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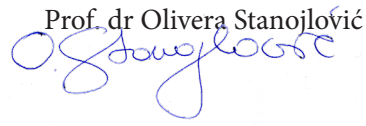

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REVIEW

Open aortic aneurysm repair in the endovascular era

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Summary

Open repair (OR) of aortic aneurysms is still relatively mutilating and risky in older and high-risk patients. Since the introduction of EVAR, a significantly lower perioperative mortality has been noted. Apart from advantages, endovascular treatment has some disadvantages as well, due to which OR still has a very important role in the endovascular era.

In a vast majority of the patients younger than 65, with good overall condition, long life expectancy and favorable anatomy, as well as in patients with hostile aneurysm neck anatomy, heritable connective tissue disorders, complete thrombosis of abdominal aortic aneurysm (AAA) and potent accessory renal arteries, OR is the first treatment option in comparison with the endovascular treatment. EVAR is recommended as the first treatment option in patients with inflammatory aneurysms and OR should be considered only in better shaped patients with inflammatory AAA and significant hydronephrosis.

Late open surgical conversion (LOSC) is a noted event after endovascular treatment and is associated with a significantly higher perioperative mortality and other serious perioperative complications compared to primary OR.

Multicenter randomized controlled trials (RCT) did not find a significant difference regarding 30-day mortality between open and endovascular repair of ruptured AAA. However, not all ruptured AAA are suitable for endovascular repair. In a hemodynamically unstable patients, when there is no time for MDCT angiography, EVAR is not possible, and OR is the only option. The incidence of abdominal compartment syndrome after OR is significantly lower in comparison with EVAR thanks to surgical evacuation and drainage of retroperitoneal hematoma.

The improvement of the results of aortic aneurysm treatment largely depends on the volume of yearly aortic operations. Having in mind all the mentioned advantages and disadvantages of OR and endovascular repair, we can conclude that in high volume centers, younger generations of vascular surgeons should be educated in standard and complex open aortic surgery.

Keywords: aortic aneurysm, endovascular treatment, EVAR, open repair

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INTRODUCTION

In the first half of the twentieth century, wrapping has been used in the treatment of aortic aneurysms. The aneurysm is wrapped in omentum or cellophane to strengthen the wall and prevent rupture. (1) Nyssen treated Einstein's abdominal aortic aneurysm (AAA) in 1948. The results lasted for seven years when AAA ruptured. However, Einstein refused to undergo a more modern operation. Those were his words exactly: *"I want to go when I want. I have done my share, it is time to go. I will do it elegantly"*. He died on April 12th, 1955. (2)

Open repair (OR) of aortic aneurysm that is performed today was introduced about 70 years ago. (3-5) Despite an improvement during the past decades, OR of aortic aneurysms is still relatively mutilating and risky in older and high-risk patients. An approach to aortic aneurysms is mutilating enough. Namely, OR of AAA requires laparotomy, OR of thoracic aneurysms (TAA) requires thoracotomy, while OR of thoracoabdominal aortic aneurysms (TAAA) requires thoraco-phreno-lumbotomy. It is followed by dissection, aortic cross clamping (ACC), and finally with aneurysm replacement using prosthetic graft. In addition, in OR of TAAA, revascularization of the spinal cord and all visceral organs is necessary. However, it requires cerebrospinal fluid drainage, segmental sequential ACC, mechanical circulatory support, moderate hypothermia, and selective retrograde perfusion of visceral organs. (6) It is associated with very high perioperative mortality in older and high-risk patients.

At the beginning of the last decade of the 20th century, Volodos and Parodi introduced endovascular aneurysm repair (EVAR). (7, 8) Owing to EVAR laparotomy, thoracotomy, or thoraco-phreno-lumbotomy and ACC are avoided. Instead of that, a stent-graft is placed through the femoral artery in the groin, often under local anesthesia, to the spot of the aortic aneurysm. The final step is stent-graft deployment in the aneurysmal sac. Owing to this, the aneurysm is excluded from circulation. EVAR results in a significantly lower perioperative blood loss, shorter hospitalization, faster recovery, and finally a significantly lower perioperative mortality. (9)

However, apart from the described advantages, EVAR has some disadvantages as well. This is the reason why OR of aortic aneurysms still has a very important role in the endovascular era. In the following part of this paper the main indications for OR of aortic aneurysms will be explained. Those recommendations are based on the literature analysis and on the significant experience of the Clinic for Vascular and Endovascular Surgery of the UCC of Serbia.

DEGENERATIVE AORTIC ANEURYSMS WITH FAVORABLE ANATOMY

There is no evidence in recent literature to support EVAR as first-line therapy in patients below the age of 65. (10) We disagree that patients' motivation and surgeons' experience should be the main reasons for EVAR in younger, well-conditioned patients with degenerative AAA with suitable anatomy. That is especially supported having in mind long term results. According to EVAR trial 1, endovascular repair of AAA had a significantly higher total and aneurysm-related mortality after 8 years of follow-up in comparison with OR. The increased aneurysm-related mortality in the EVAR group was mainly caused by secondary aneurysmal sac rupture. The incidence of life-threatening re-interventions was also significantly higher in the EVAR group after eight years. (11) To be more precise, the reported single-center late open surgical conversion (LOSC) rates after EVAR ranged from 0.67% to even 22.8%. (12)

Despite advances in the OR of descending thoracic aneurysms during the past few decades, TEVAR is associated with a significantly lower 30-day mortality, as well as with a significantly lower incidence of spinal cord ischemia, respiratory failure and renal insufficiency. However, there is no difference in long-term survival after the second year of the follow-up. (13) At the same time, the incidence of LOSC after TEVAR is higher than previously thought, even in very experienced endovascular centers. (14) Some of the most recently published studies have not found a significant difference regarding early mortality and neurological complications comparing open and total endovascular repair of TAAA. (15) At the same time, OR provides a much lower rate of required re-interventions. (16)

All being said, OR should be considered as first treatment option for degenerative aortic aneurysms with favorable anatomy, in good-risk patients with long life expectancy. (17, 18)

DEGENERATIVE AORTIC ANEURYSMS WITH UNFAVORABLE ANATOMY

Using these five neck hostility criteria, a Delphi Consensus document identifies patients in whom standard EVAR is feasible; those in whom standard EVAR is not the first choice; those in whom standard EVAR is not advised due to moderate or high risk of failure, and finally, those in whom standard EVAR is not applicable. (19) According to this document, a standard EVAR is not applicable when the neck of the aneurysm is below the length of 10 mm, when the diameter is higher than 32 mm and the angulation is higher than 75^0, when circumferential calcification is at least 50%, as well as when its shape is conical. (19) According to a relatively old study, 35% of AAA in male and even 60% in female patients, are not suitable for standard EVAR because of unfavorable aneurysm neck. (20)

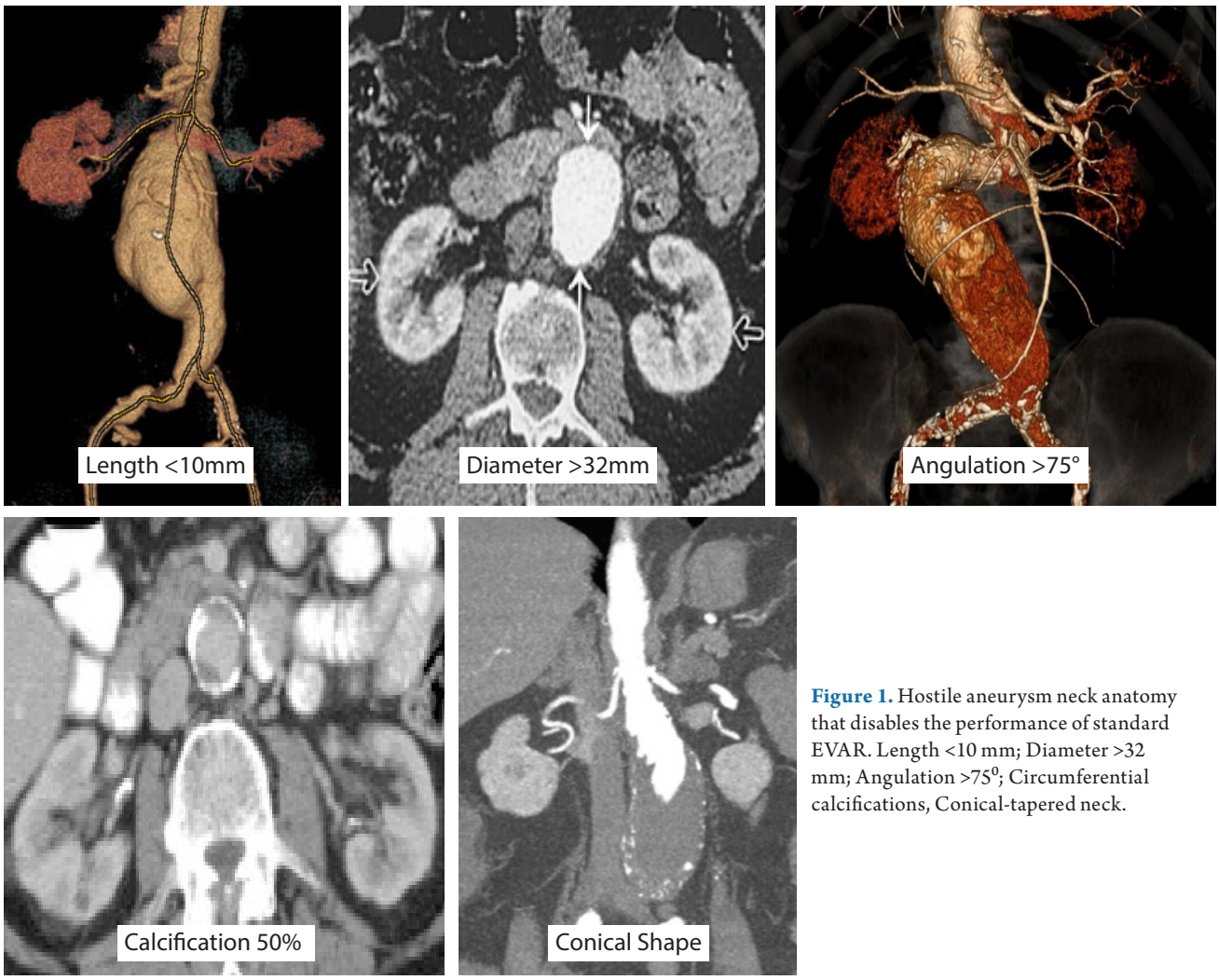

Figure 1. Hostile aneurysm neck anatomy that disables the performance of standard EVAR. Length <10 mm; Diameter >32 mm; Angulation >75^0; Circumferential calcifications, Conical-tapered neck.

New, more flexible generations of thoracic stent-grafts enable their easy implantation in very angulated aneurysms. However, long-term results are not that satisfying. Namely, a significant angulation is an important cause of long-term stent-graft migration, which was presented in our case. (14)

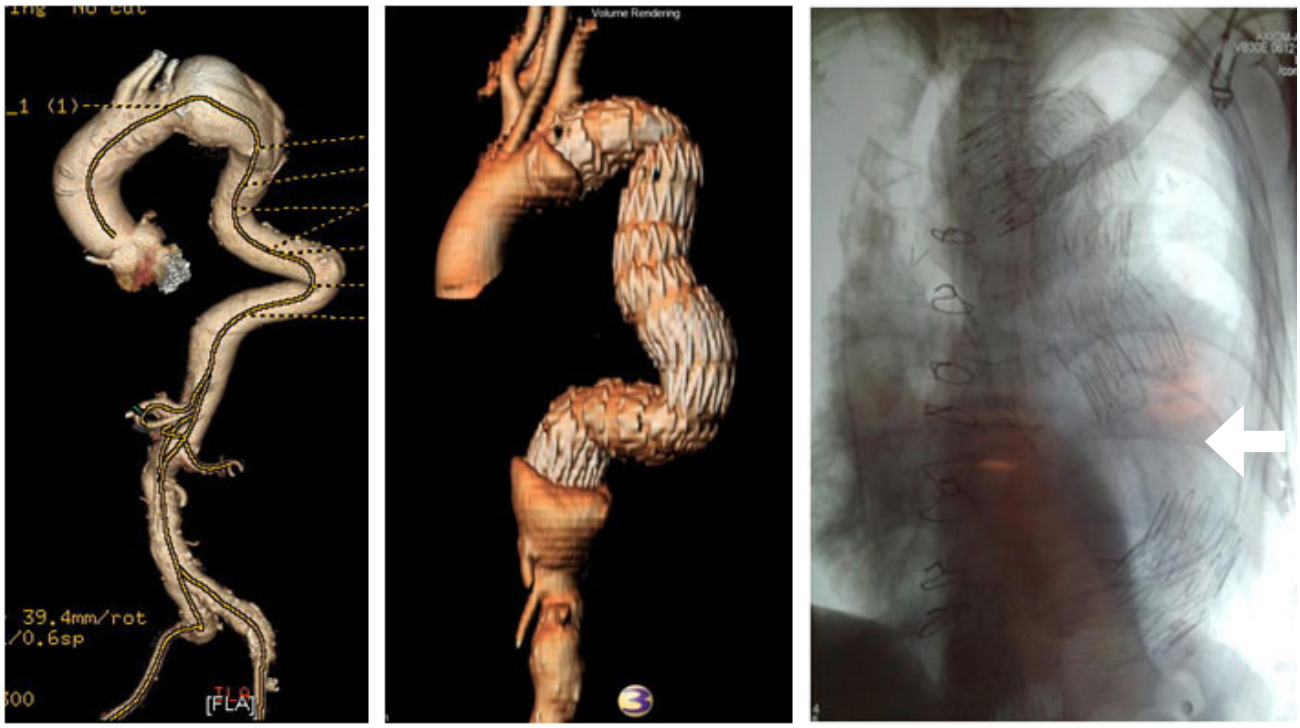

Figure 2. MDCT angiography presents the aneurysm of the descending thoracic aorta with significant angulation (left) before and (middle) after TEVAR (right). Chest radiography presents migration of the distal component of the thoracic stent graft (white arrow).

Severe tortuosity and small diameter of iliac arteries can also be limiting factors for standard EVAR or TEVAR.

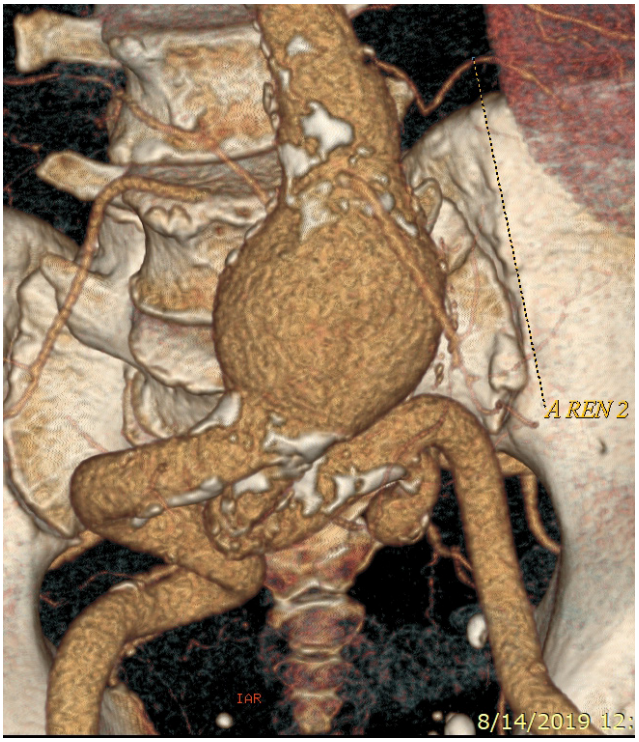

Figure 3. Severe tortuosity of iliac arteries, which disables standard EVAR.

Because of a short distal landing zone, severe angulation of the thoracic aorta, an occlusion of infrarenal aorta, visceral artery stenosis, as well as tortuosity and small diameter of iliac arteries, between 20 and 40% of TAAA are unsuitable for total endovascular repair. (21, 22)

OR should be considered as first treatment option for degenerative aortic aneurysms with unfavorable anatomy. (17, 18)

HERITABLE DISORDERS OF CONNECTIVE TISSUE

Endovascular aneurysm repair is not recommended in patients with heritable disorders of connective tissue. Namely, the friability of the aortic wall in these patients seems to be incompatible with the radial force of stent-grafts. At the same time, generalized disease in these patients very frequently causes dilatation of the non-stented aortic segments. Therefore, type 1 endoleak and graft migration can occur. (23) Due to this, endovascular aneurysm repair is recommended in patients with heritable disorders of connective tissue only as a "bridge" to open surgery in emergency cases, including rupture and severe malperfusion. (17, 24) Endovascular aneurysm repair should also be considered if these patents have significant comorbidity. (25) In a vast majority of patients with heritable disorders of connective tissue, OR is the method of choice for the treatment of aortic aneurysms.

MYCOTIC AORTIC ANEURYSMS

A recommendation from the ESVS guidelines regarding the mycotic AAA is not clearly defined. (17) According to the Swedish national vascular registry, there is no difference in long-term survival and infection-related death outcome between in-situ open and endovascular repair in patients with mycotic AAAs. (26) In our opinion, surgical excision of mycotic AAA followed with an extra-anatomic axillo-bifemoral bypass provides lower early mortality rate nd lower long-term re-infection rates in comparison with in-situ open or endovascular repair. Endovascular treatment of mycotic TAA and TAAA, as well as primary aorto-duodenal (ADF), aorto-pulmonary (APF) and aorto-esophageal (AEF) caused by aneurysm rupture, provides an early survival benefit. However, it is associated with a very high re-infection rate. Due to this reason, endovascular repair can be used only as a "bridge" to a definitive open surgery. (27-29)

INFLAMMATORY AORTIC ANEURYSMS

OR of inflammatory AAAs is associated with a high risk of intraoperative injury of surrounding structures as well as with higher in-hospital mortality. (30) Due to this, EVAR is recommended as first treatment option in patients with inflammatory AAA. (17) OR should be considered only in well-conditioned patients with inflammatory AAA who have significant hydronephrosis. (31)

COMPLETE THROMBOSIS OF ABDOMINAL AORTIC ANEURYSMS

Unlike peripheral aneurysms, complete acute or chronic AAA thrombosis is unusual. However, if AAA thrombosis occurs, EVAR is not feasible. (32) OR is the only option for these patients.

