–7. 10.1097/HJH.0000000000000906
33. Drazner MH. The progression of hypertensive heart disease. *Circulation*. 2011;123(3):327–34. 10.1161/CIRCULATIONAHA.108.845792
34. Bastać D. et al. :Razlike u distribuciji tipa geometrijske remodelacije u hipertrofiji leve komore izazvane hipertenzijom i gojaznošću . Zbornik radova IV Kongres Interne medicine Jugoslavije ,Igalo 30.09.1997.
35. Bastać D. et al. Udruženost insulinske rezistencije i hipertrofije miokarda. Zbornik radova VI Kongres Interne medicine Jugoslavije, Beograd 2000.
36. Neeland IJ, Ross R, Després JP, Matsuzawa Y, Yamashita S, at al. International Atherosclerosis Society; International Chair on Cardiometabolic Risk Working Group on Visceral Obesity. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. Lancet Diabetes Endocrinol. 2019;7(9):715-725. doi: 10.1016/S2213-8587(19)30084-1. Epub 2019 Jul 10. PMID: 31301983.

SENSITIVITY TO GLUTEN

Aleksandar Zejak
MEDICINSKI FAKULTET, NOVI SAD, HAJDUK VELJKOVA 3

Summary: Introduction: Cereals were introduced as staple diet approximately 10,000 years ago, and today the global wheat production is at an incredible level. Gluten sensitivity is a condition that affects millions of people worldwide and includes a reaction to the gluten protein in grains, not just products from wheat, but also from many others. It's gluten which is important for doctors because it is connected to many diseases and is often mistaken for other sensitivities to the certain ingredients in food (allergies).
The aim of the paper: The aim of this paper is to explain what "gluten allergy" is, i.e. its real name, whether it really exists and how to distinguish it from grain allergy, as well as what the consequences of unreasonable gluten free diet are.
Allergy or intolerance? There is no such thing as gluten allergy, its real name is sensitivity to gluten. The majority of people who are intolerant use the word allergy because it is easier for people to understand it and that name is popular in the public. It is also important to know that wheat allergy is not the same as sensitivity to gluten and that these two different conditions require different types of diet.
Symptoms of gluten intolerance: Symptoms of gluten sensitivity appear after a few hours or days from consuming food containing gluten and most often include gastrointestinal symptoms. Gluten sensitivity is manifested similarly to irritable bowel syndrome and can include pain in the stomach, flatulence, diarrhea, constipation, but also systemic manifestations. There is no specific test or laboratory finding to make a diagnosis for gluten sensitivity, but the diagnosis is made starting a gluten-free diet and then adding one food at a time or products which contains gluten. Also, there exists a whole range of disorders connected with gluten.
Potential side effects of a gluten-free diet: People who choose a gluten-free diet do not have any health grounds for that. It is known that most athletes opt for this diet believing it improves athletic performance and reduces inflammation. However, this diet is often poor in micronutrients, expensive and instead of weight loss, it leads to weight gain.
Conclusion: Cereals are the main source of carbohydrates, they are rich in fibers, vitamins and minerals and should not be avoided unless there is a medical reason to do so. Many doctors are still undecided about whether it is sensitivity to gluten without celiac disease or some other hidden disorder, so that there needs further proof that this condition really exists and what its real mechanism of origin is. All people who are suspected of having a problem with consuming gluten or FODMAPs should consult with a doctor or a nutritionist.
Key words: gluten, gluten sensitivity without celiac disease (OGBC), gluten sensitivity, allergy to gluten, allergy to cereals

INTRODUCTION

Humanity has existed for about 2.5 million years, but cereals as the main component of human nutrition were introduced only about 10000 years ago. By introducing cereals people went from hunting to agriculture, which caused a sharp increase in grain harvest and consumption. Today, global production of wheat exceeds 700 million tons per year [1]. The protein found in wheat is called gluten, however this is a common name for similar proteins found in barley, rye and oats. Gluten in humans can cause several different disorders, among which is allergy to gluten [2]. This "natural" need to improve production has led to artificial breeding and selection of wheat that was better adapted to extreme climatic conditions and was resistant to the diseases. Such manipulation in wheat has led to drastic changes in genetic diversity and quality of wheat.

Gluten is extremely important in making bread and other products. Gluten (eng. glue - glue) is the component that holds the bread, i.e. it ensures that the dough rises and forms bubbles in fermentation process. Bakery products have a characteristic texture thanks to gluten. Today,

the awareness of the importance of gluten in food production has led to the extraction of gluten from plant seeds and its use not only in most bakery products, but also in the production of sweets, crackers, snacks, candies and the like.
It is believed that this genetic modification of wheat and gluten was too much of a shock for our organism and it did not give time for our immunological system to develop natural adjustment mechanisms [2].
This very protein and sensitivity to it has become a major topic of interest and research of the wider public and the interest of the people has led to a huge literature and information that is not necessary reliable [3]. "Allergy to gluten" is acondition which affects millions of people in the world and includes a reaction to the gluten protein in cereals, and not only in wheat products, but also in many others, the proper name for this condition is gluten sensitivity or glutensensitivity without celiac disease.
Demand for and consumption of gluten-free food has significantly increased in the last 30 years . In In 2016 almost twice as much money was spent on gluten-free food compared to 2011. Social networks, the media and marketing encouraged a large number of people to interested in gluten-free diet, and the problem is that most people have adopted this way of eating because of beliefs that consumption of food with gluten leads to harmful consequences [4] Today, an increasing number of people opts for a gluten-free diet without a prior recommendation from a doctor, which later makes it more difficult to reach the correct diagnosis.

The aim of this paper

Most people who choose a gluten-free diet do so based on information from the media and popular literature, without prior consultation with a doctor. This not only makes it difficult to see the real state of health of a person, but it can also have a negative impact on the individual's health. Gluten is important to doctors because it is associated with many diseases and is often confused with other allergies. The aim of this paper is to explain what "gluten allergy" is, i.e. its real name, whether it really exists and how to distinguish it from a grain allergy, as well as what consequences of groundless restricted gluten-free diet are .

Allergy or sensitivity?

Gluten allergy does not actually exist [2]. This term is incorrect because there is no such thing as allergy to gluten. People who have celiac disease describe their condition as an allergy, because this is the term easier to understand or even they themselves do not know the difference between an autoimmune disease and a sensitivity or allergies. Celiac disease is an autoimmune disease that results in damage to the small intestine that is triggered by consuming food containing gluten [5]. Gluten sensitivity is a condition that exists and is more correct to say that someone is sensitive to gluten, not that they have an allergy. Gluten sensitivity without celiac disease is characterized by intestinal and extraintestinal symptoms related to the intake of food containing gluten, while the person does not have celiac disease or wheat allergy [6]. Unlike celiac disease, patients who are sensitive to gluten do not have celiac disease, that is, the associated antibodies and may be HLA-DK2/8 negative (human leukocyte antigen) nor histological abnormalities of the small intestine. Studies have shown that these people have normal intestinal permeability and do not react to gluten through the activation of immune response [4].
So there is gluten sensitivity, but not gluten allergy. On the other hand, one should know the difference between sensitivity to gluten and allergies to wheat. These two terms do not imply the same problems. Cereal allergies are common and the most common is allergy to wheat which can result in atopic dermatitis, anaphylaxis caused exercise, eosinophilic esophagitis or celiac disease [3]. People who are sensitive to gluten should avoid all types of grains that contain gluten, while people with a grain (wheat) allergy should avoid only wheat while they can eat other cereals [7].

Symptoms of sensitivity to gluten

Humans have enzymes that help break down the food they eat. The protein-processing enzyme cannot fully break down gluten and it reaches the small intestine as such. Most people won't have any symptoms after undigested gluten enters the small intestine, but in some it may cause a serious autoimmune response or other unpleasant symptoms. Those symptoms can be intestinal or extraintestinal [8].
Symptoms of sensitivity to gluten are connected with consumption of food which contains gluten and usually they disappear completely when a person does not consume it. Symptoms then

disappear after a couple of hours or days. Manifestation of gluten sensitivity is very similar to irritable bowel syndrome (nervous intestines syndrome) and includes the following:

- pain in the stomach,
- flatulence,
- abnormality in the work of bowels (diarrhea or constipation),
- systemic manifestations (cognitive dysfunction, a headache, fatigue, pain in the joints or muscles, numbness in the legs or arms, dermatitis (eczema or rash),
- depression,
- anemia [9].

If symptoms appear in childhood, typical gastrointestinal symptoms appear (pain in the stomach and/or chronic diarrhea), while fatigue is the most common among systematic ones [9]. Diagnosis of sensitivity to gluten should be considered in all patients who have persistent intestinal or systematic complaints, and at the same time have a regular serological finding. Unfortunately, there still doesn't exist a single precise biomarker which can with certainty point to the existence of sensitivity to gluten. Today this diagnosis is made based on the appearance of symptoms and intake of gluten, compared to placebo-controlled "food challenge" symptoms [6]. When the person goes to the doctor and gluten sensitivity is suspected, the diagnosing process begins. This is done by starting a gluten-free diet (getting rid of all foods, drinks, medicines, cosmetics, etc. that contain gluten). When all of the symptoms withdraw we continue with the introduction of one item after the other and wait for the symptoms to appear. When the symptoms appear after the introduction of a new item, we know which food or product the patient reacts Badbadly to [3].

There are a couple of disorders that gluten can cause when it is consumed and the individual does not react well to it. Some of those disorders are:

OGBC - gluten sensitivity without celiac disease, which was discussed in this article. This term is used to describe a condition where an individual does not have celiac disease or a gluten allergy, but has intestinal troubles after consumption of food which contains gluten;

Celiac disease - the main cause of celiac disease is sensitivity to gluten, and this is a condition in which the immune system attacks its own tissues when gluten is consumed. These changes mostly they disappear after the start of a gluten-free diet;

Gluten ataxia - there is still no clear evidence of how this ataxia occurs, but we suppose that the antibodies that are formed affect the cerebellum. A gluten-free diet can improve neurological deficits, but it is not always useful, because sometimes damage to the cerebellum can be irreversible;

Dermatitis Herpetiformis - this disorder represents unusual skin changes which are directly related to gluten and celiac disease, and arise as an autoimmune response to gluten intake. It is characterized by persistent itching, inflammatory papules on the skin and vesicles on the forearms, knees, head and buttocks [10].

Potential side-effects of gluten-free diet

Most people who are on a gluten-free diet, as previously stated, do not have any diseases or intolerance to gluten, but still opt for this way of nourishment. The main reason for this is a belief that a gluten-free diet is healthier than a typical high-calorie or grain-rich diet. People who have this way of eating often try to alleviate some symptoms that have not been confirmed by a diagnosis or want a general improvement in their health condition, without any previous symptoms. Many people believe that a gluten-free diet is associated with weight loss. There is even one study that confirmed this theory (a loss of girth in the waist was observed, as well as body weight loss and higher levels of lipoprotein), but the test group was unreliable, so this still remains only a theory [4].

Even athletes advocated gluten-free diet, claiming that improves performance and endurance [4]. Athletes have to plan their own nutrition in detail in order to have optimal performance and of course, for the purpose of reducing gastrointestinal symptoms. It is also believed that gluten-free diet reduces inflammation, however, no theory has yet confirmed this. If an athlete has better performance that can be because he may haveundiagnosed celiac disease or simply is losing weightand therebyfeels better and moves more easily [11].

A 2015 study of 910 non-celiac athletes found

that 41% practiced gluten-free diet more than 50% of the time, and only 13% of them did so because of a previously diagnosed medical condition. 57% reported gluten sensitivity which they noticed themselves (stomach ailments and fatigue). 28.7% respondents found their main source of information online, 26.2% received information from coachesor physiotherapists, while 17.4% received information from other athletes[4].

The negative side of the gluten-free diet is very important. Foods containing gluten (cereals) are at the bottom of food pyramid and are so important for our health. These foods are good option for satisfying daily caloric needs. The consequences of a gluten-free diet are:
A lack of nutrients - cereals from the whole grain are rich in fibers, vitamins and minerals. The majority of gluten-free pasta and bread are not enriched with these micronutrients, which makes their natural intake difficult.
Adding weight - although it wasobserved that weight can be lost snacks and refined breads can have more fats, sugar and calories, which leads to weight increase .
Price - gluten-free diet is expensive especially for our market. In addition to increased financial sociopsychological influences were observed. This diet requires persistent commitment to limited diet and way of life. A person can feel isolated or have negative comments from the environment [4].

OGBC like special clinical entity

Today in the medical world there is much debate about whether gluten sensitivity without celiac disease really exists. Gluten is perhaps one of the most controversial and misunderstood food compounds. And if certain persons are considered to have sensitivity to gluten, many doctors and experts do not accept sensitivity to gluten without celiac disease like special clinical entity. Why is that so?
One of the best examples is precisely the proof that gluten sensitivity without celiac disease actually does not exist. Although the existence of gluten sensitivity (without celiac disease) was proven in one study, later the same people conducted a study and published an article in which they claimed and proved the opposite. The first paper (which showed the existence of this) was published in 2011 and then a study was conducted where it was shown that a diet with gluten can cause gastrointestinal problems even in people who do not suffer from celiac disease [12]. However, another paper (showing the absence of OGBC) published in 2013 after conducting a study on a small group of respondents, showed that there are no certain, specific responses to gluten. After analyzing the data, it was reported that each diet that was given to respondents, whether it contained gluten or not, encouraged the respondents to report deterioration of symptoms. Even when subjects were given a placebo, respondents again reported deterioration of symptoms. Although the group of respondents was small (37 people), the data clearly indicated that gluten was not to blame for the symptoms, but the reasons were psychological [12]. Precisely because of studies like this, most doctors do not accept the diagnosis of OGBC or sensitivity to gluten without some others, accompanying disorders.
At the same time, the etiology of gluten sensitivity is not clearly understood, and although it is believed that there exists an immunological response to gluten, no study has proved it yet. The other potential culprits include amylase-trypsin inhibitors (ATI) and fructans (found in FODMAPs) [14]. FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) are part of wheat and may play a role in NCGS pathophysiology and development of the symptoms. Placebo controlled study revealed that the symptoms improved with reduced intake of these components, so the conclusion is that the improvement of the symptoms was not due to non-consumption of gluten, but because of FODMAPs. Besides, this study showed that two gluten-free weeks caused a reduction in symptoms compared to that reported during a low-fat diet FODMAPs [15].
There is still much uncertainty about OGBC, and the causes may be gastrointestinal symptoms of gastrointestinal infection, medications, previous surgical procedures, etc. It requires a lot of time to fully understand the mechanism and the real cause of origin of sensitivity to gluten.