ABDOMINAL AORTIC ANEURYSMS WITH ASSOCIATED ACCESSORY RENAL ARTERIES

Current guidelines recommend that accessory renal arteries with diameter larger than 3 mm should be preserved during open and endovascular repair of AAA. (17, 33) On the other hand, EVAR very often requires covering of accessory renal arteries to achieve an adequate proximal landing zone. It is always followed by partial renal infarction, which is not accepted and recommended in patients with preexisting renal failure. (34) OR provides an optimal exposition of accessory renal arteries and their preservation (reattachment). Due to this, in a vast majority of cases OR is a method of choice for the treatment of AAA with associated significant accessory renal arteries. (35, 36)

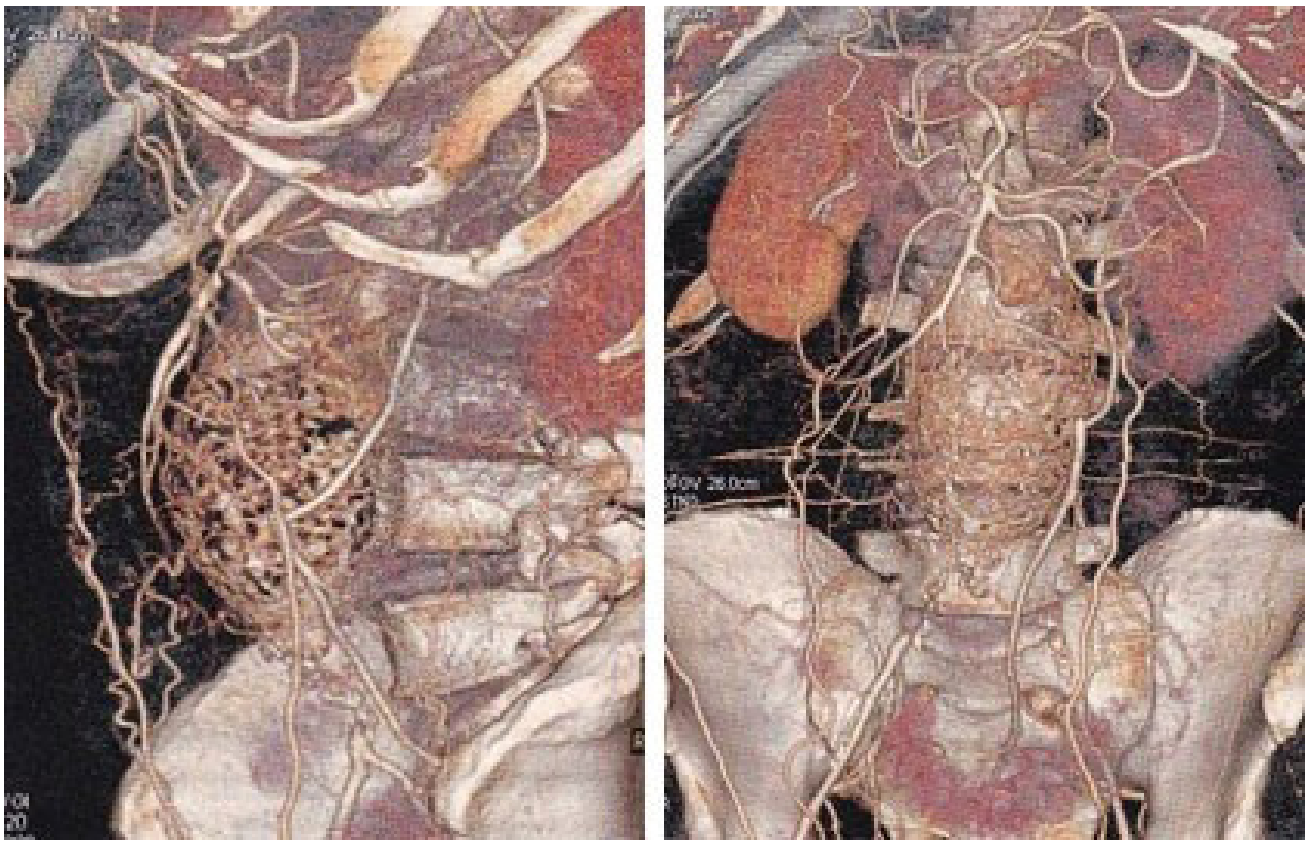

Figure 4. Complete thrombosis of the abdominal aortic aneurysm that disables EVAR.

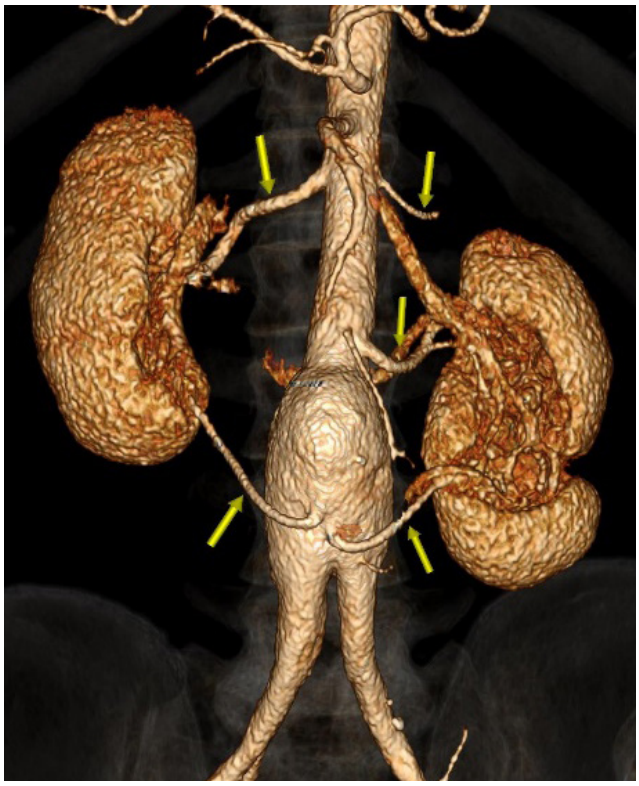

Figure 5. MDCT angiography presents the infrarenal aorta with two normal and three accessory renal arteries. Two of them originate from the AAA.

LATE OPEN SURGICAL CONVERSION AFTER ENDOVASCULAR ANEURYSM REPAIR

Some long-term complications after previous endovascular aneurysm repair require late open surgical conversion (LOSC). (12) To be more precise, different types of endoleaks, stent-graft collapse, migration and infection, as well as late rupture of the aneurysmal sac are indications for LOSC after EVAR. At the same time, endoleak type I with aneurysm enlargement, aneurysm enlargement without endoleak, collapse, migration and infection of the thoracic stent-graft, distal aneurysm formation and finally secondary AEF and APF, mostly require LOSC after TEVAR. (14)

However, LOSC after both EVAR and TEVAR is associated with significantly higher perioperative mortality and other very serious perioperative complications in comparison with primary OR of TAA and TAAA. (12, 14, 37)

RUPTURED ABDOMINAL AORTIC ANEURYSMS

Multicenter randomized controlled trials (RCT) did not find a significant difference regarding 30-day mortality between open and endovascular repair of ruptured AAA (AJAX trial: EVAR-21%, OR-25% (38), IMPROVE trial: EVAR-35% (39), OR-37%; ECAR trial: EVAR-18%, OR-24% (40)). This has also been confirmed with the most recently published Japanese national study. (41) Apart

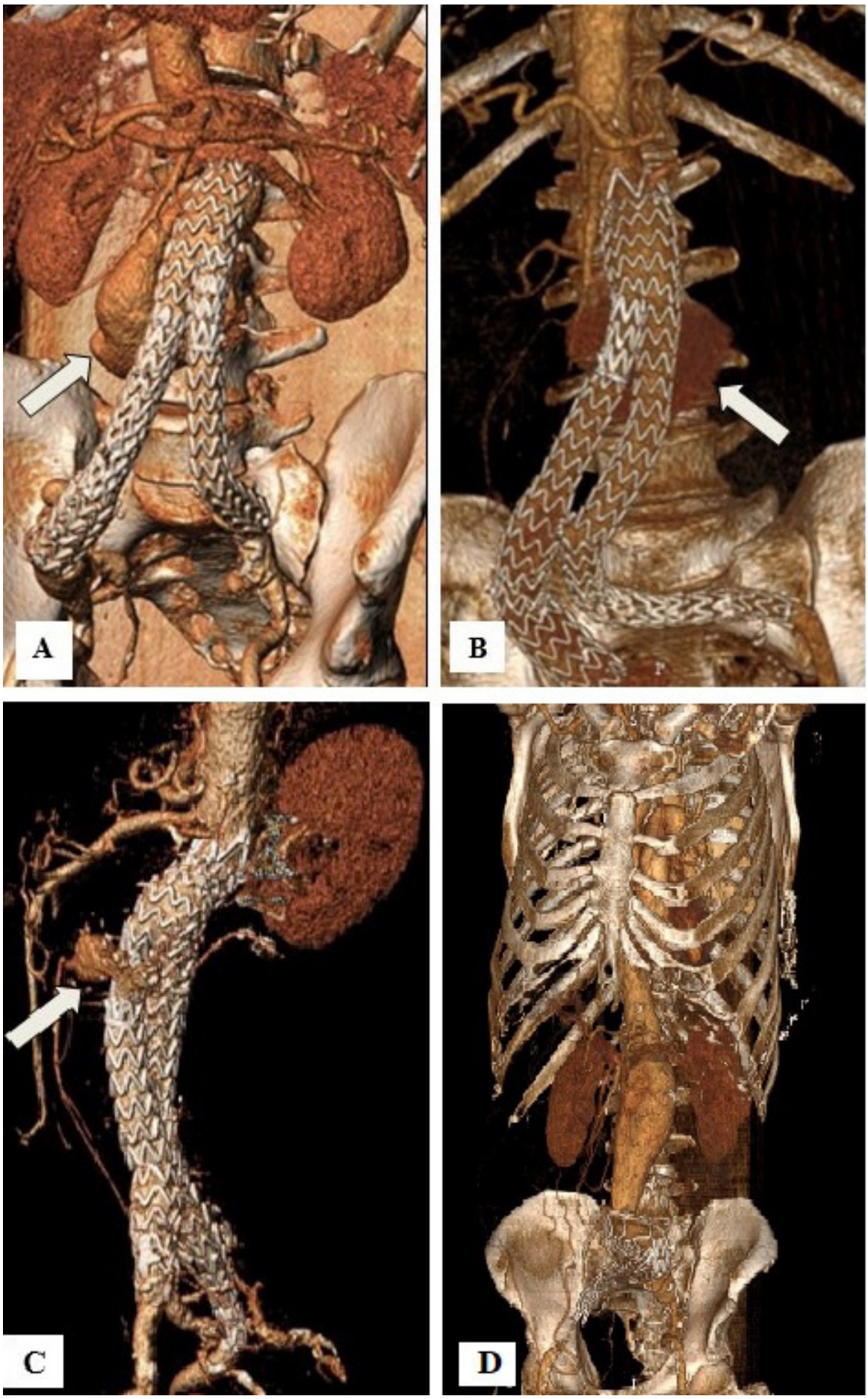

Figure 6. MDCT angiography presents (A) endoleak type I; (B) endoleak type II; (C) endoleak type III; (D) stent graft migration after EVAR.

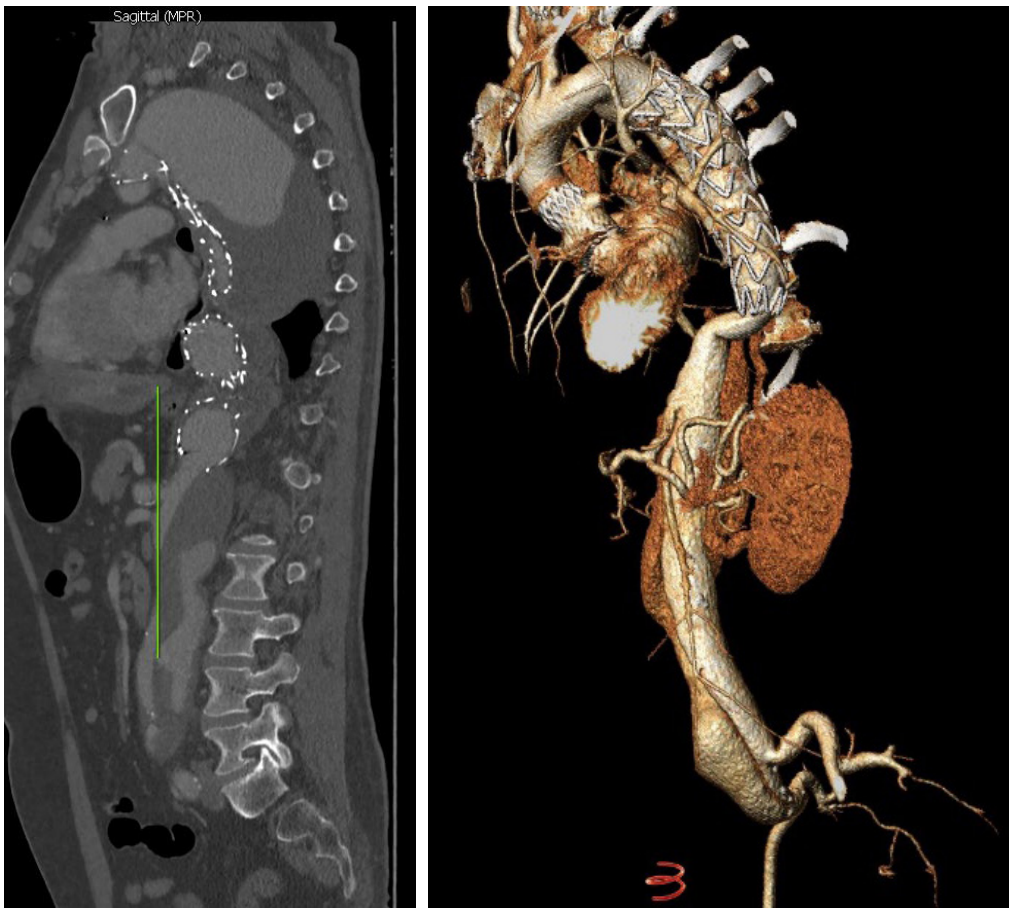

Figure 7. MDCT angiography presents (left) the collapse of the thoracic stent graft; (right) distal aneurysm formation after TEVAR.

from that, the majority of vascular surgeons believe that EVAR is the first treatment option for the majority of patients with ruptured AAAs. However, not all ruptured AAAs are suitable for endovascular repair.

A significant number of patients with ruptured AAA is in hemodynamic unstable condition, and if not treated immediately upon admission, more than 80% will die within two hours. (42) In some cases, there is not enough time to perform MDCT angiography, and yet, without it, EVAR is not possible. (43) These patients should be treated after duplex ultrasonography confirmation of ruptured AAA. OR is the only option in such circumstances.

According to IMPROVE trial, 30-day mortality after EVAR in relatively hemodynamic stabile patients with good aortic anatomy is 25%, but this group represents only 60% of patients with RAAA. (39) At the same time, long-term mortality and complications after endovascular repair of ruptured AAA are associated with unfavorable anatomy. (44)

Abdominal compartment syndrome after both open and endovascular repair of ruptured AAA is associated with high mortality. (45, 46) Owing to surgical evacuation and drainage of retroperitoneal hematoma, the incidence of abdominal compartment syndrome after OR is significantly lower compared to EVAR. (47)

CONCLUSION

With all being said about the importance of OR of aortic aneurysms in endovascular era, the question about how to improve the results still remains. First of all, the hospital volume is an independent predictor of an early outcome after OR of aortic aneurysms. (48, 49) Our Clinic is considered a high-volume center for aortic surgery and owing to this fact, a 30-day mortality after elective OR of AAA has been below 1%. in the past few years (50) The most recently published studies confirm that a country-based centralization of AAA treatment also reduced perioperative mortality. (51-53) However, what exactly does the high-volume aortic center mean? Recommendations are different. According to SVS guidelines, an elective AAA OR can be performed at centers with the volume of at least 10 procedures each year and with perioperative mortality of 5% or less. (33) In our opinion, it is impossible to guarantee such a low rate of perioperative mortality with such small experience. Due to this, representatives of our Clinic who participated in writing the current ESVS guidelines insisted on the hospital volume higher than 30 procedures per year. (17)

This article has shown that several groups of patients with aortic aneurysms may benefit from the OR. Due to this, younger generations of vascular surgeons should be educated in standard and complex open aortic surgery.

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We have no conflict of interests to declare.

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OTVORENA REPARACIJA ANEURIZME AORTE U ENDOVASKULARNOJ ERI

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Sažetak

Otvorena rekonstrukcija (*OR*) aneurizme aorte je i dalje relativno mutilantna i rizična procedura kod starijih pacijenata i pacijenata sa komorbiditetima. Od uvođenja *EVAR*-a zabeležen je značajno manji perioperativni mortalitet. Pored prednosti, endovaskularni tretman ima i nedostatke, zbog kojih *OR* i dalje ima veoma važnu ulogu u endovaskularnoj eri.

Kod velike većine pacijenata mlađih od 65 godina, zadovoljavajućeg opšteg stanja, sa dugim očekivanim životnim vekom i povoljnom anatomijom, kao i kod pacijenata sa hostilnom anatomijom vrata aneurizme, naslednim poremećajima vezivnog tkiva, potpunom trombozom aneurizme abdominalne aorte (*AAA*) i potentnom aksesornom bubrežnom arterijom, *OR* je prva opcija lečenja u odnosu na endovaskularni tretman. *EVAR* se preporučuje kao prva opcija lečenja kod pacijenata sa inflamatornim aneurizmama, a *OR* treba uzeti u obzir samo kod pacijenata koji su zadovoljavajućeg opšteg stanja, sa inflamatornom *AAA* i značajnom hidronefrozom. Kasna otvorena hirurška konverzija (*LOSC*) je zabeležen događaj nakon endovaskularnog tretmana i povezan je sa značajno većim perioperativnim mortalitetom i drugim ozbiljnim perioperativnim komplikacijama u poređenju sa primarnim *OR*. Multicentrična randomizovana kontrolisana ispitivanja (*RCT*) nisu pronašla značajnu razliku u pogledu 30-dnevnog mortaliteta između otvorene i endovaskularne reparacije rupture *AAA*. Međutim, nisu svi pacijenti sa rupturiranom *AAA* kandidati za endovaskularnu proceduru. Kod hemodinamski nestabilnih pacijenata, kada nema vremena za *MDCT* angiografiju, *EVAR* nije moguć i *OR* je jedina opcija. Incidenca sindroma abdominalnog kompartmenta posle *OR* je značajno niža u poređenju sa *EVAR*-om zahvaljujući hirurškoj evakuaciji i drenaži retropertonealnog hematoma.

Poboljšanje rezultata lečenja aneurizme aorte u velikoj meri zavisi od obima godišnjih operacija aorte. Imajući u vidu sve navedene prednosti i nedostatke OR i endovaskularne rekonstrukcije, možemo zaključiti da bi u centrima velikog obima mlađe generacije vaskularnih hirurga trebalo da se obrazuju iz standardne i složene otvorene hirurgije aorte.

Ključne reči: aneurizma aorte, endovaskularni tretman, EVAR, otvorena hirurgija aorte

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RESEARCH ARTICLE

Transient tachypnea of the newborn – need for supplemental oxygen and possible complications

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Summary

Transient tachypnea of the newborn, which is a self-limiting condition, in some cases requires invasive respiratory support. This study aimed to investigate the influence of gestational age and mode of delivery on oxygen therapy, and the occurence of complications.

This retrospective study covered data about children diagnosed with transient tachypnea who were born during the period of one year. The duration of oxygen therapy and the assessment of complications were analyzed according to the mode of delivery and gestational age.

In 77,3% of cases transient tachypnea was well-managed with the use of oxygen therapy in incubator. In relation to the mode of delivery and gestational age, no significant differences in the duration of different oxygen therapy types were observed. Two newborns developed persistent pulmonary hypertension, and one newborn had pneumothorax.

Invasive respiratory support is not frequently used in transient tachypnea. Persistent pulmonary hypertension and air leak syndrome are possible but very rare complications of this condition.

Keywords: Transient Tachypnea of the Newborn; Gestational Age; Cesarean Section; Oxygen Inhalation Therapy;

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INTRODUCTION

Respiratory distress (RD) represents a group of pathological conditions with the incidence of about 7% in all neonates, and 0.5-2.8% for transient tachypnea of the newborn (TTN) as one of its leading causes (19). TTN or "wet lung" syndrome, is self-limmiting RD disorder occuring within the first few hours after birth, and lasting between two and four days. In most cases, TTN occures in late preterm (34–36+6 weeks' gestation), and term neonates born between 37 and 39 weeks (6). Insufficient evacuation of fetal lung fluid is an underlying condition, leading to compliance decrease, a reduction of functional residual capacity and tidal volume, and finally inadequate minute ventilation, the state responsible for breathing acceleration and development of other TTN's clinical features (23). Tachypnea and distinctive radiological findings are the most representative clinical signs, sufficient for diagnosis of TTN. Recognized risk factors for TTN are: cesarean section (CS), male gender, macrosomia, preterm delivery, maternal sedation, perinatal asphyxia, meconium amniotic fluid, chorioamnionitis, and olygoamnion (17, 21, 22). In full-term newborns, additionally proposed risk factors are the following: assisted reproducive technologies, operative vaginal delivery (forceps or vacuum extraction), and the 5th minute Apgar score (AS) < 8 (22). Further on, previous investigations reported that maternal asthma and gestational diabetes were independent risk factors for developing TTN (3, 15). Although the treatment of TTN mostly requires the use of conventional non-invasive oxygen (O_2) therapy, sometimes invasive types of respiratory support, including nasal continous positive airway pressure (nCPAP) and mechanical ventilation (MV) are benefitial to patient care. Maintenance of tachypnea and the need of prolonged use of supplemental O_2 may be responsible for the development of TTN complications, such as persistent pulmonary hypertension (PPHN) and air leak syndrome (10).

THE AIM

Since there is a lack of relevant data about the incidence and clinical characteristics of TTN in our population, this study aimed to investigate the influence of gestational age and mode of delivery on TTN incidence, posibble appearance of TTN complications (PPHN and air leak syndrome), as well as the need for different types of respiratory support, and duration of oxygen therapy.

MATERIALS AND METHODS

This observational retrospective study was carried out at the Department of Neonatology, The Clinic of Gynecology and Obstetrics "Narodni Front", Belgrade, Serbia, in accordance with the ethical standards laid down in 1964 Declaration of Helsinki and its later amendments, and after the approval of the institutional ethics review committee. The research included the data between January 1st and December 31st, 2016. During this period, 7380 newborns were born at the clinic.

All relevant data were gathered from medical records. Clinical findings for the newborns with TTN were: 1. tachypnea (> 60 breaths per minute), within 6 hours after delivery; 2. chest radiography – lung hyperinflation evidenced by flattening and depression of the diaphragmatic domes or increased anteroposterior diameter, or both, prominent perihilar vascular marking and enlarged interlobar fissures containing pleural fluid; 3. need for respiratory support – (O2 in incubator, nCPAP and MV).

Exclusion criteria were clinical, laboratory, bacteriological, and radiological findings for other conditions leading to respiratory distress (1, 9). Additional exclusion criteria were multifetal pregnancies, operative vaginal deliveries (forceps or vacuum), 5th minute AS < 8, birth weight (BW) < 2500 or > 4000 grams, and delivery before 34 weeks gestation.

Newborns included in this study were compared according to the mode of delivery (vaginal vs. CS) and gestational age (late preterm (34-36+6 weeks) and full-term neonates (37-42 weeks')). Frequency and duration of different types of O_2 therapy (O_2 in incubator, nCPAP, MV) were analyzed depending on the mode of delivery and gestational age. The assessment of possible development of TTN complications was conducted through consecutive ultrasonography heart examination (PPHN) and chest radiography (air leak syndrome).

Statistical analyses were performed using IBM SPSS Statistics for Windows Software (Version 25.0; IBM Corp, Armonk, NY, USA). Statistical significance between categorical data was determined by Pearson's chi-square test ($\chi 2$). Statistical significance between numerical data was determined by Student's t-test and Mann-Whitney U-test. The logistic regression analysis was used to compare types of O_2 therapy and its duration in relation to the week of gestation and mode of delivery. All P values below 0.05 were considered significant.

Table 1. Distribution of TTN patients according to the gender, mode of delivery and gestational age of birth.

		N	%	P value [a]
Gender	Male	54	72	P < 0.001
	Female	21	28	
Mode of delivery	Vaginal	25	33.3	P < 0.001
	CS	50	66.7	
Gestational age	34-36+6	53	70.7	P < 0.001
	37-40	22	29.3	

[a] Chi-square test;
N - number of patients; CS –cesarean section

Table 2. Correlation between gender, mode of delivery and gestational age of birth in TTN patients.

			Gender		
			Male	Female	P value [a]
Delivery	vaginal	N (%)	19 (76)	6 (24)	0.585
	CS	N (%)	35 (70)	15 (30)	
Gestational age	34-36+6	N (%)	37 (69.8)	16 (30.2)	0.512
	37-40	N (%)	17 (77.3)	5 (22.7)	
			Gestational age		
			34-36	37-40	
Delivery	Vaginal	N (%)	19 (35.8)	6 (27.3)	0.473
	CS	N (%)	34 (64.2)	16 (72.7)	

[a] Chi-square test;
N - number of patients; CS –cesarean section

RESULTS

During the investigated one year period, 75 out of 7380 newborns developed TTN (1,02%). Among newborns with TTN, male gender was significantly more represented than female gender ($P < 0,001$), and CS was performed about twice more frequently compared to vaginal delivery. Median for gestational age at birth was 36, with earliest delivery in 34 and latest in 40 weeks of gestation. More than two thirds of TTN patients were born between 34 and 36+6 weeks, and the rest belonged to the group of full-term newborns **(Table 1)**.

There was no statistically significant difference for gender distribution in relation to the mode of delivery (P=0,585), or gestational age at birth (P=0.512) **(Table 2)**. Also, the number of SC and vaginal deliveries was not significantly different in late preterm group compared to the term neonates group (P=0.473) **(Table 2)**.

Mostly, TTN was a mild clinical condition and well-managed with the use of O_2 therapy in the incubator (58 cases, 77, 3%). Other types of respiratory support were used in 10 (13, 3%) and 7 (9, 3%) patients (nCPAP and MV). The duration of oxygen therapy shorter than two days was recorded in 34 (45, 3%) newborns with TTN, whereas the need for supplement oxygen > 2 days was present in 41 (54, 7%) patients. The duration of respiratory support did not show a statistical difference in relation to the mode of delivery **(Table 3)** (p=0,251). Further on, after dividing TTN patients according to the type of O2 therapy used, the difference between the duration of all three types of supplemental oxygen therapy in correlation to the mode of delivery was not statistically significant **(Table 3)**.

Table 3. Frequency of oxygen therapy duration according to the mode of delivery in TTN patients.

Type of O_2 therapy	Delivery		Therapy duration		P value[a]
			< 2 days	> 2 days	
O_2 in incubator	Vaginal	N (%)	8 (38.1)	13 (61.9)	0.331
	CS	N (%)	19 (51.4)	18 (48.6)	
nCPAP	Vaginal	N (%)	1 (25)	3 (75)	1.000
	CS	N (%)	2 (33.3)	4 (66.7)	
MV	CS	N (%)	4 (57.1)	3 (42.9)	
Total O_2 therapy	Vaginal	N (%)	9 (36)	16 (64)	0.251
	CS	N (%)	25 (50)	25 (50)	

[a] Chi-square test;
N - number of patients; CS - cesarean section; nCPAP - nasal continuous positive airway pressure; MV - mechanical ventilation;

Table 4. Frequency of oxygen therapy duration according to the gestational week of birth in TTN patients.

Type of O_2 therapy	Gestational age		Therapy duration		P value[a]
			< 2 days	> 2 days	
O_2 in incubator	34-36+6	N (%)	22 (50)	22 (50)	0.351
	37-40	N (%)	5 (35.7)	9 (64.3)	
nCPAP	34-36+6	N (%)	22 (50)	22 (50)	0.500
	37-40	N (%)	1 (16.7)	5 (83.3)	
MV	34-36+6	N (%)	4 (80)	1 (20)	0.143
	37-40	N (%)	0 (0)	2 (100)	
Total O_2 therapy	34-36+6	N (%)	28 (52.8)	25 (47.2)	0.043
	37-40	N (%)	6 (27.3)	16 (72.7)	

[a] Chi-square test; N - number of patients; nCPAP - nasal continuous positive airway pressure; MV - mechanical ventilation;

According to the gestational age, the term newborns group significantly more often required supplemental O_2 for more than two days, compared to the late preterm group (p=0,043) **(Table 4)**. However, after dividing TTN patients into subgroups according to the type of respiratory support used, we did not found a statistical difference between O_2 therapy duration in relation to the gestational age (incubatory O_2 (p=0,351), nCPAP (p=0,500), MV (p=0,143)) **(Table 4)**.

Complications of TTN were observed in only 3 out of 75 TTN cases (4%). Two newborns developed PPHN, and one had pneumothorax. PPHN patients were born in 35 and 36 weeks of gestation, and gestational age of the patient with pneumothorax was 37 weeks. All 3 cases were delivered with CS and required MV use.

DISCUSSION

Our study has shown that TTN was diagnosed in 1.02% newborns during the period of one year. This is in line with previously reported data demonstrating TTN frequency between 0.5% and 2.8% (19). Today, 3 out of 4 preterm babies are born near term (4). Previous studies have shown significantly higher incidence of respiratory morbidity in the group of newborns delivered before 39 weeks of gestation (16, 20). TTN is a common cause of RD in early neonatal period, especially in the group of neonates born near term (18, 20). Possible explanations for frequent RD occurrence in the group of late preterm newborns are partial surfactant deficiency and cessation in lung development during the transitional phase when vesicles switch to the alveolar stage (10). Even in 37 weeks of gestation the risk of TTN is 3 times higher than in 39 and 40 weeks (12).

Changes in maternal and fetal hormonal milieu during the last few weeks of pregnancy, together with the onset of spontaneous labor are the factors responsible for rapid maturation and fetal preparation for delivery and adaptation to extrauterine life (12). Our study showed 2,5 fold increase of TTN incidence in the group of late preterm neonates (70,7%) compared to the newborns delivered in 37 weeks of gestation and later (29,3%). These results are in accordance with previously reported findings indicating that lungs of preterm fetuses are not ready for transition to extrauterine life, while lungs of term fetuses are physiologically prepared for evacuation of lung fluid stimulated by spontaneous labor (24). Moreover, immaturity of lung epithelial mechanism for Na^+ transport is described as one of the reasons for TTN development (24). Previous investigation found that alpha-subunit of epithelial Na^+ channels (ENaC) played a role in disturbance of lung fluid clearance and consequently lead to premature deaths in mice (11).

Lower gestational age, CS and male gender are described as risk factors for TTN (6). Our results are similar, showing CS frequency to be twice higher than vaginal delivery in newborns with TTN. It is estimated that elective CS is responsible for about 50% of RD cases, with TTN as the most frequent cause (19). A crucial event for normal extrauterine respiratory adaptation is the process of lung fluid evacuation. This is accomplished via compressions on the child's chest by physical forces present during vaginal delivery and with uterine contractions, which are absent in elective CS (23). Numerous studies tried to determine a correlation between the development of TTN and CS performed after signs of spontaneous delivery occurred. One study did not show a decreased risk of TTN development in preterm neonates born after CS with previous signs of spontaneous delivery (6). Nevertheless, researchers described that respiratory symptoms were significantly more frequent after planned Cesarean delivery (16). Fetal increase of catecholamine concentrations provoked by spontaneous labor and rupture of fetal membranes, are additional factors which regulate the absorption of lung fluid and stimulate surfactant release (2). Studies have shown a significantly lower catecholamine levels and changes in lung function in a term infant after an elective CS in comparison to vaginal delivery (14).

We found a similar number of CS and vaginal deliveries in both late preterm and term newborns with TTN. This is in accordance with previous studies describing that preterm neonates are more prone to TTN development, regardless the mode of delivery (6). After 37 weeks of gestation, a significant decrease in incidence of TTN and other RD conditions is observed, regardless the mode of delivery (13).

Beside lower gestational age and CS, our results also showed that male gender was significantly more often present in TTN group. Male gender, as a risk factor for TTN was described and recognized in earlier studies as well (6, 10, 19).

Although in most cases represented as a benign condition, TTN requires the use of respiratory support (10, 19). Our results showed that therapy with O_2 in incubator was used in 77.3% newborns with TTN. This is in line with the fact that TTN is most commonly a benign condition demanding minimal therapeutic measures. This research showed that invasive types of respiratory support were mostly required in the late preterm group, probably due to the lung immaturity which made adaptation to extrauterine life difficult. A previous study described the need for assisted ventilation longer than three days in 9.3% TTN cases (8). The duration of oxygen therapy for more than two days was more frequent in the group of term newborns compared to the late preterm group. However, analyzing the duration of different respiratory support types, this statistical significance was lost. Since TTN is most often a self-limiting process, lasting for 48-72 h, the reason for a prolonged need of oxygen support in term newborns might be additional pathological con-

ditions. One research showed longer use of O_2 therapy, more frequent MV need and longer hospitalization in the group of children delivered after CS without symptoms of spontaneous labor (1). Preterm birth, low AS, and umbilical artery acidosis were described as independent risk factors for a worse TTN outcome (1).

Nasal CPAP is demonstrated as a useful method in TTN treatment, due to a decrease in the occurrence of TTN therapy side effects (9). Researchers described a significantly shorter neonatal intensive care unit stay, the need for minimal O_2 fraction, and similar incidence of air leak syndrome in the nCPAP group in comparison with the oxygen supplementation group (9). Additionally, different MV types were compared with nCPAP in order to define the best TTN treatment option. Nasal high frequency percussive ventilation (NHFPV) was proposed as safe in TTN treatment. Compared to CPAP, NHFPV use was well-tolerated, more effective, with a significantly shorter duration, demanding lower O2 concentrations, and showing no complications (7). Nasal intermittent mandatory ventilation (NIMV) showed similar efficacy and tolerance, without a significant difference in the duration of respiratory support, hospitalization and the occurrence of TTN complications in comparison with nCPAP (5).

Although TTN is most often a self-limiting condition, lung air leak syndrome and PPHN might occur as a result of hypoxemia (10, 19). A contribution to these conditions might be the immaturity of the system for surfactant production, which has been already recognized as a mechanism for TTN development (10, 19). Only 3 our patients manifested a TTN complication. Pulmonary hypertension was observed in two preterm neonates, whereas pneumothorax developed in one term newborn. All three were born with the CS.

CONCLUSIONS

TTN is RD disorder, most frequently present among late preterm and term neonates. Our study, in accordance with previously published results, has shown that lower gestational age, Cesarean delivery and male gender are independent risk factors for TTN development. In most cases, TTN did not require invasive respiratory support. As was noticed in our patients, PPHN and air leak syndrome are rare but possible complications of this condition.

This study is the first one performed on our population giving the information about TTN clinical course. There is a need for large, prospective studies that would provide information about other potential TTN causes, and possible long-term complications. Furthermore, in order to clarify the pathophysiological mechanisms responsible for the occurrence of TTN and its clinical course, it is necessary to carry out studies which will examine the possible presence and amount of retained fluid in the lungs of neonates, the maturity of the surfactant production system, and changes in the catecholamine level in the mother's blood during delivery.

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TRANZITORNA TAHIPNEA NOVOROĐENČADI – POTREBA ZA DODATNIM KISEONIKOM I MOGUĆE KOMPLIKACIJE

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Sažetak

Tranzitorna tahipneja novorođenčeta (TTN) predstavlja samoograničavajući proces, koji zahteva primenu invazivne oksigenoterapije. Cilj ovog rada je da se ispita uticaj gestacijske starosti i načina porođaja na incidenciju TTN, pojava komplikacija, potreba za oksigenoterapijom i dužina njene primene.