Conclusion

Although many people notice gastrointestinal complaints after consuming grains and food with gluten, non-celiac gluten sensitivity is still not recognized as a distinct clinical entity. The reason for this is that there is no clear evidence

to show that a person has a sensitivity to gluten, without having some other hidden condition or that the symptoms are not exclusively of psychological nature.

Cereals are the main source of carbohydrates and their absorption takes place in small intestine, providing energy to us. One should always choose whole grain cereals with as little sugar and preservatives as possible. If there is no clear indication for that, one should not decide on a gluten-free diet. If there is any doubt that gluten sensitivity still exists, adoctor should be consulted. In case there is a clear diagnosis for this a person should start with this diet.

These people should avoid flour, bread, crackers, baking mixes, pasta, cereals, sauces, spices, processed meat, beer, etc. Rice, corn, potatoes, soybeans, fruits, vegetables, meat, eggs, wine and distilled spirits are gluten-free and acceptable to eat or drink, but only when these products are of completely natural origin, because gluten is sometimes used as an additive. Many other products may not have gluten in them, but gluten may have been used in their preparation or packaging. Patients should consult a doctor or a nutritionist.

Debates and conversations about non-celiac gluten sensitivity happen every day, but we have a long way ahead of us in order to understand this condition properly.

LITERATURE:

1. Aziz I., Branchi F., Sanders D. S. The rise and fall of gluten! The Proceedings of the Nutrition Society, 2015;74(3): 221–226. Dostupno na: https://doi.org/10.1017/S0029665115000038
2. Pozderac I., Mijandrušić Sinčić B. Gluten-related disorders. Medicina Fluminensis, 2019;55(1): 53–58. Dostupno na: https://doi.org/10.21860/medflum2019_216320
3. Akhondi H., Ross A. B. Gluten Associated Medical Problems. StatPearls Publishing. 2022. PMID: 30860740
4. Niland B., Cash B. D. Health benefits and adverse effects of a gluten-free diet in non-celiac disease patients. Gastroenterology & Hepatology, 2018;14(2): 82–91.
5. The truth about gluten allergy. Beyond Celiac. 2020. Dostupno na: https://www.beyondceliac.org/celiac-disease/non-celiac-gluten-sensitivity/gluten-allergy-%20truth/
6. Catassi C. Gluten sensitivity. Annals of Nutrition & Metabolism, 2015;67(Suppl. 2): 16–26. Dostupno na: https://doi.org/10.1159/000440990
7. Wheat allergy diet. Dostupno na: https://www.hopkinsmedicine.org/health/wellness-and-prevention/wheat-allergy-diet
8. What is gluten and what does it do? Dostupno na: https://www.hopkinsmedicine.org/health/wellness-and-prevention/what-is-gluten-and-what-does-it-do#:~:text=%E2%80%9CGluten%20is%20a%20protein%20found,together%20and%20give%20them%20shape.
9. Catassi C., Bai J. C., Bonaz B., Bouma G., Calabrò A., Carroccio A., et al. Non-Celiac Gluten sensitivity: the new frontier of gluten related disorders. Nutrients, 2013;5(10): 3839–3853. Dostupno na: https://doi.org/10.3390/nu5103839.
10. Akhondi H. Ross AB. Gluten Associated Medical Problems. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2022. Dostupno na: https://www.ncbi.nlm.nih.gov/books/NBK538505/
11. Harris M. M., Meyer N. Go gluten-free: Diets for athletes and active people. ACSM's Health & Fitness Journal, 2013;17(1): 22–26. Dostupno na: https://doi.org/10.1249/fit.0b013e3182798371
12. Biesiekierski Jessica R et al. "Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial." The American journal of gastroenterology vol. 2011;106(3): 508-14; quiz 515. doi:10.1038/ajg.2010.487
13. Biesiekierski, Jessica R et al. "No effects of gluten in patients with self-reported non- celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short- chain carbohydrates." Gastroenterology 2013;145(2):320-8.e1-3. doi:10.1053/j.gastro.2013.04.051
14. Al-Toma, Abdulbaqi et al. "European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders." United European gastroenterology journal 2019; 7(5): 583-613. doi:10.1177/2050640619844125
15. Barbaro MR, Cremon C, Stanghellini V, Barbara G. Recent advances in understanding non-celiac gluten sensitivity. F1000Res. 2018;7:F1000 Faculty Rev-1631. Published 2018 Oct 11. doi:10.12688/f1000research.15849.1

THE RELATIONSHIP BETWEEN PHYSICAL ACTIVITY AND DEPRESSION

Aleksandar Zejak
MEDICINSKI FAKULTET, NOVI SAD, HAJDUK VELJKOVA 3

Summary: Introduction: Physical activity is any movement of skeletal muscles that uses energy. The earliest records of purposeful physical activity date as far back as 2500 BC from China, which tells us that even then people knew that it was essential for maintaining health. However, today man is more and more busy and generally sits most of the day and has no time to move. All this affects our mental health. Depression as one of the main problems of today is interesting when it comes to physical activity because it is believed that movement can improve its symptoms.
The aim of the study: The aim of our work is to explain what depression is, what are its symptoms and how it is generally treated. However, the main goal is to explain how physical activity affects the improvement of depression symptoms.
Depression: Depression is a mental disorder characterized by feelings of sadness and loss of will and interest in most things. It is classified into five different entities. Important for our work is major depressive disorder, which, according to statistical data, occurs more and more often. The occurrence of depressive disorder is influenced by genetics and environmental factors.
Physical activity and depression: The positive impact of exercise on mental health is an increasingly common subject of research and interest in the general population. There are a number of ways that regular physical activity can improve mood and alleviate symptoms of depression. However, certain physical activity can also have a negative impact on the psyche.
Conclusion: In order for physical activity to have a positive impact on health, it is important that it is carried out regularly and correctly. A person with depression should choose an activity that suits them, preferably in nature. It is also important to eat healthy food, get enough sleep and drink enough water.
Key words: depression, major depressive disorder, physical activity, mental health, feelings of sadness

Introduction

By physical activity we mean any movement of skeletal muscles that requires energy. Also, it is a movement of the body that is made possible by the musculoskeletal system and results in energy consumption that is greater than what the body consumes while it is at rest. Physical activity can be doing housework, recreational activities such as cycling or running, or going to the gym and lifting weights [1]. Physical activity was a condition for survival, the survival of the individual and the whole community. (Stevo Popović). The earliest records of targeted and organized exercise come from ancient China (2500 BC). Back then, people were encouraged to do exercises modeled after the movements of animals (tiger) and today our association of Kung Fu with violent fighting is wrong. This skill actually started as medical gymnastics, and some believe it was adapted from yoga, which was still popular in India at the time [2].