Ova retrospektivna studija je obuhvatila podatke o deci rođenoj tokom perioda od godinu dana. Na osnovu kriterijuma za uključenje i isključenje iz studije izdvojena su novorođenčad sa TTN. Ispitivana je dužina primenjene oksigenoterapije i procena pojave TTN komplikacija. Kod 77,3% slučajeva, TTN je bila blagog kliničkog toka, sa potrebom za oksigenoterapijom u inkubatoru. Statističkom analizom je pokazano da ne postoji značajna razlika u dužini primene oksigenoterapije posmatrano u odnosu na način završetka porođaja, kao i u odnosu na gestacijsku nedelju rođenja. Dvoje novorođenčadi je razvilo kliničku sliku perzistentne plućne hipertenzije, a kod jednog je došlo do razvoja pneumotoraksa. TTN u većini slučajeva ne zahteva potrebu za invazivnom respiratornom potporom. Perzistentna plućna hipertenzija i sindrom curenja vazduha su vrlo retke, ali moguće komplikacije TTN.

Ključne reči: tranzitorna tahipneja novorođenčeta, gestaciona starost, carski rez, oksigenoterapija.

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RESEARCH ARTICLE

Influence of metabolic parameters on LDL and HDL size and subclasses in adolescents with type 1 diabetes

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Summary

Alterations in the serum of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) size and subclass contribute to the atherogenesis in coronary artery disease in diabetic patients.

The purpose of this study is to evaluate the effect of metabolic parameters on LDL and HDL size and subclasses in adolescents with type 1 diabetes.

The cross-sectional study included 43 adolescents (23 females, 20 males) with type 1 diabetes of mean age 15.09±1.94 years, with mean disease duration of 5.86 ± 3.08 years. LDL and HDL particles were separated by polyacrylamide gradient gel electrophoresis, while serum lipid parameters were determined by routine laboratory methods.

Patients with inadequate metabolic control (HbA1c ≥ 7.5%) had a higher mean value of triglycerides (TG) (p = 0.041), higher proportions of small, dense LDL particles (p = 0.045), higher proportions of LDL IIA subclasses (p=0.03) and smaller LDL diameter (p = 0.02) and HDL diameter (p = 0.04) than patients with optimal metabolic control (HbA1c < 7.5%). Higher HbA1c and higher TG levels were statistically significantly related to small, dense LDL (ρ=0.341, p=0.025; ρ= 0.394, p= 0.009) and HDL particles (ρ=0.684, p=0.000; ρ=0.421, p=0.005). Predictors of small, dense LDL and HDL particles, which contribute to atherogenesis, were high HbA1c (HR = 1.52, 95% CI: 0.97-2.40; HR 3.87, 95% CI: 2.11-7.10) and elevated TG (HR= 1.10, 95% CI: 1.00-1.20; HR 1.85, 95% CI: 1.07-3.21).

Diabetic adolescents require particular attention in order to minimize factors such as high HbA1c and elevated TGs in the development of future cardiovascular events.

Keywords: type 1 diabetes, adolescents, LDL, HDL

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INTRODUCTION

Clinical manifestations of cardiovascular disease (CVD) are extremely rare in childhood, but the atherosclerotic process starts as early as the first years of life and is significantly accelerated by type 1 diabetes (1,2). Hyperglycemia is considered the primary mediator of atherosclerosis in type 1 diabetes, where for each percent of absolute raise in glycated hemoglobin (HbA1c) the relative risk for future CVD events is increased by 7% (1-4). People with type 1 diabetes and good metabolic control have similar lipid profiles as the healthy population, but it is not clear whether their lipid composition is more atherogenic (5-8). On the other hand, sub-optimal metabolic control could lead to diabetic dyslipidemia, which is characterized by high levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), and low levels of high-density lipoprotein cholesterol (HDL-C) (9). Alterations in serum lipids and lipoprotein levels, especially the presence of small, dense LDL and HDL particles contribute to atherogenesis in coronary artery disease (CAD) in the general population as well as in diabetic patients, although studies in children and adolescents with type 1 diabetes are limited. (8).

In this cross-sectional study, we investigated the effect of metabolic parameters on LDL and HDL size and subclasses in adolescents with type 1 diabetes. There have been no reports specifically addressed to the evaluation of risk factors of lipoprotein size and subclass distribution that have been involved in premature atherosclerosis in type 1 diabetic adolescents.

PATIENTS AND METHODS

In a cross-sectional study involving 43 adolescents (23 females, 20 males) with type 1 diabetes of mean age 15.09±1.94 years, with mean disease duration of 5.86 ± 3.08 years, we evaluated lipoprotein subclasses and their connection with metabolic risk factors. The patients were treated at the University Children's Hospital of Belgrade, Serbia. The patients were selected according to the following criteria: the duration of type 1 diabetes over 2 years and patients' age of over 11 years. They were classified into two groups according to the HbA1c: adolescents with optimal metabolic control (HbA1c < 7.5%) and adolescents with inadequate metabolic control (HbA1c ≥ 7.5%). None of the patients had any known family history of dyslipidemia or early CVD. Adolescents were checked four times a year or more often if required and assessed at the end of the year. Assessment consisted of measurements of HbA1c, body mass index (BMI), total cholesterol (TC), TGs and calculations of insulin doses during the first visit to the hospital, updated at each following visit. All the patients were on an intensive insulin therapy regimen. Ambulatory blood pressure monitoring (ABPM) was performed and lipoprotein subclasses were determined when adolescents underwent their annual check-up during the 24-hour hospitalization. Adolescents with type 1 diabetes and associated diseases, which may interfere with lipoprotein levels, were excluded. The stage of puberty was evaluated according to Tanner. All the adolescents had either Tanner stage 2-4 (67.4%) or completed pubertal development (32.6%). Using oscillometric type of SpaceLabs 90207 units and appropriate cuffs placed on the non-dominant arm, the ABPM recorded 24-hour values of systolic blood pressure (SBP) and diastolic blood pressure (DBP).

METABOLIC PARAMETERS

Glycated hemoglobin (HbA1c) was measured by turbidimetric immunoassay using the Beckman Synchron CX5 Clinical System apparatus. In healthy persons, normal HbA1c test results using this method range from 4.0% to 6.5%.

Blood samples were drawn for analyzing LDL-C, HDL-C, TC, TGs and LDL and HDL subclass distribution. Electrophoretic separation and determination of 7 LDL and 5 HDL subclasses was performed at the research laboratory of the Department for Medical Biochemistry at the Faculty of Pharmacy, University of Belgrade. In brief, for the separation of lipoprotein subclasses we used in-house casted polyacrylamide gradient (3-31%) gels. Electrophoresis was conducted by using the Hoefer SE 600 Ruby electrophoresis unit (Amersham Pharmacia Biotech, Vienna, Austria). For the calibration of the gels, we applied Pharmacia High Molecular Weight protein standards and carboxylate polystyrene microsphere beads. Following electrophoretic separation, protein standards and lipoprotein subclasses were visualized by staining with Coomassie brilliant blue G-250 and Sudan Black, respectively. The analysis of separated fractions and determination of LDL and HDL subclasses distribution was performed by using Image Scanner (Amersham Pharmacia Biotech, Vienna, Austria) and Image Quant software (version 5.2;1999; Molecular Dynamics, GE Healthcare, Waukesha, WI, USA). Dominant LDL and HDL particle diameters were estimated as diameters of major peaks in the LDL and HDL region of the scan. The relative proportion of each subclass was determined as the percentage of the entire LDL or HDL densitometric scan area, which corresponds to the peak of each subclass. The relative proportion of small, dense LDL was assessed by adding the relative proportions of LDL III and IV subclasses. Accordingly, the relative proportion of small HDL subclasses was determined as a sum of percentages of HDL 3a, 3b and 3c subclasses.

STATISTICAL ANALYSES

For statistical data processing, in our study we used the statistical package SPSS for Windows. The obtained data were presented as mean ± SD. The comparison between the two independent groups was evaluated using the independent two-sample Student's t-test or Mann-Whitney U-test when appropriate. The default of $\alpha < 0.05$ specified the level of significance in all the tests. The correlation between the numerical variables was calculated by Spearman's correlation coefficient (ρ). Univariate analysis for predictors of small, dense LDL and HDL particles was performed using simple logistic regression. The study was approved by the Medical Ethics Committee of the University Children's Hospital, affiliated to the Faculty of Medicine, University of Belgrade, Serbia (approval number: 2019-053).

RESULTS

Clinical data and lipid profiles of adolescents with type 1 diabetes with optimal and inadequate metabolic control are presented in **Table 1**. Forty-three subjects, 23 females (53.5%) and 20 males (46.5%) met the inclusion criteria for the study. The mean HbA1c was 7.93 ± 1.38%; 18 (41.9%) patients had inadequate metabolic control with mean value 8.30 ±1.54% which statistically differs from that in patients with optimal metabolic control 7.51±1.04%. The patients with inadequate metabolic control had a higher mean value of TGs (1.03 ± 0.63 vs 0.83 ± 0.39 mmol/L; p = 0.041), higher proportions of small, dense LDL particles (53.62 ± 13.80 vs 49.86 ± 18.83%; p = 0.045), higher proportions of LDL IIA subclasses (12.37 ± 5.54 vs 11 ± 3.65%; p=0.03) and smaller LDL diameter (21.42 ± 1.59 vs 25.88 ± 2.26 nm; p = 0.02) and HDL diameter (9.33 ± 0.94 vs 10.34 ± 0.98 nm, p = 0.04) than patients with optimal metabolic control. With respect to all other proportions of lipoprotein subclasses, there was no statistically significant difference.

Table 1. Clinical data and lipid profiles of diabetic adolescents with optimal and inadequate metabolic control (X±SD)

Characteristics	**HbA1c ≥ 7.5% N=18**	**HbA1c < 7.5% N=25**	**Total N=43**	**p value**
Age (years)	15.78 ± 1.67	14.3 ± 1.97	15.09 ± 1.94	0.97
Gender (male/female) (%)	61.1/38.9	52/48	46.5/53.5	0.36
Mean diabetes duration (years)	6.88 ± 3.21	4.75 ± 2.57	5.86 ± 3.08	0.71
Pubertal Tanner stage 2-4/5 (%)	69.6/30.4	65/35	67.4/32.6	0.12
BMI (kg/m^2)	22.05 ± 2.63	19.37 ± 2.64	20.71 ± 2.91	0.45
HbA1c (%)	8.30 ± 1.54	7.51 ± 1.04	7.93 ± 1.38	0.03*
Mean insulin dose (units/kg/day)	0.81± 0.34	0.85 ± 0.34	0.83 ± 0.34	0.95
SBP (mmHg)	109.50±11.6	107.1±10.3	108.29 ± 11.15	0.65
DBP (mmHg)	69.60 ± 5.10	67.80 ± 9.30	68.90 ± 7.29	0.75
Triglycerides (mmol/L)	1.03 ± 0.63	0.83 ± 0.39	0.92 ± 0.52	0.041*
Total cholesterol (mmol/L)	4.72 ± 0.92	4.61 ± 0.68	4.68 ± 0.82	0.16
HDL-C (mmol/L)	1.82 ± 0.38	1.73 ± 0.41	1.77 ± 0.39	0.052
LDL-C (mmol/L)	2.57 ± 0.76	2.20 ± 0.58	2.38 ± 0.67	0.11
Small, dense LDL (%)	53.62 ± 13.80	49.86 ± 18.83	51.61 ± 16.60	0.045*
LDL diameter (nm)	21.42 ± 1.59	25.88 ± 2.26	25.86 ± 2.14	0.02*
LDL I (%)	23.53 ± 11.25	21.42 ± 8.59	22.55 ± 10.04	0.25
LDL IIA (%)	12.37 ± 5.54	11 ± 3.65	11.73 ± 4.75	0.03*
LDL IIB (%)	14.23 ± 4.85	13.95 ± 3.55	14.10 ± 4.25	0.34
LDL IIIA (%)	12.52 ± 3.30	13.32 ± 2.86	12.89 ± 3.09	0.36
LDL IIIB (%)	6.37 ± 2.26	6.98 ± 1.92	6.65 ± 2.10	0.36
LDL IVA (%)	12.62 ± 5.60	12.53± 4.40	12.58 ± 5.02	0.19
LDL IVB (%)	18.32 ± 10.71	20.8 ± 8.45	19.47 ± 9.69	0.10
Small HDL (%)	28.03 ± 12.56	29.63 ± 12.34	28.78 ± 12.34	0.97
HDL diameter (nm)	9.33 ± 0.94	10.34 ± 0.98	10.22 ± 0.95	0.04*
HDL 2a (%)	19.39 ± 5.72	20.42 ± 6.14	19.87 ± 5.87	0.64
HDL 2b (%)	52.56 ± 12.77	49.94 ± 13.73	51.34 ± 13.14	0.50
HDL 3a (%)	10.58 ± 4.25	11.93 ± 5.06	11.21 ± 4.64	0.20
HDL 3b (%)	6.29 ± 5.31	6.24 ± 4.22	6.26 ± 4.78	0.78
HDL 3c (%)	11.16 ± 6.46	11.45 ± 6.62	11.29 ± 6.46	0.85

X – mean value; SD – standard deviation; BMI – body mass index (kg/m^2); HbA1c – glycosylated hemoglobin (%); SBP: Systolic Blood Pressure (mmHg); DBP: Diastolic Blood Pressure (mmHg); HDL-C – high-density lipoprotein cholesterol (mmol/L); LDL-C – low-density lipoprotein cholesterol (mmol/L); *p < 0.05 between diabetic adolescents with optimal and inadequate metabolic control

Table 2. Results of univariate logistic regression analysis for small, dense LDL and HDL particles

	Small, dense LDL particles		Small HDL particles	
Variable	p value	Odds ratio (95% CI) mean (range)	p value	Odds ratio (95% CI) mean (range)
HbA1c (≥7.5%)	0.04*	1.52 (0.97-2.40)	0.034*	3.87 (2.11-7.10)
BMI (kg/m^2)	0.78	0.84 (0.25-2.87)	0.73	1.40 (0.20-9.50)
TG (>1.5mmol/L)	0.04*	1.10 (1.00-1.20)	0.02*	1.85 (1.07-3.21)
TC (>5.2mmol/L)	0.42	1.01 (0.98-1.05)	0.76	1.03 (0.84-1.27)
LDL-C (>2.6mmol/L)	0.05	13.18 (2.62-66.19)	0.50	0.58 (0.12-2.88)
HDL-C (<1.1mmol/L)	0.80	1.43 (0.09-2.11)	0.78	1.07 (0.67-1.70)
SBP (mmHg)	0.77	0.99 (0.93-1.05)	0.73	1.39 (0.20-9.48)
DBP (mmHg)	0.95	1.00 (0.92-1.09)	0.49	1.04 (0.93-1.15)

HbA1c – glycosylated hemoglobin (%),BMI – body mass index (kg/m^2), TG – triglycerides (mmol/L), TC – total cholesterol (mmol/L), LDL-C – low-density lipoprotein cholesterol (mmol/L), HDL-C – high-density lipoprotein cholesterol (mmol/L), SBP: Systolic Blood Pressure (mmHg), DBP: Diastolic Blood Pressure (mmHg)); *p < 0.05

We found a statistically significant correlation between HbA1c, TGs and small, dense LDL particles (ρ=0.341, p=0.025; ρ= 0.394, p= 0.009), indicating the association between increased HbA1c, TGs, and small, dense LDL particles and vice versa. Also, the small HDL particles were in a statistically significant correlation with HbA1c and TGs (ρ=0.684, p=0.000; ρ=0.421, p=0.005). No correlation was found between the duration of diabetes, insulin doses, TC, LDL-C, HDL-C, SBP, DBP and small, dense LDL and HDL particles.

In our patients, higher TG levels were in a statistically significant negative correlation with LDL and HDL diameters (ρ=-0.650, p=0.000; ρ=-0.394 p=0.009;).

We constructed univariate logistic regression models to examine factors associated with atherosclerosis in CAD in diabetic adolescents **(Table 2)**. Factors associated with small, dense LDL and HDL particles were high HbA1c (hazard ratio (HR)= 1.52, 95% confidence interval (CI): 0.97-2.40; HR 3.87, 95% CI: 2.11-7.10) and elevated TGs (HR= 1.10, 95% CI: 1.00-1.20; HR 1.85, 95% CI: 1.07-3.21) **(Table 2)**.

DISCUSSION

Pediatric patients with type 1 diabetes have a higher risk of CVD development at an earlier age. (9). Hyperglycemia predisposes atherogenesis in type 1 diabetes and silent coronary atherosclerosis in young adults with diabetes is strongly associated with poor glycemic control (9-11). Poor glycemic control is also associated with a potentially more atherogenic lipoprotein profile (12). Well-controlled type 1 diabetes is not associated with gross blood lipid disturbance, but more advanced lipoprotein subclass examinations reveal atherogenic profiles (13). In patients on intensive insulin therapy or continuous subcutaneous insulin infusion, the TG level is usually optimal and we showed that diabetic adolescents with inadequate metabolic control didn't have hypertriglyceridemia (>1.5 mmol/L) but they had significantly higher TGs, higher proportions of small, dense LDL particles, smaller LDL and HDL particle sizes and more LDL IIA subclasses than adolescents with optimal metabolic control.

Previous studies documented a presence of smaller LDL and HDL particles in people with type 1 diabetes (14,15), but this is the first study to report abnormal lipoprotein composition (LDL and HDL size and subclasses) in adolescents with type 1 diabetes. Cholesterol levels of our type 1 diabetic adolescents did not significantly correlate with LDL and HDL size and with the amount of small, dense LDL and HDL particles possibly because of a small sample of subjects. Also, several studies showed that the TC levels of the diabetic children did not vary throughout puberty in contrast to TG levels (1,7,16). Our results indicated that high HbA1c and higher TGs were the main factors associated with the higher amount of small, dense LDL and HDL particles and higher TG was associated with smaller LDL and HDL particle sizes. Our current data extend previous limited observations on lipid profile in people with type 1 diabetes with the finding of significantly reduced HDL size, but not LDL size. Investigations confirmed a strong association of smaller HDL size with elevated oxidative stress and low-grade inflammation in asymptomatic individuals, suggesting that the abnormalities in HDL particles occur even before the onset of atherosclerosis (15,16). A correlation between higher TG and smaller LDL size has not been reported previously and the precise mechanism underlying this association is unknown. These studies also showed that highly increased TGs rich in lipoprotein subclasses are observed in relation to reduced lipoprotein lipase activity, as well as the increased presence of small, dense LDL and HDL particles which contribute to early atherosclerosis (15-17).

STUDY LIMITATIONS

The main limitation of our study is the inclusion of a relatively small group of participants. However, taking into

consideration that we analyzed adolescents over the age of 11, with the duration of type 1 diabetes of over two years, results can be considered valuable. To obtain more reliable data, it would be advisable to perform a similar analysis on a large sample of adolescents with type 1 diabetes.

CONCLUSION

In conclusion, the risk factors identified for the presence of small, dense LDL and HDL particles in our adolescents with type 1 diabetes were poorer glycemic control and elevated TG levels. Since these particles could be one of the factors that accelerate the development of atherosclerosis in type 1 diabetes, screening for their presence and identification of the factors affecting their excessive production, could have beneficial effects on reducing the risk of future cardiovascular events.

Conflict of interest

None to declare.

Author contributions

The conception or design of the work – Maja Ješić, Smiljka Kovačević; the acquisition- Smiljka Kovačević, Vera Zdravković, Stefan Đorđević, analysis, or interpretation of data- Maja Ješić, Smiljka Kovačević, Aleksandra Zeljković, Dejana Stanisavljević; preparing the draft of the manuscript or interpretation of revised version of manuscript- Maja Ješić, Miloš Ješić, Milica Vuković.

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UTICAJ METABOLIČKIH PARAMETARA NA VELIČINU I SUBKLASU LDL I HDL KOD ADOLESCENATA SA DIJABETESOM TIP 1

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Sažetak

Promene veličine i potklasa lipoproteina male gustine (LDL) i lipoproteina velike gustine (HDL) u serumu doprinose nastanku aterogeneze tokom razvoja koronarne arterijske bolesti kod pacijenata sa dijabetesom.

Cilj rada je proceniti uticaj metaboličkih parametara na veličinu i podklasu LDL i HDL čestica kod adolescenata sa dijabetesom tipa 1.

U studiju preseka bilo je uključeno 43 adolescenta (23 žene, 20 muškaraca) sa dijabetesom tipa 1 prosečne starosti 15,09 ± 1,94 godina, sa prosečnim trajanjem bolesti od 5,86 ± 3,08 godina. Čestice LDL i HDL razdvojene su elektroforezom u gradijentnom poliakrilamidnom gradijentu, dok su vrednosti parametara serumskih lipida određene rutinskim laboratorijskim metodama.

Pacijenti sa neadekvatnom metaboličkom kontrolom (HbA1c ≥ 7,5%) imali su veću srednju vrednost triacilglicerola (TG) (p = 0,041), veći udeo potklase malih, gustih LDL čestica (p = 0,045), veći udeo potklase LDL IIA (p = 0,03) i manji prečnik LDL -a (p = 0,02) i prečnika HDL -a (p = 0,04) od pacijenata sa optimalnom metaboličkom kontrolom (HbA1c <7,5%). Više koncetracije HbA1c i TG bile su statistički značajno povezanie sa postojanjem malih, gustih LDL čestica (r = 0,341, p = 0,025? r = 0,394, p = 0,009) i HDL česticama (r = 0,684, p = 0,000? r = 0,421, p = 0,005). Prediktori malih, gustih čestica LDL i HDL, koji doprinose aterogenezi, bili su visoki HbA1c (HR = 1,52, 95% CI: 0,97-2,40; HR 3,87, 95% CI: 2,11-7,10) i povišena koncentracija TG (HR = 1,10, 95% CI: 1,00-1,20; HR 1,85, 95% CI: 1,07 - 3,21).

Da bi se kod adolescenata obolelih od dijabetesa sprečio razvoj budućih kardiovaskularnih poremećaja posebnu pažnju treba obratiti na faktore kao što su visoke koncentracije HbA1c i TG.

Ključne reči: tip 1 dijabetes, adolescenti, HDL, LDL.

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REVIEW

Unbalanced diet as a cardiometabolic risk factor

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Summary

A well-balanced diet is an important factor in the promotion and maintenance of good health throughout one's life. The role of a diet as a determinant of chronic non-communicable diseases is well established and it occupies a prominent position in prevention. The burden of chronic diseases is rapidly increasing worldwide. Namely, chronic non-communicable diseases are the leading cause of death worldwide. Preterm mortality in people under 70 accounts for over 40% of the total of 38 million deaths due to chronic non-communicable diseases. Obesity, metabolic syndrome, and diabetes mellitus are also showing worrying trends, not only because they already affect a large part of the population, but also because they have started to occur earlier in life. Thus, the metabolic syndrome is a cluster of more or less related metabolic and cardiovascular derangements including visceral obesity, insulin resistance, dyslipidemia, hypertension and glucose intolerance. This syndrome is characterized by a primary cellular defect in insulin action due to disorders in insulin signal transduction (insulin is unable to adequately achieve its biological effects). Under these conditions, insulin resistance, in combination with hyperinsulinemia causes numerous metabolic and cardiovascular disorders, which are leading causes of morbidity and mortality worldwide. From the pathophysiological point of view, a diet rich in carbohydrates and saturated fats significantly contributes to the development of many chronic diseases (diabetes mellitus type 2, hypertension, accelerated atherosclerosis and its cardiovascular and cerebrovascular complications, nonalcoholic fatty liver disease, polycystic ovary syndrome, and some malignant diseases – breast cancer, etc.). In this review, we provide an overview of recent literature data and practical knowledge related to an unbalanced diet as a cardiometabolic risk factor. Further investigations in the field of molecular prevention may contribute to the development of new biomarkers, or help the setting of strategies for molecular prevention of chronic non-communicable diseases. In other words, they represent the directive for applying nutrigenomics to population sciences.

Keywords: unbalanced diet; obesity; insulin resistance; cardiovascular derangements; nutrigenetics; nutrigenomics

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INTRODUCTION

Whatsoever was the father of a disease, an ill diet was the mother.

George Herbert

Metabolic syndrome (MS) represents a combined phenomenon of glucose intolerance, arterial hypertension, dyslipidemia, central (abdominal/visceral) obesity type, as well as other metabolic disorders with underlaying insulin resistance (IR). This syndrome is principally characterized by a primary cellular defect of insulin action, i.e. insulin is unable to fulfill its biological role because of inadequate signal transduction. Under such conditions, IR in combination with consequent hyperinsulinemia causes numerous metabolic and cardiovascular (CVD) disorders, which are pandemic-like, and are the leading cause of morbidity and mortality in the world [1–9].

MS is a clinical entity that significantly contributes to the origin and development of a wide range of chronic non-communicable diseases, such as diabetes mellitus (DM) type 2, arterial hypertension, accelerated atherosclerosis with its CVD and cerebrovascular complications, polycystic ovary syndrome and some malignancies (breast cancer, etc.) [1, 8, 10, 11]. This very common set of pathophysiological disorders of metabolic origin, also referred to as syndrome X and IR syndrome, is present in approximately one in four adults [1, 12]. It is also a risk factor for the development of CVD disease, which is why it is called the "deadly quartet" [1].

MS has been the main culprit for the development of CVD in the last decade. People with MS have a 2-fold increased risk of mortality from CVD and are three times more likely to develop myocardial infarction or stroke than healthy people [1]. In addition, these individuals have a much higher risk of developing DM type 2 [1, 3]. Also, all components of MS are independent causes of CVD events, such as stroke, cardiomyopathy, coronary artery disease, myocardial infarction, heart failure, and sudden cardiac death [1]. In addition, MS is a significant risk factor for the emergence and development of non-alcoholic fatty liver disease (NAFLD) [11]. Moreover, NAFLD, as a hepatic manifestation of MS and the most common chronic liver disease, is now one of the independent risk factors for heart (left ventricular dysfunction and hypertrophy, atrial fibrillation, and valvular calcification) and vascular disease, as well as chronic kidney disease. It is also associated with other chronic diseases, such as sleep apnea, malignant diseases (colorectal carcinoma and breast cancer), osteoporosis, psoriasis and endocrinopathies (polycystic ovary syndrome, etc.) [4, 7].

There are several different definitions of MS. In clinical practice, the definitions given by experts from the International Diabetes Federation (IDF), as well as experts from the American Heart Association (AHA) and the National Heart, Lung and Blood Institute (NHLBI) are most commonly used [1, 2]. According to the IDF consensus, MS represents the incidence of population-specific abdominal obesity **(Table 1)**, together with at least two other criteria from the next group (plasma triglyceride /TG/ concentration greater than 1.7 mmol/L or hypertriglyceridemia drug treatment; high density lipoprotein /HDL/ in plasma lower than 1.03 mmol/L in men, and below 1.3 mmol/L in women; arterial blood pressure greater than 130/85 mm Hg or arterial hypertension pharmacological therapy, glycemia above 5.6 mmol/L or previously diagnosed type 2 DM) [1].

AHA and NHLBI experts have accepted the IDF criteria for the clinical diagnosis of MS, where the presence of central obesity was verified by waist circumference greater than 102 cm in men and greater than 88 cm in women [1, 10]. In addition, in order to take into account the overall picture of MS, especially in diabetics and patients with CVD, the IDF consensus emphasizes the need for additional examination of adipose tissue distribution, IR, lipid status and vascular function. Besides, it is necessary to determine the hormonal status (pituitary-adrenal axis), inflammatory process mediators (C-reactive protein /CRP/, inflammatory cytokines, adiponectin, etc.), as well as coagulation factors (fibrinogen, etc.) and fibrinolysis [2].

Table 1. IDF criteria for visceral obesity in metabolic syndrome

Ethnicity	*Sex*	*Waist circumference (cm)*
Europe	Male	≥ 94
	Female	≥ 80
South Asia	Male	≥ 90
	Female	≥ 80
Japan	Male	≥ 90
	Female	≥ 80
China	Male	≥ 90
	Female	≥ 80
South and Central America	Male	≥ 90
	Female	≥ 80
Sub-Saharan Africa	Male	≥ 94
	Female	≥ 80
Eastern Mediterranean and the Middle East	Male	≥ 94
	Female	≥ 80

Table 2. Classification of body mass according to body mass index (BMI)

Status	*BMI (kg/m²)*	*Disease development risk*
Underweight	< 18.5	Increased
Normal	18.5–24.9	Normal
Overweight	25–29.9	Increased
Obesity class 1	30–34.9	High
Obesity class 2	35–39.9	Very high
Obesity class 3	> 40	Extremely high

MS is based on the interaction of endogenous (genetic) factors and exogenous factors (obesity, physical inactivity, high energy food intake /food rich in carbohydrates and fats/, age, sex, race, positive family history for obesity and/or arterial hypertension and/or DM, difficulty adapting to stressful situations, chronic stress, etc.), which lead to the development of IR and an increase in the amount of visceral adipose tissue [1–25].

According to the disability adjusted life years (DALYs), obesity is among the top ten risk factors for chronic non-communicable diseases, and thus MS [26]. It is often defined as a condition of pathological or excessive accumulation of fat in adipose tissue to a degree that can endanger health, if energy intake is higher than energy consumption over a long period [8, 27]. Obesity can also be defined as the body mass index (BMI) greater than 30 kg/m² [8, 28]. The BMI-based body weight classification is shown in **Table 2**. According to this classification, the BMI between 18.5 kg/m² and 25 kg/m² is considered normal, while a 20% increase in body weight (BMI> 27 kg/m²) poses a health risk [8].

In 2014, the World Health Organization (WHO) published the data stating that 1.9 billion adults were obese. This organization predicts that by 2025, 2.3 billion adults will suffer from obesity [12]. Another devastating point in the WHO data includes the fact that 20 million children in the world under the age of five are overweight [8, 29]. In addition, the average BMI of the adult population in Europe is 26.5 kg/m². This means that 400 million Europeans are overweight, while 130 million Europeans are obese. Besides, the nutritional status of children in Europe is worrying as well, given that 20% of children are overweight and 33% are obese [12, 30].

The prevalence of MS varies significantly depending on the criteria used for its diagnosis, as well as the age, sex, and ethnicity of the patients [1]. In this regard, the prevalence of MS in the United States is 16% in the Afroamerican population, 25% in Caucasian and 36% in the Hispanic population [10]. In contrast, the incidence of MS in teen population of the United States is 9.1% in boys, and 3.7% in girls [31]. However, the prevalence of MS has been shown to increase with age and is 44% in people aged 60–69 [8]. Also, the result of an extensive study conducted in Australia indicates that every fifth inhabitant of this continent suffers from MS [31]. Similarly, every sixth inhabitant of Europe has MS, while in the countries of the European Union every third inhabitant suffers from this syndrome [12].

In Serbia, half of the adult population is overweight, while every fifth adult is obese [12]. In addition, in this geographical region, chronic non-communicable diseases are the leading cause of morbidity and mortality, with the share of CVD in overall mortality being 55.2% [8]. In addition, in the territory of Vojvodina, it was determined that 74.3% of the population of both sexes, aged 45 and older, were overweight and/or obese, while 33.3% of people of this age were obese. In this regard, in Vojvodina, in population of both sexes, aged 45 years and older, the incidence of MS is 16.9%. About 15% of children in this area are obese, with a tendency of MS to develop in every third child [8, 12]. If the number of obese people continues to increase, WHO experts predict that by 2025, 3.27 million adults in Serbia will be overweight, and it is estimated that as many as 249,000 school-age children will be included in the group of obese or overweight [12].

A nutritional explanation for the high prevalence of MS and its consequences in our country and other developing and developed countries is the increase in daily energy intake and energy density of food (high fat content in daily energy intake), as well as insufficient physical activity [1, 25–28, 32, 33]. Thus, in the period from 1964 to 2000, the average daily energy intake of an individual in the world increased from 2358 kcal to 2803 kcal, while fat intake increased from 53 grams to 73 grams [8]. It is important to note that approximately 50% of increased calorie intake is due to the consumption of sugary drinks [34]. It has also been shown that the percentage ratio of fat intake and daily energy intake – fat to energy ratio (FER) is the most important indicator of food energy density. Therefore, the higher the FER, the higher the risk of developing MS and its consequences [6, 17, 25]. It is also estimated that reducing the use of salt in diet from 9 to 12 grams per day, which is the current world average, to the recommended 5 grams per day, could significantly reduce the incidence of hypertension and other metabolic disorders underlying IR [6, 8, 11].

UNBALANCED DIET AND METABOLIC SYNDROME

Increased total intake of fats, cholesterol and certain fatty acids, as well as excessive energy intake have an adverse effect on lipid metabolism, resulting in the development of obesity and MS [1, 8, 11, 17, 28]. In recent years, investigations have focused on the components of food, which are detected as dietary signals by cellular sensory systems, associated with the expression of genes and proteins and the consequent synthesis of metabolites [17, 35]. From the aspect of chronic diseases development, the influence of cholesterol and fatty acids from food is especially significant for genetic expression [28]. Namely, cholesterol ingested with food leads to inhibition of transcription of the gene for β-hydroxy-β-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase). In addition, polyunsaturated fatty acids (PUFA) from food suppress the production of lipoprotein synthase in the liver at the level of messenger ribonucleic acid (mRNA). This ability to suppress excess mRNA for lipogenic protein synthesis depends on the degree of unsaturation of fatty acids from food [16]. In this sense, eicosapentaenoic acid (EPA) from fish oil has a stronger effect than arachidonic acid [14]. It is also known that ω-3 fatty acids from food reduce the amount of mRNA for platelet-derived growth factor (PDGF) and interleukin-1β (IL-1β) [13]. In addition, food components affect gene expression through transcription factors, which are also the most important nutritional sensors **(Table 3)** [36]. In total, 48 transcription factors (nuclear hormone receptors) have been identified in the human genome, many of which have the ability to bind to food ingredients and their metabolites **(Table 3)**. Thus, the transcription factor binds to the nucleus receptor - a specific nucleotide sequence (responsive element) in the promoter region of a large number of genes. During ligand binding, the nuclear receptor experiences a conformational change, which results in the coordinated dissociation of the corepressors and the engagement of coactivation proteins in order to carry out the transcription process. In metabolically active organs (liver, intestinal tract, and adipose tissue), these transcription factors act as nutritional sensors, altering the level of transcription of DNA-specific genes in response to nutritional changes [25, 35].

Research conducted thus far indicates the importance of diet in the regulation of the expression and function of the cytochrome P450 gene (CYP). It is a large family of enzymes that catalyze the oxidation of substrate molecules. This enzyme system is responsible for the oxidative biotransformation of a number of exogenous and endogenous substances, including drugs [37]. It has been found that each step in the cycle of CYP enzymatic reactions can also be inhibited by compounds present in food. In addition, the expression of constitutive CYP enzymes is known to be regulated by growth factors and peptide hormones (e.g., growth hormone, etc.) via the Jak-STAT signaling pathway. The protein-1 activator complex (AP1) also participates in the basic regulation of certain CYP genes. Exogenous stress, including the action of prooxidative compounds that may be present in food, has the ability to alter the cell profile of AP1 protein, and thus significantly affect the gene expression of CYP [9, 35, 36]. In addition, food ingredients (fatty acids, etc.) directly or indirectly modulate receptors for steroid hormones that regulate CYP gene expression [17, 23, 25].

Numerous studies have confirmed the effect of the diet rich in saturated fats and/or carbohydrates on the ex-

Table 3. Transcription factors as mediators of nutrient-gene interactions

Food components	Active molecule	Transcription factor
Macronutrients	/	/
Fat	Fatty acids	PPAR, SREBP, LXR, HNF4, ChREBP
Carbohydrates	Glucose	USF, SREBP, ChREBP
Proteins	Aminoacids	C/EBP
Micronutrients	/	/
Vitamins	Vitamin A	RAR, RXR
/	Vitamin D	VDR
/	Vitamin E	PXR
Minerals	Calcium	Calcineurin/NF-AT
/	Iron	IRP1, IRP2
/	Zinc	MTF1
Other food components	/	/
/	Flavonoids	ER, NFκB, AP1
/	Xenobiotics	CAR, PXR

SREBP (protein that binds sterol-regulatory element); LXR (X receptor in the liver); HNF (hepatocyte nuclear factor); ChREBP (protein that binds a carbohydrate responsive element); FXR (farnesoid-X receptor /bile acid receptor/); USF (upstream stimulatory factor); RAR (retinoic acid receptor); RXR (retinoid X receptor); VDR (vitamin D receptor); PXR (pregnane X receptor); NF-AT (activated T cells nuclear factor); IRP (iron regulatory protein); MTF (metal-responsive transcription factor); ER (estrogen receptor); NFκB (nuclear factor κB); AP1 (activator protein 1); CAR (constitutive androstane receptor)

pression of CYP enzymes in the liver [17, 20, 23, 25, 32]. Namely, in experimental models of obesity, induction of CYP2E1 and 4A gene expression and enzyme activity are observed after the application of a diet rich in fat, as well as in the fat-free diet (so-called orotic acid / sucrose model), where carbohydrates increased production of acetyl-coenzyme A (acetyl-CoA) and TG, and they further up-regulated PPARα-responsive CYP4A enzymes [32, 38]. Peroxisome proliferator activated receptor-α (PPARα) is in itself a significant regulator of liver lipid content and is a link connecting nutrition to gene transcription in the liver [35]. In other words, PPARα, found in hepatocytes, regulates TG utilization by controlling genes responsible for lipid transport and oxidation [38]. Similarly, the transcription factor PPARγ, found in adipocytes, plays a role in the control of lipid deposition (regulation of lipogenesis and fat cell differentiation) [35]. CYP enzymes are known to potentially form free radicals during catalysis, which means that their induction by food agents can contribute to the processes of peroxidation of membrane lipids and proteins, especially in hepatocytes [35, 38]. Simultaneous use of inducers and CYP2E1 substrate (ethanol, carbon tetrachloride / CCl4/, etc.) worsens toxic damage caused by excessive production of free radicals. By this mechanism, induction of CYP enzyme expression may exacerbate pre-existing cell damage in obesity, DM, and MS [6, 17, 25]. An association between diet and progression of these diseases has also been established, suggesting that regulation of CYP enzymes by diet may contribute to pathogenetic mechanisms [17, 25].