Today, man has less and less time for these activities because modernization has led to such conditions that everything is easier for man. Shopping and payment are over the Internet, work is done from home, mostly in a sitting position, and walking and physical activity have become a luxury [3].

The Centers for Disease Control and Prevention, as well as many other institutions, recommend that the general population, and even people with certain medical conditions, engage in regular physical activity. This is the best way to improve public health and prevent disease. 30 minutes of physical activity of moderate intensity, a couple of days a week, and ideally every day, has a positive effect on the prevention and control of hypertension, diabetes mellitus (insulin dependent), osteoporosis and similar conditions. But what about mental health, ie depression? It is considered that physical activity can be very effective for the prevention and control of psychiatric diseases [4]. Of course, apart from physical activity, it is important what kind of air we breathe, what kind of food we eat

and what kind of water we drink, as well as in what quantity. It seems that these last aspects are given special importance, and we rarely hear that physical activity is equally important [5]. Depression is defined as a mood disorder characterized by persistent feelings of sadness and loss of interest [6]. When a person is suffering from depression it often seems like the last thing they want to do is any kind of physical activity, however this can be extremely helpful. This is precisely what our work deals with.

The goal of the work

The goal of our work is to explain what depression is, how it manifests itself and how to recognize it. We will also explain how depression is diagnosed and how it is most often treated. The main goal of our work is to explain what physical activity is and how it has a positive effect on mental health, specifically on depression, and who should engage in physical activity and to what extent. Also, we will mention the negative sides of persistent training.

Depression

Depression is by definition a mood disorder that makes a person sad and prone to losing interest and more often affects women. Most people will not seek medical help, 60% because of false perceptions, and the rest because of stigma and prejudice from the environment.

Depressive disorders are classified into five categories and each of them is characterized by sadness, emptiness, irritable mood that can be accompanied by somatic or cognitive changes. The categories of depression are as follows:

Mood regulation disorder,
major depressive disorder,
Persistent depressive disorder (dysthymia),
Premenstrual dysphoric disorder,
Depressive disorder due to another medical condition [6].

The World Health Organization estimates that the proportion of the population (globally) that has depression is 4.4%. These are data from 2015, which would mean that there were 322 million people with depression at that time. Today, those numbers are much higher, even the number from 2015 increased by 18.4% compared to 2005 [7]. In 2022, the share of depression increased by a whopping 25%, and the main reason was the COVID-19 pandemic [8]. As we can conclude, depression is not at all a naive problem and it is extremely important to understand why it occurs and how it manifests itself, in order to be able to control it properly. In our work, we will specifically deal with major depressive disorder.

Etiology and symptoms

The etiology of major depressive disorder is multifactorial, that is, its appearance is influenced by both genetic and environmental factors. Depression can also occur in people who do not have a positive family history, but the chances are three times higher in those whose parents suffer from depression. Diseases such as Alzheimer's or Parkinson's, stroke, cancer, chronic pain or similar conditions increase the chances of developing depression. Most people react badly to the loss of a close person or some unfavorable situation in life, so this can also be a reason for depression [6].

Symptoms of depression can be:

Common symptoms of depression include:
Constantly sad, anxious or "empty" mood,
Feelings of hopelessness or pessimism,
Feeling irritable, frustrated or restless,
Feelings of guilt, worthlessness or helplessness,
Loss of interest or pleasure in hobbies or activities,
Decreased energy (fatigue),
Difficulty concentrating, remembering or making decisions,
Difficulty sleeping, early morning awakening or oversleeping,
Changes in appetite or unplanned weight changes,
Pain, headaches, cramps, or digestive problems with no clear physical cause and that are not relieved even by treatment,

Suicide attempts or thoughts of death or suicide.

For a person to be diagnosed with depression, they must have five symptoms every day, almost all day, for at least 2 weeks. One of the symptoms that must occur is a depressed mood or loss of interest in all activities. It is important to distinguish between irritability and depression [9].

Physical activity and depression

Depression is usually treated with medication, psychotherapy, or a combination of both. What kind of therapy will be depends solely on the severity of the symptoms and the depression itself [9]. However, sometimes the drugs do not have the desired effect, but have a counter-effect and the patient falls into even greater mental problems. Few people know the impact of

regular physical activity on mental health, and even fewer know how physical activity can affect depression.

The positive impact of physical activity on the prevention and control of physical diseases is clear, and today there is increasing interest in the impact on mental health and depression [5]. Even a large number of studies have proven the positive effects of exercise on mental health, and one even showed that regular physical activity significantly reduces the risk of depression. Even a single exercise session has also been proven to improve mood and reduce symptoms of depression [1].

Physical activity is a cheap and effective solution for all people who suffer from depression or simply want to preserve their mental health, and at the same time do not want to take medication. One study showed that people who exercise continuously for a couple of years have a 22% lower risk of mental illness. It is very important to understand that you should not engage in physical activity only if you are at risk of developing depression, or if you already have a diagnosis. Even if you're in a bad mood, exercise can help you feel better and alleviate feelings of sadness or loneliness, while also helping you sleep better [5].

Mechanism of action and recommended dose of exercise

The mechanism of the beneficial effect of regular physical activity on depression is described as follows:

distraction,

Social contact and

Self-efficacy.

The effect of distraction is explained by the fact that a person diverts attention from unfavorable stimuli during and after exercise and directly improves mood. The effect of self-efficacy is reflected in the fact that the physical activity itself is a challenge for the individual and the ability to successfully perform it leads to an improvement in mood and an increase in the sense of self-confidence. Social interaction is perhaps the most obvious, given that we previously stated that people with depression are often isolated and have no desire for interactions or any activities. Interacting with others helps them have someone to talk to and gives them support. Apart from these three mechanisms, the effect of physical activity on depression is also reflected in the release of hormones. During exercise, the neurotransmitter monoamine is secreted, and its synaptic transmission increases and is said to function as an antidepressant. The hormone endorphin (enogenic opioid), which is secreted during exercise, causes a feeling of calmness and improves mood [4].

Different studies have shown different results and most have come to the conclusion that you should train five times a week. The recommended time and duration of exercise varied, some suggested 150 minutes a week, some more than 240 and so on [10]. However, the duration of physical activity is less important in our opinion. What is important is that the person focuses as much as possible on that physical activity and applies it regularly. The positive physical and mental effects will be apparent after a while, but it is also equally important that a person eats healthy and drinks enough water.

Excessive exercise and the impact on mental health

For some people, physical activity turns into an obsession, that is, they become preoccupied with training, which can affect the psyche and personal and professional relationships. As a consequence of this obsession, a person can develop eating disorders, muscle dysmorphia (dissatisfaction with appearance), use of anabolic steroids, obsession with intense training, mood disorders, cycle disorders in women and simply too much training [4]. It is important to listen to your body and do only what pleases the person and makes him feel better.

Conclusion

From all of the above, we can conclude that regular and proper physical activity can help prevent many diseases, as well as depression. However, it can be harmful at the same time if a person overdoes it and does not implement it properly. You should choose physical activities that you genuinely enjoy, that suit your lifestyle, and it is always advised that they be outside in nature.