There is no single dietary regimen for all types of hyperlipoproteinemia, but a combination of multiple dietary measures is commonly used **(Table 4)** [28].

Table 4. Dietetic approach to hyperlipoproteinemias

Total fat intake reduction
Cholesterol intake reduction
Reducing the intake of certain saturated and trans fatty acids
Increased intake of unsaturated fatty acids of cis configuration
Other dietary measures: • reduced intake of concentrated carbohydrates • reduction of total energy intake (hypoenergetic diet) • increased intake of dietary fibers • increased intake of plant origin proteins • increased intake of antioxidants • prohibition or restriction of alcohol intake

Increased total fat intake

Lipids that are ingested through food contain three types of fatty acids (saturated, monounsaturated fatty acids (MUFA) and PUFA). The classification was made based on the number of double bonds between two carbon atoms (C) in a fatty acid molecule. Each of these three types of fatty acids has a different effect on the balance and/or profile of lipoproteins or cholesterol in the blood, as well as on thrombogenic mechanisms [14, 28].

Numerous epidemiological data indicate an association between total fat intake (mainly saturated fatty acids) and coronary heart disease mortality [1, 6, 8, 10, 11, 25, 26, 28]. The results of some studies have shown that the replacement of saturated fatty acids with unsaturated forms of these lipid molecules is more effective in reducing blood cholesterol levels than reducing the total fat intake [8, 15, 17, 20, 39]. In addition, it has been found that low total fat intake can cause a decrease in HDL, as well as a reduction in the intake of essential fatty acids and vitamin E [26]. Also, scientific research has shown a connection between high fat intake and thrombosis tendency, i.e., a positive correlation was observed between high postprandial TG levels and an increase in coagulation factor VIIa concentration, which increases the risk of coronary heart disease [3, 28]. In addition, high intake of lipids as the most energy-rich nutrients can lead to a positive energy balance, excessive weight, obesity and MS [1, 28]. Therefore, it is recommended to replace one part of fat with carbohydrates that have a lower energy value [17]. A higher degree of replacement would lead to a reduction in HDL particle levels, bearing in mind that all fatty acids increase the level of HDL lipoprotein fraction to a greater or lesser extent, stimulating the secretion of apolipoprotein AI (apo AI), with saturated fatty acids effect of MUFA being greater than PUFA [16, 23]. In this regard, studies in one region of Finland (North Karelia) showed that reduced energy intake and reduced total fat intake, with changes in the ratio between saturated and polyunsaturated fats, after six weeks lead to a decrease in total cholesterol by 24%, and TG by 26%. It is important to mention that reducing the daily energy content of fat from 40% to 30% leads to a reduction in cholesterol levels by 0.5 mmol/L, while normalization of body weight of a moderately obese person is accompanied by a decrease in cholesterol by about 0.8 mmol/L [8]. Therefore, it is recommended that total fat intake should be less than 30% of total daily energy intake, i.e., less than 75 g/day (85 g/day in high-intake countries). It is also recommended to avoid frying, baking and breading when preparing meals, as well as to use skimmed or semi-skimmed dairy products and lean meat in the diet, and to avoid cured processed meat products and fatty pastries containing the so-called "hidden fats" [8, 27].

Increased cholesterol intake

Cholesterol is the most abundant lipid in the body. It is present in free (nonesterified) form and esterified form. Plasma contains about 75% of cholesterol in esterified form, most often with polyunsaturated linoleic fatty acid. Free cholesterol is found mostly in tissues. About 2/3 of cholesterol is synthesized in the body (approximately 900 mg per day), and the rest is ingested through food [11, 28].

Blood cholesterol levels are affected by an increased intake of cholesterol itself, some long chain saturated fatty acids and *trans* isomers of unsaturated fatty acids. Excessive energy intake also affects the concentration of cholesterol in the blood [7, 28].

The average daily intake of cholesterol in many countries, especially in the developed world, is 450–500 mg. On the other hand, when it comes to this lipid, it has been proven that the physiological daily needs of an adult are 150–300 mg. According to the recommendations given by the AHA, in the first stages of a diet, which refers to milder cases of lipid metabolism disorders, the daily intake of cholesterol is limited below 300 mg, and in the second degree (severe forms of lipid metabolism abnormalities) below 200 mg. It has been proven that for every 100 mg of increased cholesterol in the diet per day, the concentration of cholesterol in the blood increases by 0.21–0.26 mmol/L [8, 28].

Particularly rich sources of cholesterol are egg yolks (one chicken egg yolk contains about 280 mg of cholesterol), all offals (mostly brain, liver, kidneys, and heart), fish eggs, caviar, butter, whole milk and its products (cheese, sour cream, ice cream, etc.), mayonnaise, fatty meats, fatty meat products and animal fat. Generally speaking, meat does not contain large amounts of cholesterol, but it is an everyday part of the diet of our population, and therefore significantly contributes to increasing cholesterol intake through food [8].

When it comes to limiting cholesterol intake, it should be emphasized that its biggest source in the diet is egg yolks, since eggs are a very common ingredient in food, although some other foods contain a significantly higher percentage of cholesterol (for example, brain and other offal, fish caviar, lobster meat, etc.) [40].

Vegetarian studies also support the role of fats of milk origin and the importance of eggs as a source of cholesterol. Thus, vegetarians who base their diet on milk, dairy products and eggs (lacto-vegetarians) have the same or even higher values of total cholesterol, LDL particles and TG than people who eat a standard mixed diet. In contrast, strict vegetarians, who not consume milk, dairy products and eggs, have very low blood lipids [8].

It has been found that increased intake of dietary (exogenous) cholesterol leads to an increase in serum cholesterol to a much lesser extent than some saturated fatty acids. Since foods rich in cholesterol contain a significant amount of saturated fatty acids, a strategy based on reducing the intake of these fatty acids will also reduce cholesterol intake **(Table 5)** [20, 23]. In this regard, the recommended reduction of calorie intake depends on age, sex, and levels of physical activity [8]. It is also known that exercise and moderate alcohol consumption increase HDL values, while obesity and tobacco smoking reduce them [11]. In addition, chronic activation of the immune system, caused by overeating, can be observed before the clinical manifestations of obesity [3].

Saturated fatty acids

There is strong evidence for a link between saturated fatty acid intake and levels of not only total serum cholesterol, but also LDL and HDL lipoprotein fractions. This is especially true of palmitic, myristic and lauric acid, while stearic acid, which also has a long chain, does not manifest this effect [23]. Numerous studies, including the so called The Seven Countries Study, which included Serbia, found that populations that consumed large amounts of saturated fatty acids had relatively high blood cholesterol levels [8]. In contrast, low saturated fatty acid intake is accompanied by low concentrations of total cholesterol [28].

Saturated fatty acids are found in fats of animal origin (fatty meats and fatty meat products/sausages, salami, paté, bacon, various luncheon meats, hot dogs, etc./, whole milk and dairy products), as well as in some vegetable oils (coconut and palm oil), solid margarines and various toppings. The highest amounts of saturated fatty acids are present primarily in pork, beef and lamb red meat. However, poultry and other types of meat can have significant amounts of saturated fatty acids, so when preparing a meal, it is necessary to remove all visible fat impurities from the meat [8, 20].

The fact that a large intake of saturated fatty acids is realized in environments where there is an extensive network of fast-food restaurants (hamburgers and similar

Table 5. WHO recommendations for dietary reduction of high serum cholesterol concentration

Nutrients	Recommendations
Total fats	15–30%
Saturated fatty acids (% energy intake)	< 7%; trans< 1% energy intake
PUFA	6–10% energy intake (5–8% ω-6; 1–2% ω-3)
MUFA	10–15% energy intake
Cholesterol	The lowest possible intake
Sodium	< 1700 mg
Fish (n–3)	1–2 servings per week (200–500 mg EPA per serving)
Fruit and vegetables	400–500 g daily

products) is often overlooked, which is the case in Serbia as well. Also, another very important source of saturated fatty acids are whole milk and its products. Therefore, it is necessary to exclude cow milk of 3.2–4% milk fat, sheep milk (which contains twice the amount of fatty substances compared to cow milk), whole cheeses, sour cream, butter, ice cream, etc. These products need to be replaced with semi-skimmed or skimmed milk (from 2.2% fat in milder forms of hyperlipoproteinemia, or 0.2–1.6% fat in more severe forms of these disorders) and products made from such milk [8].

In order to avoid excessive intake of saturated fatty acids, one should pay attention to foods that contain the so-called "hidden fats" (various types of fatty pastries, croissants, donuts, fatty pies, cakes, fatty crackers, etc.). Since eggs are often added to such products, they thus become a very rich source of cholesterol [40].

Taking into consideration the aforementioned facts, it is recommended that the share of saturated fatty acids in the total daily energy intake be up to 7% (Table 5), i.e., less than 25 g/day [8].

Unsaturated fatty acids

The term unsaturated fatty acids nowadays refers to unsaturated fatty acids of *cis* configuration, while *trans* isomers are separated into a separate group [7]. As previously pointed out, the intake of unsaturated fatty acids of *cis* configuration should be increased, especially MUFAs [16, 23].

MUFAs are known to lower total serum cholesterol and LDL particles [6, 15]. The main MUFA in the diet is oleic acid, which is most present in olive oil (72%), followed by canola oil (54%) and peanuts (49%) [15]. In addition, the presence of this acid in the so called high oleic type sunflower is also of importance. Larger amounts of MUFAs are also found in hazelnuts, almonds, walnuts and dried pumpkin seeds. To a lesser extent, MUFAs are present in meat and meat products [8]. In this regard, the diet in the Mediterranean countries (the so-called Mediterranean diet) results in lower incidence of atherosclerosis and its complications, because, among other things, it is based on high intake of oleic acid through olive oil [15].

Of particular interest from the dietary point of view are the ω-6 (n-6) and ω-3 (n-3) families of PUFA (the number indicates the position of the double bond in the C atom chain). ω-6 PUFAs, of which linoleic acid is the most abundant, are of plant origin (sunflower and soybean oil, corn oil, etc.) and moderately lower total cholesterol, LDL particles, and to some extent HDL particles [16]. ω-3 PUFAs are found in fatty fish, fish oil, some vegetable oils (flaxseed oil, etc.), nuts, and leafy green vegetables [39]. α-linolenic acid and its two metabolites (EPA and docosahexaenoic acid /DHA/) are the most important ω-3 PUFA [14]. They are formed in the chloroplasts of plants and phytoplankton and are therefore present especially in the oil and meat of marine fish that feed on phytoplankton. It has been established that these fatty acids predominantly lower the level of TG, as well as reduce the level of cholesterol only if there is a marked increase in TG at the same time. Conversely, when there is only an increase in cholesterol, these PUFAs can even lead to a further increase in cholesterol content, which is their side effect [13, 39]. On the other hand, the beneficial effect of ω-3 PUFA is largely achieved by reducing platelet aggregation in the blood vessel wall, improving endothelial function, moderate reduction in blood pressure, etc. [14, 39].

Some PUFAs are essential (linoleic and α-linolenic acid), so it is necessary to take them daily [8]. However, it should be borne in mind that excessive intake of PUFA can cause some side effects (accelerated development of osteoporosis, increased production of gallstones, etc.) [8, 39].

The modern diet is most often characterized by a lack of ω-3 PUFA and a combined excess of saturated fatty acids, ω-6 PUFA and *trans* isomers of unsaturated fatty acids [11]. The reasons for this diet are the use of large amounts of vegetable oils, margarine and food of animal origin, and insufficient intake of leafy green vegetables and seafood (sources ω-3 PUFA) [13, 15]. In such circumstances, excess ω-6 PUFA is susceptible to the formation of lipid peroxides whose action is atherogenic and carcinogenic. In addition, there is an imbalance of ω-6 and ω-3 PUFA in food, which is as high as 25–30:1 [39]. Thus, for example, in the case of intake of a large amount of ω-6 linolenic acid, the production of EPA and DHA from ω-3 α-linolenic acid is difficult. The type of eicosanoides that will be synthesized in the body also depends on the relationship between ω-6 and ω-3 PUFA in food, because these acids are their precursors. If the diet is dominated by ω-6 in relation to ω-3 PUFA, the immune response will be weaker, the inflammatory reaction stronger, vasoconstriction and increase in blood pressure will also be evident, which is a predisposition for the development of atherosclerosis, thrombosis, hypertension, cardiac arrhythmias, etc. Therefore, it is recommended that the ratio between ω-6 and ω-3 PUFA need to be 2 or lower [8, 13, 14]. It is also suggested to consume fish in the amount of 200–500 grams 1–2 times a week **(Table 5)**, primarily saltwater fish rich in ω-3 EPA and DHA (tuna, cod and anchovy), as well as cold northern sea fish (salmon and herring) [8, 41]. Pike and perch have the most favorable fatty acid composition of all freshwater fish [8].

Trans isomers of unsaturated fatty acids

All unsaturated fatty acids have a *cis* or *trans* geometric isomeric shape. When we talk about MUFA and PUFA in general, it is common to think exclusively of their *cis* form, while *trans* forms are singled out in a special group. The geometric isomerism of unsaturated fatty acids depends on the orientation of the radical around the double bond. If the radicals are on the same side of the double bond, it is

a *cis* shape, and if the radicals are on opposite sides, it is a *trans* configuration [7]. Spatial configuration is extremely important, since *trans* isomers have harmful effects on the body (accelerate the process of atherogenesis, adversely affect the growth and development of infants and young children /disrupt the metabolism of essential fatty acids/, slow down the mechanisms of hemostasis, lead to IR and thus facilitating the development of MS and type 2 DM) [7, 11, 28]. There is a large number of fatty acids of the *trans* configuration, and the most common in the diet are *trans* monoenes (primarily elaidinic acid, and in smaller quantities vacenic acid). It is important to note that the metabolism of *trans* forms of unsaturated fatty acids in the human body is more similar to the metabolism of saturated fatty acids compared to the metabolism of unsaturated fatty acids of *cis* configuration [7].

The origin of *trans* isomers in the diet of modern man is dual. Much smaller quantities are of natural origin and are found in butter and dairy products, some fats of animal origin and in ruminant meat. It was found that these isomers were present in cow milk in the amount of 2–6%. They are also present in the milk of other animal species. Beef tallow is also an important source of these fatty acids [7, 8]. The largest amounts of *trans* isomers of fatty acids are found in fats obtained by partial hydrogenation of vegetable and fish oils [11]. During the conversion of liquid oils into solid fats, one part of unsaturated fatty acids is converted into saturated fatty acids (complete hydrogenation), and the other is converted from *cis* to *trans* form (partial hydrogenation). Namely, *trans* isomers are formed when hydrogen atoms are added to liquid oils. It should be mentioned that these adverse effects are further exacerbated during the oil refining process, which leads to the conclusion that natural and cold pressed oils, according to today's understanding, have the most favorable composition from a dietary point of view [7, 11].

It is known that the highest content of *trans* isomers is found in many types of margarine, margarine-based products, various dressings and coatings, and most importantly, in vegetable fats and fish oils of solid consistency, and such lipid substances are most often used in fast food [8, 11]. To illustrate, for example, one donut contains 3.2 grams, a large portion of French fries 6.8 grams, and a bag of popcorn over 10 grams of *trans* isomers of fatty acids. It is also known that 100 grams of low-calorie margarine obtained by partial hydrogenation process contains about 12 grams of *trans* fatty acids. It is important to point out that the amounts of *trans* fatty acids in industrially hydrogenated fat can reach as much as 60% of the total fatty acid content, unlike natural products where the content of these fatty acids is far lower (maximum 6%) [7, 8, 11]. It should be emphasized that there are significant differences in the action of *trans* fatty acids of natural origin, compared to *trans* isomers that are industrially produced by partial hydrogenation [8]. In this regard, it was found that industrially produced trans *fatty* acids were extremely atherogenic, because they affected, on one hand, the increase in total cholesterol, LDL particles, and Lp(a), and on the other hand led to lower HDL particles [7, 11]. These isomers also lead to an increase in the concentration of TG in the blood [28]. The adverse effect of *trans* fatty acid isomers on lipid status has been shown to be greater than the effect of long chain saturated fatty acids. These isomers lead to a damage to LDL receptors on cell membranes, thus reducing their activity **(Figure 1)** [11].

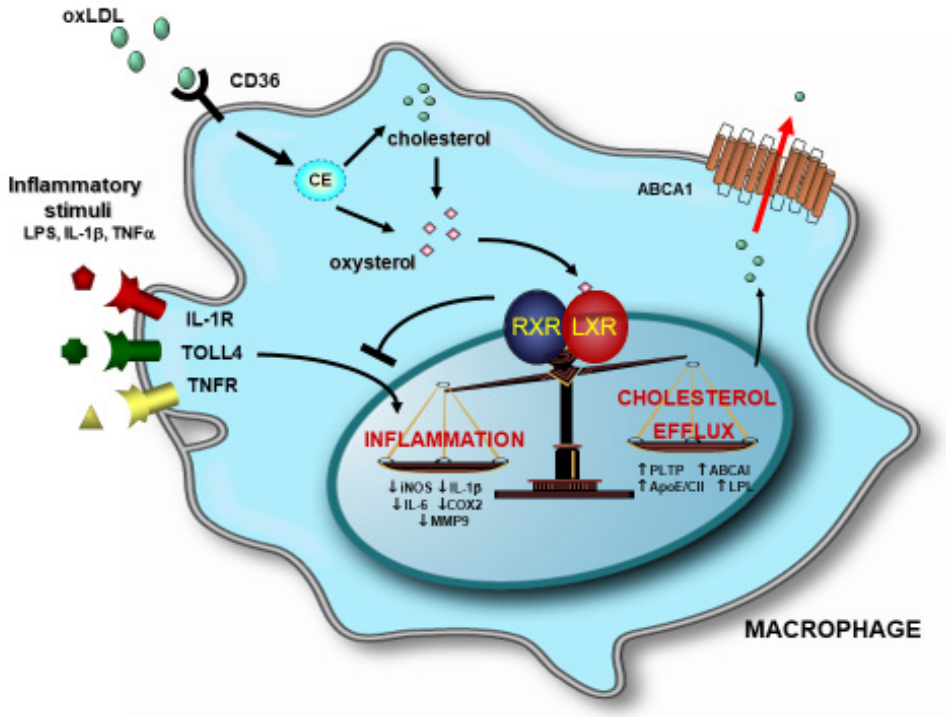

Figure 1. A macrophage response to inflammatory stimuli

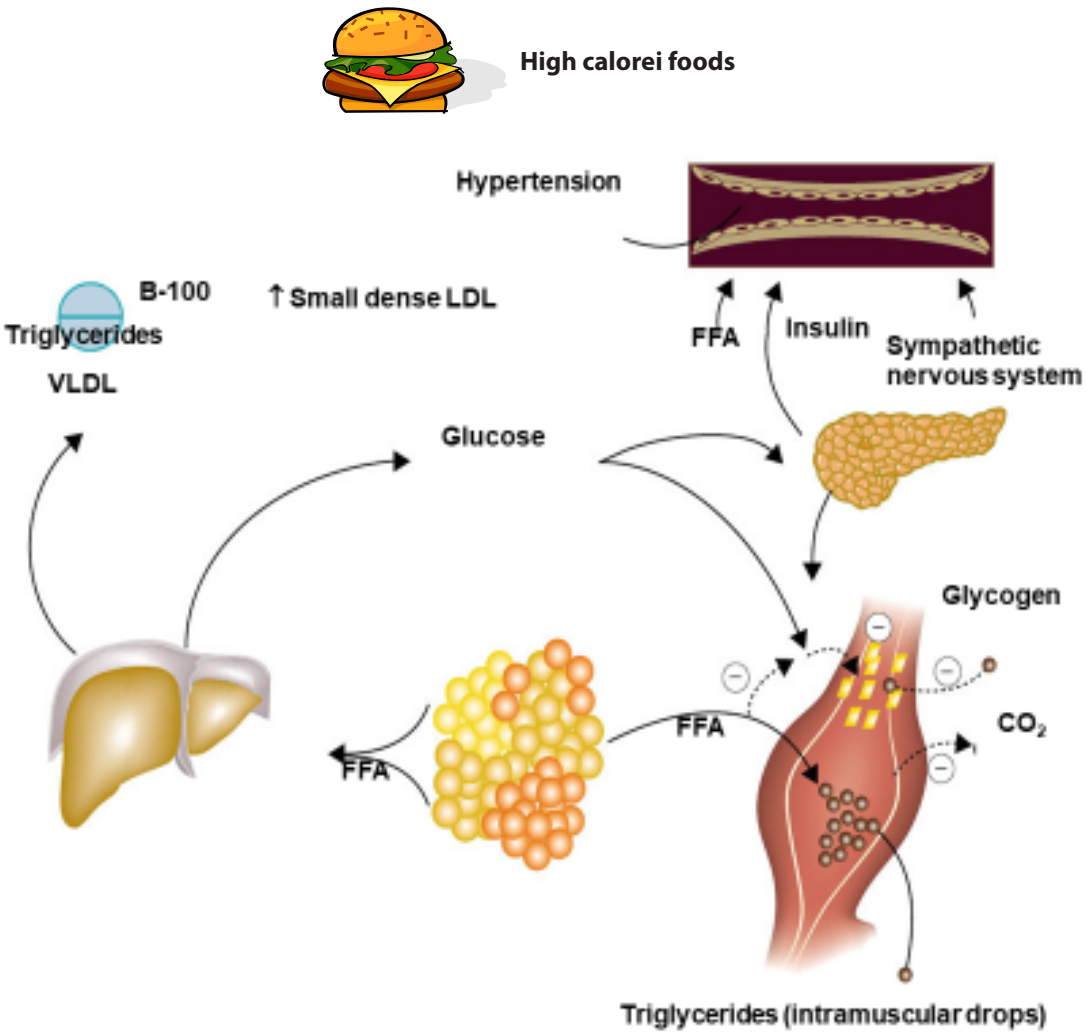

Figure 2. Insulin resistance and metabolic syndrome - FFA, free fatty acids

In addition, industrially produced *trans* isomers increase the activity of the protein responsible for cholesterol ester transport (CETP), which has been found to play an important role in lipoprotein particle metabolism (redistributes cholesterol esters from HDL to VLDL and LDL fraction) [7]. It has also been noticed that a gram of industrially produced *trans* isomers of fatty acids, compared to consuming the same amount of saturated fatty acids, is ten times more harmful concerning the development of heart and blood vessel diseases. A positive correlation was also registered between the alimentary intake of industrially produced *trans* fatty acids and the relative risk of developing MS and type 2 DM **(Figure 2)** [7, 8, 11].

Today, the question arises as to what amount of *trans* isomers of industrial origin is acceptable in a well-balanced diet. According to AHA recommendations, their intake should be limited to a maximum of 1% of daily energy intake (Table 5) [11]. However, according to numerous studies, their intake in the daily diet is far higher, and ranges to the extreme 50 grams. In Serbia, the exact data on the alimentary intake of *trans* isomers of industrial origin are not known, but it is quite certain that the intake of these harmful substances is significantly higher than the stated allowable amount [8, 12].

With all the harmful effects of industrially produced *trans* isomers of fatty acids in mind, residents in many countries, especially in Scandinavia and most Western European countries, have significantly reduced their intake. Moreover, in Denmark, for example, these fatty acid isomers are completely out of use, primarily due to new technological processes in the food industry ("soft" type of margarine, etc.) [8]. Until the content of *trans* isomers of unsaturated fatty acids of industrial origin in margarines in our country is reduced from the existing 12.13% to a negligible level, it is necessary to well inform the population about the principles of proper nutrition. In addition, detailed declarations on the content of certain types of fatty acids in food products, and not only information on the total fat content in their composition, from a health point of view will significantly facilitate the selection of the most favorable foods and food products [8, 12].

The research results on eating habits of the Serbian population indicate the need to raise the awareness level and knowledge quality related to proper nutrition, since only every tenth adult inhabitant of Serbia eats adequately. In addition, it was found that only 15.5% of adults in Serbia consume two servings of fruit every day, while only 12.2% regularly consume three or more servings of vegetables every day [8].

NUTRIGENETICS AND NUTRIGENOMICS

Nutrigenomics deals with the study of the influence of diet on metabolic pathways and homeokinesis, i.e., their regulation in the early stages of diet-related diseases, as well as the degree to which a person with the appropriate genotype is susceptible to these diseases. It is the science of the effect of nutrients on gene expression, which opens the possibility of identifying genes that affect the risk of diet-related diseases. In this sense, in this new scientific field on the example of MS, as multifactorial and polygenic diseases, the so called "genomic-based" phenotypic biomarkers are actively sought, which would be valid and enable detection of diseases in the preclinical phase and effective implementation of dietary strategies in prevention [35-37, 42]. The complementarity of the two approaches is emphasized was less than 1%. - diet, which is important for the earliest stages of the disease and preservation of homeokinesis, and drugs, which are necessary for the treatment of later stages of the disease [42].

Nutrigenetics tries to answer why food and diets have different effects on each individual. The study of the role of genetic variation in explaining individual diversity in response to diet is the basis for studying susceptibility to diet-related diseases. Historically, diet has influenced gene expression, enabling the formation of phenotypic characteristics that have been able to successfully respond to stimuli from the external environment and allow more efficient exploitation of food resources. Such adaptation has been crucial for human growth and development [36, 42].

Today, the so called "omics" sciences (transcriptomics, proteomics, metabolomics, etc.) are being intensively developed, which enable the determination of interactions between nutrients and other bioactive components of food and genes, and such relationships are important for more successful treatment and personalized nutrition [42, 43]. In this regard, epigenetic mechanisms underlying phenotype modification, whose modulation is possible through nutrients, are considered. In recent years, there has been a growing interest in epigenetic mechanisms whose dysregulation may be important for the development of disease in the human population [42].

According to the so-called fetal hypothesis about the origin of the disease, there are clear relations between maternal nutrition, fetal epigenetic programming and the appearance of the disease in adulthood. This emphasizes that the diet in the earliest periods of life "programs" unwanted outcomes in adulthood. Such effects of early nutritional exposure to the risk of developing adult obesity, hypertension, and IR have been shown in various animal models [42, 44].

In research in the field of nutrigenomics, two strategies are generally applied. The first provides detailed data at the molecular level on the interactions between nutrients and genomes, while the second focuses on human nutrition [42]. The first approach identifies transcription factors that serve as nutritional sensors and target genes **(Table 3)**, reveals signaling pathways and characterizes major nutritional signals, measures gene expression and metabolic consequences of specific micronutrients and macronutrients, and identifies genotypes that are risk factors for diet-related diseases such as DM, hypertension and atherosclerosis and quantifies their impact. Another approach involves the application of nutritional biology in the detection of biomarkers of early metabolic dysregulation and susceptibility to dietary influences [42, 45].

Incorporating genomics into nutritional practice offers the potential for personalized nutrition and prevention assistance by targeting nutrient-responsive molecular mechanisms that respond to nutrients [42]. The best example of this is phenylketonuria, in which proper nutrition minimizes the consequences of the disease [42, 46]. In these patients, the implementation of dietary treatment begins in the first days of life, and the essence is in the lifelong use of special preparations that do not contain phenylalanine [42]. In addition, research in the field of molecular prevention is expected to lead to the discovery of new biomarkers, more accurate measurement of disease susceptibility (personalized risk assessment), as well as new knowledge about the effects of interactions related to gene-environment and especially food-genes [42, 47]. In that way, the application of genomics in the population sciences would be useful both for the improvement of health status and for the prevention and treatment of diseases [42, 48].

CONCLUSION

Despite the continuous mastery of biomedical knowledge and techniques, scientists are still far from fully understanding the etiopathogenesis of chronic non-communicable diseases. In this regard, it is necessary to fight against these diseases and their consequences in a more efficient way. For that purpose, given the tendency of increasing prevalence of MS in the coming decades, it is necessary to take preventive measures to combat risk factors that may be affected (inadequate diet rich in carbohydrates and saturated fatty acids, obesity, smoking, sedentary lifestyle and physical inactivity). In addition to lifestyle changes, the use of a low-calorie diet and increased physical activity, patients with MS also need the use of appropriate drug therapy for certain components of the syndrome. We remain hopeful that further research in the field of molecular prevention will be able to contribute to the discovery of new biomarkers, help create strategies for molecular prevention and control of chronic non-communicable diseases and be a guideline for the application of nutrigenomics in population sciences.

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Sažetak

Izbalansirana ishrana je važan faktor promocije i održavanja dobrog zdravlja u toku čitavog života. Njen značaj kao determinante hroničnih nezaraznih bolesti dobro je poznat i ima važnu ulogu u prevenciji. Opterećenost hroničnim nezaraznim bolestima rapidno se povećava širom sveta. Naime, hronične nezarazne bolesti su vodeći uzrok umiranja na globalnom nivou. Od 38 miliona smrtnih ishoda u svetu zbog hroničnih nezaraznih bolesti, više od 40% čini prevremeni mortalitet koji se odnosi na osobe mlađe od 70 godina. Gojaznost, metabolički sindrom i dijabetes melitus takođe pokazuju zabrinjavajuće trendove, ne samo zbog naglašenog ispoljavanja kod velikog dela stanovništva, već i zbog sve češćeg prisustva u ranijim godinama života. Tako, metabolički sindrom predstavlja udruženu pojavu intolerancije glukoze, arterijske hipertenzije, dislipidemije, centralnog (abdominalnog /visceralnog/) tipa gojaznosti, kao i postojanje drugih metaboličkih poremećaja u čijoj se osnovi nalazi insulinska rezistencija. Ovaj sindrom prevashodno odlikuje primarni ćelijski defekt dejstva insulina, to jest insulin usled defekta u signalnoj transdukciji nije u mogućnosti da ostvari svoje biološke efekte. U takvim uslovima, insulinska rezistencija u kombinaciji sa posledičnom hiperinsulinemijom izaziva brojne metaboličke i kardiovaskularne poremećaje, koji imaju pandemijski karakter i predstavljaju vodeći uzrok morbiditeta i mortaliteta u svetu. U patofiziološkom smislu, ishrana bogata ugljenim hidratima i zasićenim masnim kiselinama značajno doprinosi nastanku i razvoju širokog spektra hroničnih nezaraznih bolesti, kao što su dijabetes melitus tip 2, hipertenzija, ubrzana ateroskleroza sa svojim kardiovaskularnim i cerebrovaskularnim komplikacijama, nealkoholna masna bolest jetre, sindrom policističnih ovarijuma i pojedine maligne bolesti (karcinom dojke i dr.). U okviru ovog preglednog članka dat je prikaz najnovijih literaturnih podataka i praktičnih saznanja o nepravilnoj ishrani kao kardiometaboličkom faktoru rizika. Buduća istraživanja u oblasti molekularne prevencije mogu da doprinesu otkrivanju novih biomarkera, pomognu u stvaranju strategija za molekularnu prevenciju hroničnih nezaraznih bolesti i budu smernica za aplikaciju nutrigenomike u populacionim naukama.

Ključne reči: nepravilna ishrana, gojaznost, insulinska rezistencija, kardiovaskularni poremećaji, nutrigenetika, nutrigenomika

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RESEARCH ARTICLE

The role of social networks and mobile applications in physical activity during the COVID-19 epidemic in Serbia

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Summary

After the outbreak of the novel SARS-COV-2 coronavirus, in the Chinese province of Wuhan that spread rapidly across the world, the Government of the Republic of Serbia introduced protection measures in March 2020, to prevent the spread of the infectious disease COVID-19 in Serbia. All gatherings indoors (sport, cultural and other events), as well as in parks and public places intended for recreation and sports, were prohibited. Shortly after, a lockdown took place which prohibited leaving home with the exception of basic needs, work from home was recommended and online schooling was introduced. The World Health Organization has recommended the use of online resources to maintain basic physical activity. In these circumstances of social distancing, this study examines the prevalence of physical activity supported by social networks and mobile applications during the COVID-19 lockdown in Serbia. The study was conducted as a cross-sectional study, using questionnaire distributed through social networks. The study found that more than a third of respondents (38.3%) used social networks or mobile apps to perform physical activity during the lockdown in Serbia; 27.1% used social networks/mobile apps before the pandemic, while 11.2% began to use social networks/mobile apps to perform physical activity during the lockdown. Easy access and review of exercises were the most common reasons for using social networks/mobile apps. 40% of the participants in the study agreed that social networks/mobile apps, make it easier to engage in physical activity. Based on the presented results, it can be concluded that the promotion of physical activity at home through social networks and mobile apps can provide an invaluable contribution to maintaining physical activity globally during pandemics such as COVID-19.

Keywords: physical activity, mobile applications, social networks, COVID-19, pandemics, lockdown

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INTRODUCTION

After the outbreak of the novel SARS-COV-2 coronavirus, in the Chinese province of Wuhan that spread rapidly across the world, the Government of the Republic of Serbia introduced protection measures in March 2020, to prevent the spread of the infectious disease COVID-19 in Serbia. All gatherings indoors (sport, cultural and other events), as well as in parks and public places intended for recreation and sports, were prohibited. Shortly after, a lockdown took place which prohibited leaving home with the exception of basic needs, work from home was recommended and online schooling was introduced. Having been constricted to the confinement of their homes, people experienced a decline in their physical activity (1). The World Health Organization (WHO) recommended performing a minimum of 150 minutes of moderate or intense activity per week as sufficient for the normal functioning of the cardiovascular system. Populous was advised to continue exercising in their homes and the use of online resources was suggested to maintain basic physical activity. As a consequence, gyms, sports halls and yoga classes have been brought into our homes. Social networks, mobile applications, video clips, endless streams of information, ready and easily accessible for use, had great potential to contribute to the further development of physical activity during COVID-19 pandemic. The promotion of physical activity through social networks and applications became an invaluable asset. A systematic review of studies examining the impact of mobile phones in reducing inactivity showcased a positive effect in promoting physical activity during COVID-19 pandemic (2). In circumstances of social distancing, this study aimed to examine the prevalence of physical activity supported by social networks and mobile applications during the COVID-19 epidemic in Serbia.

MATERIAL AND METHODS

The study was conducted as a cross-sectional study, using a questionnaire intended to examine habits in physical activity during the COVID-19 epidemic in Serbia. The questions from the first part of the questionnaire referred to: the demographic characteristics of the respondents, physical activity before the COVID-19 epidemic, and the attitudes about the frequency of exercise. The second part of the questionnaire examined the impact of social networks and mobile applications on the frequency of physical activity during the epidemic. The questionnaire was distributed through social networks.

Statistical analysis

Descriptive and inferential statistical methods were used in this study. Descriptive methods included measures of: central tendency (mean), variability (range, standard deviation) and absolute and relative numbers. Differences in distribution of variables between groups were analyzed using Pearson Chi-Square test. In all analyses, the significance level was set at 0.05. Statistical analysis was performed using IBM SPSS statistical software (SPSS for Windows, release 25.0, SPSS, Chicago, IL).

RESULTS

A total of 206 respondents, with equal gender distribution (50.0%) and mean age of 30.3±10.5 years were included in the study. The age of the respondents ranged from 16 years, for the youngest respondent, to 65 years, for the oldest respondent. Seventy respondents (34.0%) had secondary school education level and lower, while 66% of the surveyed population completed higher education, i.e. university education.