Depression is not a naive condition and it is important to have enough real information to be able to recognize it in time. For all people who suffer from depression or have some other psychological problem, it is advised that in addition to physical activity, they have the following:

enough sleep,

Regular and healthy meals,
Avoiding alcohol, nicotine, drugs, even medicines not prescribed by a doctor.
Regular physical activity can improve mood and is especially beneficial for mild to moderate depression. Every type of activity is useful, but only when it is done continuously and if it is not overdone. It may sound like a difficult process, but it is necessary to find the motivation and start yourself.

LITERATURE:

1. Lazarević U, et al. "Influence of Physical Activity on Degree of Depression, Anxiety and Stress in Students of University of Belgrade - Faculty of Medicine." Sport - Nauka i Praksa, 2021;11(2): 57–66. doi:10.5937/snp2102057l.
2. MacAuley D. "A History of Physical Activity, Health and Medicine." Journal of the Royal Society of Medicine, 1994;87(1):32–35. doi:10.1177/014107689408700114.
3. Krivokapic D, Popovic S.. Uticaj rekreativnih aktivnosti na psihičko zdravlje.2011. Dostupno na: https://www.researchgate.net/publication/318723266_Uticaj_rekreativnih_aktivnosti_na_psihicko_zdravlje
4. Aurélio M., et al. "Physical Activity and Mental Health: The Association between Exercise and Mood. Scielo. Br, 2005;60(1):61-70. Dostupno na: https://www.scielo.br/j/clin/a/nJtsYg7cXYppsF7VZ7hhHXw/?format=pdf&lang=en.
5. Ostojic S. Stojanovic M. Veljović D, Medjedovic B.at al. FIZIČKA AKTIVNOST I ZDRAVLJE: Definicija problema, savremena zapažanja i preporuke. 2009;3:1-13.
6. Chand S.P., Hasan A. Depression. StatPearls Publishing, 2022.
7. Depression and Other Common Mental Disorders. (WHO) Dostupno na: https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf
8. "COVID-19 Pandemic Triggers 25% Increase in Prevalence of Anxiety and Depression Worldwide." Who.int, Dostupno na: https://www.who.int/news/item/02-03-2022-covid-19-pandemic-triggers-25-increase-in-prevalence-of-anxiety-and-depression-worldwide. Accessed 19 Feb. 2023.
9. National Institute of Mental Health. Depression. Dostupno na: https://infocenter.nimh.nih.gov/sites/default/files/2022-01/depression.pdf
10. Mammen G. Faulkner G.. Physical Activity and the Prevention of Depression A Systematic Review of Prospective Studies. American journal of preventive medicine. 2013;45(5):649-57. DOI: 10.1016/j.amepre.2013.08.001.

TIMOK MEDICAL GAZETTE

Vol. 48 (2023) No. 1 Case report

DYSPEPSIA IN PRIMARY HEALTH CARE - CASE REPORT

Tanja Stefanović (1), Ester Aleksander (2)

NOVI SAD PUBLIC HEALTHCARE CENTER, WORKERS' HEALTH CENTER(1), ADA PUBLIC HEALTHCARE CENTER(2)

Abstract: Dyspepsia is a term originated from the Greek prefix dys- (bad) and the word pepsis (digestion) and it means indigestion. Dyspepsia is a symptom which indicates occasional or constant pain in the region of the upper abdomen or discomfort which is described in the form of early satiety or a feeling of fullness in the stomach. Sometimes it can be accompanied by nausea, vomiting and heartburn. The symptoms of dyspepsia are not specific enough to indicate a particular disease. And if indicated, additional diagnostics are performed in order to prove or rule out a physical disorder.

Dyspepsia is a frequent reason for visiting the doctor. About 40% of the world's population has symptoms of dyspepsia, most often the working population aged between 20-40 years, equally in both sexes. About 25% of patients seek doctor's help, while the rest seek help for their problems at a pharmacy. Dyspepsia is the reason for 40% of performed gastroenterology consultations.

This article presents the clinical picture, therapeutic and diagnostic course, as well as the outcome of the treatment of a 53-year-old patient who came to the doctor with symptoms of dyspepsia. The symptoms of dyspepsia had lasted for several years before coming to the doctor. During the first examination, an anamnesis was taken, the review of systems was performed, and a basic blood test done in the local Health center. Given that there was no data on the existence of alarming symptoms in this patient, symptomatic therapy and advised change of habits were included, as well as a planned checkup in one month. At the checkup, the patient reported a decrease in frequency and intensity of abdominal pain, so it was decided to perform additional diagnostics: test for Helicobacter pylori, fecal occult blood test, and ultrasound examination of the abdomen. Requested result of FOBT was negative, but the test for Helicobacter pylori was positive.

Ultrasound examination revealed the presence of small calculi in the gallbladder, but there were no other significant clinical findings. Eradication therapy for helicobacter infection was included, and an examination by a gastroenterologist for further diagnostics (esophagogastroduodenoscopy) was planned. Gastroscopy findings were described as chronic non-atrophic gastritis, predominantly antral. A follow-up gastroscopy was planned in five-year interval, the patient was given the proton pump inhibitors therapy, as well as dietary instructions.

Given that dyspepsia often occurs in clinical practice, it was necessary to make a proper assessment regarding further diagnostics, on the one hand for economic reasons and on the other hand for medical reasons. Here, the decision was made to carry out further diagnostics considering the duration of the health problems, the presence of the problems during symptomatic therapy, the age of the patient and his concerns. Given the absence of alarming symptoms, appointments were scheduled for all examinations, so a complete diagnosis of organic dyspepsia was reached after 13 months.

Key words: dyspepsia, clinical picture, diagnostic tests, therapy

INTRODUCTION

Dyspepsia is a term originated from the Greek prefix dys- (bad) and pepsis (digestion) and it means indigestion. Dyspepsia is a symptom that indicates occasional or constant pain in the region of the upper abdomen or discomfort that is described in the form of early satiety or a feeling of fullness in the stomach. Sometimes it can be accompanied by nausea, vomiting and heartburn. The symptoms of dyspepsia are not specific enough to indicate a particular disease.

Dyspepsia is a frequent reason for visiting the doctor. About 40% of the world's population has symptoms of dyspepsia, most often the working population aged between 20-40 years, equally in both sexes. About 25% of patients seek doctor's help, while the rest seek help at a pharmacy.

Dyspepsia is the reason for 40% of performed gastroenterology consultations.

The cause of dyspepsia can be an organic disease such as stomach ulcer disease, gastroesophageal reflux disease, stomach or pancreatic cancer and others, when it is marked as organic dyspepsia. If an organic disease is not identified, then they are marked as functional dyspepsia.

The most common causes of dyspepsia are: functional dyspepsia up to 60%, peptic ulcer 15-25%, reflux esophagitis 5-15%, stomach and esophagus cancer less than 2%. Less common causes of dyspepsia are: biliary diseases, pancreatitis, taking some medicines, ischemic bowel diseases, parasitosis, malabsorption of carbohydrates, systemic diseases, pancreatic cancer, and other abdominal tumors.

The main symptoms are burning, a feeling of discomfort and fullness in the stomach that occurs before or after eating. It can also be accompanied by a feeling of nausea, vomiting, heartburn, general weakness, as well as belching. If the predominant symptom of functional dyspepsia is pain, it is designated as ulcer-like dyspepsia, and if the predominant symptom is a feeling of discomfort in the epigastrium, it is designated as dysmotility-like dyspepsia.

Alarming symptoms are symptoms that may indicate the existence of an organic disease manifested by dyspepsia, such as ulcer disease, cancer of the esophagus or stomach. These include: sudden anemia due to bleeding from the digestive tract (within the last 10 days), severe unwanted weight loss (> 5% within 10 days), persistent vomiting within 10 days, dysphagia, and the presence of a palpable mass in the abdomen. In the presence of alarming symptoms, a quick consultation of a gastroenterologist is necessary within two weeks.

CASE REPORT

A 53-year-old patient comes to the doctor with symptoms that have been going on for several years in the form of discomfort in the upper abdomen, occasionally a feeling of early satiety, occasionally followed by pain and heartburn. The symptoms are stronger after taking some food and larger meals. Appetite is normal, he has not lost weight. The stools are tidy, without any appearance of blood and mucus. In case of the symptoms' aggravation, he takes baking soda. He occasionally drinks alcohol (once or twice a week, 0.3-0.5 l of beer), smokes about 10 cigarettes a day and has done so for the last 20 years. Due to back pain, he takes NSAIDs (ibuprofen, naproxen, ketoprofen). Family history is negative in terms of malignancy of the digestive tract. The patient's son has ulcerative colitis.

Physical examination is performed, the patient is in a good general condition, pre-obese, the review of the systems is normal, except for the light pain in the epigastrium region during deep palpation examination. The patient is given a written diet on food to avoid, as well as an advice on reducing the amount of meals he eats and the dynamics of their intake. Recommendation to avoid alcohol intake and referral to the Smoking Cessation Counseling Center. Pantoprazole 40mg is introduced half an hour before breakfast for the next two weeks, with further recommendation to reduce the dose to 20mg per day for another 2-4 weeks. In case of heartburn, sodium alginate suspensions are recommended. Checkup planned in 4-6 weeks with a basic blood test done at the local Health center.

At the checkup, the patient reports a decrease in frequency and intensity of abdominal pain, no weight loss, frequent regular stools. Blood test and biochemical results with no clinical significance. Given that the symptoms are still present, it is decided to perform additional diagnostics: test for Helicobacter pylori, fecal occult blood test, and ultrasound examination of the abdomen. Requested result of FOBT was negative, but the test for Helicobacter pylori was positive.

On ultrasound, apart from the presence of small calculi in the gallbladder, there are no other significant clinical findings. A 14-day eradication therapy for helicobacter infection is included (clarithromycin 2x500mg, amoxicillin 2x1000mg, bismuth subcitrate 4xdaily, pantoprazole 2x40mg, probiotics). After the therapy, the patient feels better, symptoms occasionally present.

For further diagnostics an examination by a gastroenterologist (esophagogastroduodenoscopy) is appointed after 4 months.

The gastroenterologist's diagnosis is Morbus refluxualis gastro-oesophageus, and the patient is put on the waiting list for gastroscopy, which is performed after 7 months. Gastroscopy findings are described as chronic non-atrophic gastritis, predominantly antral. A follow-up

gastroscopy is planned in five-year interval, the patient is given the proton pump inhibitors therapy, as well as dietary instructions. The patient suffers from dyspepsia only when he does not pay attention to his diet, during frequent use of NSAIDs analgesics and in stressful situations, but since the cause of dyspepsia symptoms is known, his concern for his own health is significantly less.

CONCLUSION

Given that dyspepsia often occurs in clinical practice, it is necessary to make a proper assessment regarding further diagnostics, on the one hand for economic reasons and on the other hand for medical reasons. Here, the decision is made to carry out further diagnostics considering the duration of the health problems, the presence of problems during symptomatic therapy, the age of the patient and his concerns. Given the absence of alarming symptoms, appointments were scheduled for all examinations, so a complete diagnosis of organic dyspepsia is reached after 13 months.

In the subsequent checkups, the patient is motivated to follow the dietary advice, it is explained to him when he needs to take proton pump inhibitors and sodium alginate and for how long. The controlled use of analgesics, mandatory with proton pump inhibitors, is explained. He stopped smoking and reduced his alcohol intake to a few times a year. Due to his stressful lifestyle, he is involved in working with a psychologist for training in relaxation techniques, which also contributes to the reduction of complaints. It is explained to him which symptoms and signs are worrisome and when it is necessary to report urgently for an examination. The patient, who rarely visited the doctor, is now interested in conducting preventive examinations, and if he has new health issues, he consults the doctor and avoids self-medication.

REFERENCES:

1. The American Journal of Gastroenterology. Nature Publishing Group 2005:100(10). Dostupno na: https://archive.org/details/sim_american-journal-of-gastroenterology_2005-10_100_10
2. Dostupno na: https://www.mayoclinic.org/diseases-conditions/functional-dyspepsia/symptoms-causes/syc-20375709
3. Dispepsija Nacionalni vodič za lekare u primarnoj zdravstvenoj zaštiti, Ministarstvo zdravlja Republike Srbije, 2004.
4. Pejin D. Interna medicina, Univerzitet u Novom Sadu-Medicinski fakultet, 2006.
5. Talley NJ, Stanghellini V, Heading RC, et al.: Functional gastroduodenal disorders. Gut, 1999.
6. Department of Health. Referral Guidelines for suspected cancer. London: The Department; 2000. (cited 26. Aug 2002) Dostupno na: http://www.doh.gov.uk/ cancer/referral.htm.
7. American Gastroenterological Association medical position steatment: Evaluation of dyspepsia. Gastroenterol 1998; 114(3): 579-81.
8. Ford Ac, Mahadeva S, Carbone MF et al., Functional dyspepsia, 2020;396(10263):1689-1702. Dostupno na: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30469-4/fulltext#%20 doi.org/10.1016/S0140-6736(20)30469-4
9. Moayyedi PM, et al., ACG et CAG clinical guideline: Menagement of dyspepsia, American Journal of Gastroenterology 2017; 112(7):988-1013. DOI: 10.1038/ajg.2017.154

INSTRUCTIONS TO ASSOCIATES OR AUTHORS

Timok medical GAZZETTE publishes previously unpublished scientific and professional papers bilingually, in Serbian and English language from all fields of medicine and related branches. Original papers, patient case reports, review articles, medical and health history articles, book and journal reviews, editorial letters and other medical information are received for publication. The authors propose a category of their work and the Editorial Board reserves the right to change the category with the consent of the author.

Manuscripts should be prepared in accordance with the Vancouver Recommendations: UNIFORM REQUIREMENTS FOR MANUSCRIPTS SUBMITTED TO BIOMEDICAL JOURNALS, recommended by ICMJE (International Committee of Medical Journal Editors - Ann Intern Med. 1997; 126: 36-47), or in accordance with the Serbian languageversion JEDNOBRAZNI ZAHTEVI ZA RUKOPISE KOJI SE PODNOSE BIOMEDICINSKIM ČASOPISIMA, Serbian Archives of Medicine, 2002; 130 (7–8): 293. The digital version is freely available on the ICMJE website, www.icmje.org, as well as at www. tmg.org.rs/saradn.htm

When writing atext in English, one should adhere to the American English language standard and use short and clear sentences. Manuscripts received by the editorial staff are not expected to contain results already published by authors in another journal or similar publication. The original manuscript must be accompanied by the certificate of authorship (you can download the form at: www.tmg.org.rs), scanned signatures of all authors of the article.

The editorial board sends all the papers for peer review - usually two reviewers. Proceedings in supplements are not peer reviewed.

In works where the described patient may be identified, the utmost care should be taken to avoid any details that can identify him/her or obtain written consent for publication from the patient himself or his immediate family. When consent exists, it should be stated in the article.

If the paper receives positive anonymous reviews (2 reviewers) it will be accepted for publication. After receiving a positive review, in order for the paper to be published in electronic version on the website www.tmg.org.rs and printed, it is necessary to pay a fee for the cost of editing the article, proofreading and printing costs for the Timok medical journal **only for the first author**, which amounts to four thousand dinars (4000 RSD) paid to the current account.

Current Account: 205-167929-22
Serbian Medical Association-Zajecar Branch;
purpose: material processing for TMG.

TECHNICAL REQUIREMENTS

The manuscripts are to be submitted exclusively in electronic form, bilingually (starting with volume 45), in Serbian (preferably Cyrillic) and in English. Papers submitted only in Serbian or English only will not be considered. Send the manuscripts in electronic form to: tmglasnik@gmail.com

The electronic format of the manuscript should be in Microsoft Office Word (with a .doc or .docx extension) and should include a final version of the manuscript. All text, references, tables and titles of tables and images and legends of images should be in one document. It is best to form the filename by the first author's last name, one keyword and type of work (for example: paunkovic_tiroidea_originalni.doc).

Use the Times New Roman font, 12p size. Write the paragraph so that only the left alignment is straight. Do not divide words into syllables at the end of the line. Insert only one blank space after the punctuation mark. Allow the titles and subheadings to be aligned with the left edge. Use bold, italic, sub, and superscript and underlined letters only where necessary. **Tables, images and charts should be inserted in the text where they should appear in the paper**. Acceptable formats for tables, charts, illustrations, and photos are doc, xls, jpeg, gif, and npg.

TYPES AND SCOPE OF MANUSCRIPTS

The title of all types of articles is followed by Summary (up to 300 words) and keywords (3 to 8).

The Original Paper (work) is a systematically published research of a problem according to scientific criteria and a clear aim of the research. **The integral parts of the paper are: a) introduction**- (the aim of the paper as the last paragraph of the introduction); **b) material and methods**; **c) results; d) discussion; e) conclusion; f) literature**. The length of the text is limited to 3500 words, with a maximum of 5 tables, charts, or pictures (up to 12 pages of text).

A Review Article covers a systematically addressed specific medical problem, in which the author made some contribution, visible on the basis of self-citations. **Integral parts of the paper are: a) introduction**- (the aim of the review paper as the last paragraph of the introduction); **b) the text of the review of literatureonthe problem , with subtitles**; **c) conclusion; d) literature**. The review article is usually commissioned by the Editorial Board, but non-commissioned manuscripts are also considered. Contact the Editorial Board before writing a review article. Text length can be up to 5000 words (18 pages).

A Case Report (patient presentation**)** sheds light on individual cases ofmedical practice. It usually describes one to three patients, or one family. The integral parts of the paper are: **a) introduction**- (the aim of the paper as the last paragraph of the introduction); **b) presentation of the patient; c) discussion and d) conclusion**. Unlike the original research, omit the section on methodology and results. The text is limited to 2500 words, max 4 tables, or 4 pictures and up to 25 references (up to 6 pages of text in total). Patient names, initials, or medical history numbers should not be used, especially in the illustrations. Casereportsmust not have more than 5 authors

Articles in the history of medicine and health culture shed light on certain aspects of medical practice in the past. Text length can be up to 2500 words (6 pages). These and the articles statedbelow do not have a prescribed structure, such as original papers, case reports, and review articles. Short contributions from the field of medical practice (diagnostics, therapy, remarks, suggestions and opinions on methodological problems, etc.) are published, too, as well as presentations from various medical meetings, symposia and congresses in the country and abroad, book reviews and articles from foreign journals up to 1000 words, 1-2 tables or images, up to 5 references (up to 3 pages of text). Editorial letters have up to 400 words, or 250 words if they contain comments on published articles. By order of the editorial board, or in agreement with the editorial board, works of didactic character are published.

If the work is part of a master's thesis, or a doctoral dissertation, or is done in the framework of a scientific project, this should be **clearlyindicated in the note after the abstract and before the text**. Also, if the work has been previously announced at a professional meeting, state the official name of the meeting, the venue and time of the event, whether the work has been published and how it has been published (eg the same or a different title or abstract).

ETHICAL CONSENT. Manuscripts on human research should include a statement in the form of a written consent of the persons interviewed in accordance with the WMADeclaration of Helsinki and the approval of the responsible ethics committee that the research can be carried out and is in accordance with legal standards. Experimental research on human material and animal testing should include a statement from the ethics committee of the institution and be in accordance with legal standards. Information on this must be provided in the section

AUTHORSHIP. All persons listed as authors of the work should qualify for authorship. Each author should have participated sufficiently in the work on the manuscript to be able to take responsibility for the entire text and the results presented in the work. Authorship is based solely on: making a significant contribution to the concept of the work, obtaining results or analyzing and interpreting the results; the planning of the manuscript or its critical revision of considerable intellectual importance; the final refinement of the print version of the manuscript. Authors should attach a description of the contributions individually for each co-author within the Submission Letter form. Financing, collecting data or generally overseeing a research team cannot by itself justify authorship. All other contributors who are not the authors of the manuscript should be listed onthe

acknowledgementpage, with a description of their contribution to the work, with written consent, of course.

STATEMENT OF CONFLICT OF INTEREST. The manuscript is accompanied by a signed statement in the form of a Submission Letter stating the authors of each possible conflict of interest or lack thereof. For more information on the different types of conflicts of interest, visit the World Association of Medical Editors' Association (WAME; http://www.wame.org), entitled "Conflict of Interest Statement Policy".At the end of the paper, below the Remarks section, in a separate section Conflict of Interest,each possible conflict of interest or its absence should be declaredfor each author individually (full name of the author or initials) For example Zoran Petrovic: Krka (lecturer) Ljiljana Aleksic: none. Mila Bastac: Pfizer, Sanofi, Bristol-Meyers Squibb (lecturer, honorary consultant, researcher on ascientific project).

PLAGIARISM. As of January 1st, 2019, all manuscripts are subjected to plagiarism / autoplagiarism through the SCIndeks Assistant-Cross Check (iThenticate). Papers containing plagiarism or self-plagiarism will be rejected and the authors sanctioned.

ABBREVIATIONS. Use only when necessary, for very long names of chemical compounds, that is, abbreviations that are already recognizable (standard abbreviations, such as DNA, AIDS, HIV, ATP). For each abbreviation, the full term should be stated when first quoted, unless it is a standard unit of measure. Do not use abbreviations in the title. Avoid using abbreviations in the abstract, but if necessary, explain each abbreviation when first referenced in the text.

ACKNOWLEDGEMENTS. List all contributors who contributed to the creation of the work but did not meet the criteria for authorship, such as those providing technical assistance, writing assistance, or managing a department that provides general support. Financial and material assistance, in the form of sponsorships, scholarships, gifts, equipment, medicines and more, should also be listed

MANUSCRIPT PREPARATION

The text of the paper contains first and foremost the title of the paper, in the following lines: full names of the authors and all co-authors; the name, place and address of the institutions from which the author and co-authors come (in parentheses, associate the names of the authors); possibleacknowledgementfor help with elaborationofthe paper;

It is obligatory to submit:

-proposal of the manuscript category (original work, review article, case report, etc.);

-**first and last name, year of birth of the author and all co-authors**;

-**full address, telephone and fax numbers, as well as the author's e-mail for correspondence**.

The following is a SUMMARY (Abstract), up to 300 words is best. A summary cannot have footnotes, tables, images, or references. A summary of **the original papers** should include: Introduction (state the objective in the last sentence), **Material and methods, Results and Conclusions**. Write each of the segments listed at the beginning of the sentence in bold. Provide the most important results (numerical values) of the statistical analysis and the levelofsignificance. The conclusion must not be general, but must be directly linked to the results of the work. **For case reports, the summary** should have the following parts: **Introduction** (state the objective in the last sentence), **Case report, Conclusion**. For other types of papers the summary has no specific structure.

The summary must not contain any claims that are not contained in the text of the article. It must be written in such a way that even an educated nonexpert can understand the content of the article. After the summary, write 3 to 8 keywords. The words in the title should not be repeated and the keywords should be relevant or descriptive and in accordance with MESH rules (available at https://www.nlm.nih.gov/mesh).

The next part of all the papers is an **INTRODUCTION** (with a subtitle of the same name), which must be brief, with a brief overview of the literature on the problem in question, and with a clear statement of **the purpose of the article** in a separate paragraph at the end of the introduction.

MATERIALS AND METHODS (with the same subtitle) must contain sufficient information to enable other researchers to repeat similar research without further information. Patient names and medical history numbers should not be used nor other details to help identify patients. The names of the apparatuses, software and statistical methods used must be indicated.

Show the **results** (with the subtitle of the same name in BOLD) clearly and concisely. You should not display the same data both in tables and charts.

DISCUSSION (with the subtitle of the same name) should discuss the interpretation of the results, their meaning in comparison with other, similar research and in accordance with the hypotheses of the research. The results already written should not be repeated.

CONCLUSION (with the subtitle of the same name) should be given in a separate chapter.

Each table, chart, or illustration must be self-explanatory, i.e. even without reading the text in the manuscript. Above the table, chart, orimage,there should be a serial number and a title. Put the legend in a footnote below the table, chart, or image and explain any non-standard abbreviations there. Illustrations (images) should be sharp and contrasting, no larger than 1024x768 pixels. The number of images should be limited to the most necessary (generally no more than 4-5). If the image, table, or chart is downloaded from the Internet or another source, the source must be indicated.

REFERENCES

LITERATURE. At the end of the paper, write a list of cited literature, which should be as current as possible and most references should not be older than 5 years. References are numbered in the order they appear in the text. Mark the references in the text with an Arabic number in square brackets [...]. The literature lists the first 3 to 6 authors of the article cited, followed by "et al". Journal titles can only be abbreviated as in Index Medicus. The journal abbreviation can be found at: http://www.nlm.nih.gov/. If the abbreviation is not known, give the name of the journal as a whole. The literature is cited as follows:

Journal articles

Standard journal article:

Gao SR, McGarry M, Ferrier TL, Pallante B, Gasparrini B, Fletcher JR, et al. Effect of cell confluence on production of cloned mice using an inbred embryonic stem cell line. Biol Reprod. 2003; 68 (2): 595-603.

Organization as author:

WHO collaborative study team on the role of breastfeeding on the prevention of infant mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. Lancet. 2000; 355: 451–5.

No authors listed:
Coffe drinking and cancer of the pancreas [editorial]. BMJ. 1981; 283 628.

A volume with a supplement:
Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig heart anaphylaxis. Pharmacol Res Commun. 1988; 20 Suppl 5: 75–8.

Books and other monographs

The author is a person (s):
Carlson BM. Human embryology and developmental biology. 3rd ed. St. Louis: Mosby; 2004.

Editor (s) as authors:
Brown AM, Stubbs DW, editors. Medical physiology. New York: Wiley; 1983.

Chapter in a book:
Blaxter PS, Farnsworth TP. Social health and class inequalities. In: Carter C, Peel JR, editors. Equalities and inequalities in health. 2nd ed. London: Academic Press; 1976. p. 165–78.

Meeting announcements: Harris AH, editor. Economics and Health: 1997: Proceedings of the 19th Australian Conference of Health Economists; 1997 Sep 13-14; Sydney, Australia. Kensington, N.S.W.: School of Health Services Management, University of New South Wales; 1998.

Conference Articles:
Anderson JC. Current status of chorion villus biopsy. In: Tudenhope D, Chenoweth J, editors. Proceedings of the 4th Congress of the Australian Perinatal Society; 1986: Brisbane, Queensland: Australian Perinatal Society; 1987. p. 190-6.

Dissertation:
Cairns RB. Infrared spectroscopy studies of solid oxygen. Dissertation. Berkley, California: University of California, 1965.

Electronic material

Article in aninternetmagazine:
Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs. 2002; 102 (6). Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Article published electronically before the printed version:
Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002-Nov-15; 100 (10): 3828-31. Epub 2002 Jul 5.

CD-ROM:
Anderson SC, Poulsen KB. Anderson's Electronic Atlas of Hematology [CD-ROM]. Philadelphia: Lippincott Williams & Wilkins; 2002.

Online monograph:
Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap.edu/books/0309074029/html/.

Website:
Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

Part of awebsite:
American Medical Association [homepage on the Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2screens]. Available from: http: //www.ama-assn.org/ama/pub/category/1736.html

NOTE. A paper that does not meet the requirements of this guide cannot be referred for review and will be returned to the authors for completion and correction. Adhering to the preparation instructions will significantly shorten the time of the entire process until the paper is published, which will positively affect the quality of the articles and the regularity of the publication of the journal.

For any additional information, please contact the address and email below.

EDITORIAL ADDRESS

Timočki Medicinski Glasnik
(Timok Medical Journal)
Zdravstveni centar Zaječar
(Zaječar Health Center)
Pedijatrijska služba Pediatric Service
Rasadnička bb, 19000 Zaječar,
Serbia (Republic of Serbia-RS)

Ordinacija "Dr Bastać",
Kosančićev venac 16 19000 Zaječar
Serbia (Republic of Serbia-RS)
063402396, 019432333
dusanbastac@gmail.com

Email: tmglasnik@gmail.com
Website: http://www.tmg.org.rs/

TIMOČKI MEDICINSKI GLASNIK

TIMOK MEDICAL GAZETTE