Figure 1 shows the attitudes of the respondents about performing regular physical activity. Out of a total of 206 respondents, 70 (34.0%) believed that it is desirable to perform physical activity almost every day. Sixty-four percent of the surveyed population considered it perferable to exercise several times a week, while 1.9% believed that performing physical activities once a week or less is sufficient **(Figure 1)**.

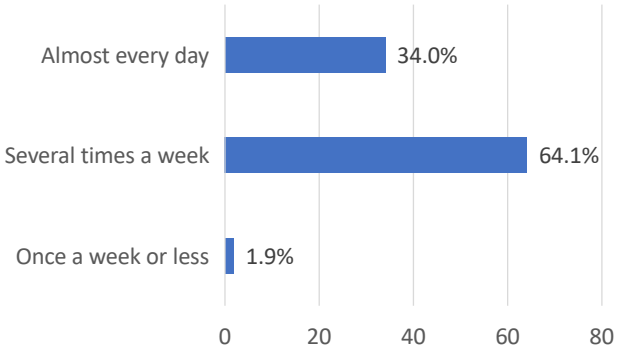

Figure 1. The attitudes of the respondents about performing regular physical activity

Men more often stated that it is necessary to perform physical activities almost every day, while women more often stated that it is enough to perform physical activity several times a week or less (p=0.039). Older respondents more often stated that it is necessary to perform physical activities almost every day, while younger respondents more often stated that it is enough to perform physical activity several times a week or less (p=0.012). Table 1 presents the distribution of respondents' attitudes regarding the performance of regular physical activity in total and by gender.

More than two thirds of respondents (71.6%) performed regular physical activity before lockdown due to the COVID-19 epidemic in Serbia. Almost half (45.6%) of

Table 1. Distribution of respondents' attitudes regarding the performance of regular physical activity in total and by gender

	Total	Gender		p
		Male	Female	
Performed physical activity before pandemic	146 (71.6)	83 (83.0)	62 (60.8)	<0.001
Performed physical activity during pandemic	142 (68.9)	73 (71.6)	68 (66.7)	0.449
Motivation for performing physical activity				
Health	111 (78.7)	61 (83.6)	50 (73.5)	0.146
Physical appearance	68 (48.2)	27 (37.0)	41 (60.3)	0.006
Energy consumption	42 (29.8)	19 (26.0)	23 (33.8)	0.312
Have free time	46 (32.6)	17 (23.3)	29 (42.6)	0.014
Felt a weakening of physical form after pandemic	117 (57.4)	63 (61.8)	54 (52.9)	0.203
Beginning of using social networks				
Used before pandemic	55 (70.5)	22 (75.9)	33 (67.3)	0.425
Started using during pandemic	23 (29.5)	7 (24.1)	16 (32.7)	
Use of social networks for performing physical activity	86 (42.4)	31 (30.4)	55 (54.5)	0.001
During pandemic, I felt:				
As usuall	39 (1.3)	24 (23.5)	15 (15.0)	0.197
As I could adjust to newly emerged situation	109 (54.0)	55 (53.9)	54 (54.0)	
Demotivated, anxious	54 (26.7)	23 (22.5)	31 (31.0)	
After pandemic:				
I have not changed my habits in performing physical activity	74 (36.3)	45 (44.1)	29 (28.4)	0.001
I stopped performing physical activity	36 (17.6)	8 (7.8)	28 (27.5)	
I continued performing physical activity	94 (46.1)	49 (48.0)	45 (44.1)	
Reason for not continuing performing physical activity:				
A lack of free time	19 (52.8)	3 (37.5)	16 (57.1)	0.434
A lack of motivation	18 (50.0)	4 (50.0)	14 (50.0)	1.000
Financies	5 (13.9)	1 (12.5)	4 (14.3)	1.000

the respondents exercised several times a week, 18% almost every day, while 6.8% exercised once a week or less. Men performed regular physical activity more often than women before the COVID-19 epidemic in Serbia (p<0.001). During the lockdown due to the COVID-19 epidemic in Serbia, two thirds (68.9%) of the respondents performed regular physical activity. 39.3% of respondents exercised several times a week, 21.8% almost every day, while 7.8% exercised once a week or less. Younger respondents performed regular physical activity more often than older ones during the COVID-19 epidemic in Serbia (p=0.059).

More than half of the surveyed population (68.6%) did not change their habits in performing physical activities during the COVID-19 epidemic in Serbia (54.4% exercised before the epidemic and continued exercising during the epidemic; 14.2% did not exercise before or during the epidemic). Discontinuation in performing physical activity during the COVID-19 epidemic was observed in 17.2% of respondents. A total of 14.2% of respondents started exercising during the epidemic. Men were more likely to give up exercise than women, while women were significantly more likely to start exercising (p=0.006). Younger respondents started exercising more often than older ones, while older respondents gave up exercising significantly more often (p = 0.023). **Figure 2** presents the performance of physical activity before and during the lockdown due to the COVID-19 epidemic in Serbia.

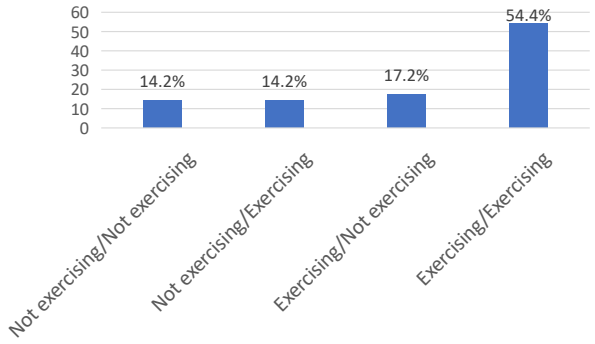

Figure 2. The performance of physical activity before and during the COVID-19 lockdown in Serbia

During the lockdown due to the COVID-19 epidemic in Serbia, the motivation for performing regular physical activity among the respondents was different. Health, as one of the drivers, was present in the majority of respondents (78.9%). Almost half (48.6%) commented physical appearance as driver, while one third stated that energy consumption and having free time were drivers for performing physical activity during the lockdown (30.3%

and 32.4%, respectively). Female respondents were more likely to have physical appearance as a motivation for performing regular physical activity, as well as having free time than male respondents (p=0.006 and p=0.014, respectively). Physical appearance and having free time were drivers for performing regular physical activity more often for younger respondents than for older ones (p<0.001 and p=0.053, respectively).

Forty two percent of respondents used mobile applications/social networks to perform physical activities before the lockdown caused by the COVID-19 epidemic in Serbia. Before pandemic, women more often used mobile applications/social networks to perform physical activities than male respondents (p=0.001). The tendency of more frequent use of mobile applications/social networks for performing physical activities was noticed rather among younger than older respondents (p=0.073). Twenty one percent of the respondents used mobile applications, 20.9% used Instagram, 7.3% used Facebook, while 13.1% of respondents used other social networks in order to perform physical activity **(Figure 3)**.

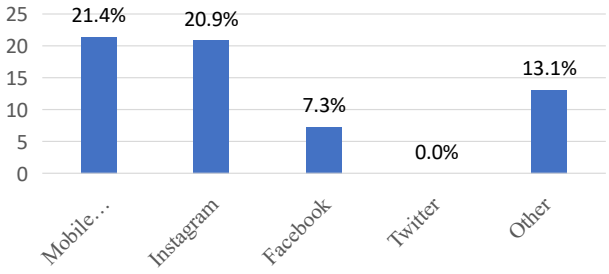

Figure 3. The use of mobile applications and social networks for the purpose of performing physical activity before the COVID-19 epidemic in Serbia

During the lockdown, more than one third of the respondents (38.3%) used social networks/mobile applications in order to perform physical activity. 27.2% of the respondents stated they used social networks before the pandemic, while 11.2% stated that they started using social networks/mobile applications for performing physical activity during the pandemic **(Figure 4)**.

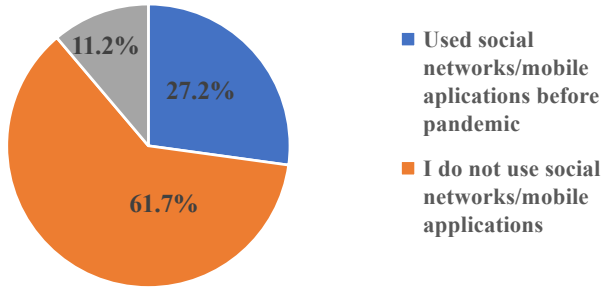

Figure 4. Use of social networks/mobile applications before and during the state of emergency due to the COVID-19 epidemic in Serbia

Availability and review of exercises were the most common reasons for using social networks/mobile applications (85.1%). Financial reasons or the absence of payment of a personal trainer was the reason in 27.6% of the surveyed population, while 23.0% of respondents stated saving time as the most common reason for using social networks/mobile applications in performing physical activity. Forty percent of the surveyed population partially or completely agrees that social networks/mobile applications make it easier for an individual to engage in physical activity. Almost one third of the respondents (32.7%) have a neutral attitude, while 27.4% of the surveyed population partially or completely disagree with the statement that social networks/mobile applications make it easier for an individual to engage in physical activity.

More than half of the respondents (53.9%) stated that they adapted to the current situation during the lockdown, while 26.6% of the surveyed population felt demotivated/ anxious, and 19.6% of the respondents stated that they felt as usuall. Respondents with a lower level of education felt more often demotivated or anxious than respondents with a higher level of education (p=0.054).

After the lockdown, almost half of the respondents continued to perform physical activities (46.1%), while 36.4% stated that they did not change their habits related to exercising. 17.5% percent of the surveyed population gave up exercising after the lockdown. Female respondents gave up performing regular physical activity more often than male respondents (p=0.001). The most common reason for giving up exercise after the lockdown was the lack of free time (52.8%). Half of the surveyed population stated the lack of motivation as the reason, while the financial problem was present in 13.9% of the surveyed population. Due to lack of time, younger respondents more often gave up performing physical activities after the state of emergency than older respondents (p=0.061).

DISCUSSION

This paper investigates the representation of digital sports activities, i.e. the role social networks and mobile applications take in the interest of promoting and providing ease of physical activity. The study was conducted during the conditions of social distancing caused by the COVID-19 pandemic in Serbia. Having the social climate shift to more isolated state, social networks would experience a rise in userbase and become a backbone of communication and information exchange across the world. Notably, the state of emergency would lead participants of recreation centres, fitness halls and sports clubs to a change in their environment. Having restricted access to spaces of physical activity they sought alternatives. The World Health Organization (WHO) would go on to recommend maintaining basic physical activity levels by using "online resources" (4). A switch would take place,

replacing any face to face interaction between trainers and trainees with the so-called online environment.

Various studies exploring "online fitness" as a growing trend during 2020 and 2021, have been conducted worldwide (5). Germany had shut doors on recreation centres and sports halls as early as March, not opening them until May 2020 and again from November 2020 all throughout the winter season. Based on the representative results of the study conducted in Germany during this time, it was concluded that the state of emergency lead to a decline in sports activities both in the elderly and young population. The study presented results that showcased 2% of the elderly population using online fitness activities in the first two weeks of the state of emergency, with a tendency to grow in the later stages of the pandemic (6). A survey conducted between April and May 2020 in the UK showed that 19-23% of the population used online activities during the state of emergency caused by the COVID-19 pandemic. Our results indicated that more than a third of repondents (38.3%) in Serbia used social networks, ie mobile applications in order to perform physical exercise (7).

A study conducted in Belgium showcased results that indicate that people who exercised using online help before the COVID-19 pandemic increased their lever of exercise during the state of emergency (8). A study in Brazil showcased results stating that 23% of the surveyed population started using online fitness classes and that 20% watched online videos regarding fitness exercises during the pandemic (9). One in five German citizens would state that they used social networks to perform physical exercise at least once during the COVID-19 pandemic, ie 23% of the total 1,508 respondents included in the study (10). Our study showcased that 27.2% of respondents used social networks to perform physical exercise even before the emergency, while 11.2% started using social networks and/or mobile applications during the state of emergency. According to the results of the study conducted in Germany (10) the share of digital sports activities increased significantly by as much as 19%. However, the trend of digital sports activities would not sustain its popularity, the conclusion of the state of emergency would see recreation centres, sport clubs and gyms open again. Furthermore, that would bring a dramatic decrease in the share of users of digital sports activities by 14%, almost returning to the numbers of the pre-pandemic period (10). The results of our study showed that more than half of the surveyed population (68.6%) did not change their habits in performing physical exercise during the COVID-19 pandemic in Serbia (54.4% exercised even before the pandemic and continued to exercise, 14.2% did not exercise before nor during the pandemic), the complete stop of physical exercise during the COVID-19 pandemic was observed in 17.2% of respondents, while 14.2% of respondents began exercising during the pandemic.

Alfavaz et al. (11) found in their study negative effects of self-isolation and quarantine on physical activity in adults, which can be explained by the difficulties of individuals having to change their routines that were previously acquired in fitness clubs and gyms. Positive attitudes were observed in our study regarding the use of social networks ie mobile applications when performing physical exercise, as well as in the study conducted in Saudi Arabia (12). Ease of availability and a review/selection of exercises were the most common reasons for using social networks/mobile applications in 85.1% of the surveyed population, according to our results. Financial reasons ie lack of funds for a payment for a personal trainer was a primary reason for 27.6% of respondents, while 23.0% stated saving time as the most common reason for using social networks/mobile applications for the purpose of performing physical exercise. The influence of social networks/mobile applications on engaging in physical activity was the topic of research in the study of Ammar (13) et al., as well as Kaur et al (14). Despite the positive observations found in the study conducted in Saudi Arabia as well as the influence of social media presented by the Ammar and Kaur studies, the results showed a different aspect, The level of physical activity obtained when home exercising was not sufficient to meet the regular physical activity patterns that existed before self-isolation conditions (12-14). AlMarzooki's research (12) showcased a strong relation between the attitude towards using social networks and levels of physical activity obtained. In addition, the results identified age, level of physical activity and average hours spent on social media as a significant predictors of attitudes toward their use. The results are in line with the finding found in the Shimoga et al (15) study, where frequency of social media use was strongly associated with physical activity.

Home digital sports activities usually require certain technical equipment, as well enough space at home. In this context, it is understandable that digital sports are more socially selective than traditional offline sports. Ng and co-workers (16) showed a finding in their study where fitness applications were more popular among young people, and persons of better financial status. The results of the study conducted in Germany (10) support these claims and show that users of digital sports are younger, better educated and in better financial condition. Such claim indicates that persons of age rarely participate in digital sports activities. Lower representation of older users of digital sports is probably a consequence of technological barriers or the lack of motivating or health-oriented content intended for older users. Digital sports have proven to be more attractive within the female population rather than the male population. This is the result of digital sport platforms being more oriented towards exercises based on body shaping, dance or yoga. The results of our study are in line with the before mentioned findings, where, before the COVID-19 pandemic in Serbia, women

more often used mobile applications and social media to perform physical exercise rather than the male respondents. Also, our study showed the younger respondents having a higher tendency to use mobile applications and social media to perform physical exercise rather than the older respondents. However, after the abolition of the state of emergency, female respondents were more likely to give up regular physical activity rather than the male respondents. Due to lack of time, being the primary reason, the younger population was more likely to give up on regular physical activity rather than the older respondents, after the abolition of the state of emergency.

According to the results of most studies, the active users of digital sports mostly used digital sports activities even before the period of the state of emergency caused by the COVID-19 pandemic. Therefore, it can be assumed that the use of social networks as well as mobile applications for performing physical exercise allowed the already active population to remain active during the pandemic. It however failed to motivate and stimulate the larger share of the inactive population to start using sports activities during the self-isolation period. Thus, digital sports activities encourage individuals to stay active and play an important role in public health during a pandemic, such as this one. Various practical implications arise from the most current research, especially when mentioning sports clubs, gyms and fitness centres, suggesting the introduction of digital sports activities to their already existing portfolio. This kind of digital data could be an extension to traditional offline activities, giving individuals with limited time or mobility an opportunity to participate in sports activities. Digital sports activities are not expected to completely replace traditional offline sports, but for many they could become a temporary and easily accessible supplement, in the post-pandemic period.

CONCLUSION

Promotion of performing physical activity at home through social networks and mobile applications can make an invaluable contribution to maintaining physical activity globally during pandemics such as COVID-19.

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ULOGA DRUŠTVENIH MREŽA I MOBILNIH APLIKACIJA U FIZIČKOJ AKTIVNOSTI TOKOM EPIDEMIJE KOVID-19 U SRBIJI

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Sažetak

Nakon što se u kineskoj provinciji Vuhan pojavio novi virus, SARS-KOV-2, koji se ubrzano raširio širom sveta, u martu 2020. godine Vlada Republike Srbije je uvela mere zaštite za sprečavanje i širenje zarazne bolesti KOVID-19 u Srbiji. Zabranjena su sva okupljanja u zatvorenom prostoru (sportske, kulturne i druge manifestacije), kao i kretanje u parkovima i javnim površinama namenjenim za rekreaciju i sport. U piku epidemije, uvedeno je vanredno stanje tokom koga je zabranjeno kretanje na javnim mestima, odnosno van stanova, prostorija i objekata za stanovanje u stambenim zgradama i izvan domaćinstva, preporučen je rad od kuće i uvedeno onlajn školovanje. Svetska Zdravstvena Organizacija preporučila je održavanje nivoa bazične fizičke aktivnosti korišćenjem tzv. onlajn resursa. Na osnovu svega navedenog, u ovom radu ispitana je zastupljenost fizičke aktivnosti potpomognute društvenim mrežama i mobilnim aplikacijama u uslovima socijalnog distanciranja nastalog usled epidemije KOVID-19 u Srbiji. Studija je sprovedena kao studija preseka, sa korišćenjem upitnika distribiuranog preko društvenih mreža. Utvrđeno je da je nešto više od trećine ispitanika (38.3%) koristilo društvene mreže, odnosno mobilne aplikacije u cilju obavljanja fizičke aktivnosti tokom vanrednog stanja u Srbiji, od čega je 27.1% koristilo društvene mreže i pre vanrednog stanja, dok je 11.2% počelo da koristi društvene mreže/mobilne aplikacije za obavljanje fizičke aktivnosti tokom vanrednog stanja.

Laka dostupnost i pregled vežbi bili su najčešći razlog korišćenja društvenih mreža/mobilnih aplikacija. 40% učesnika studije je smatralo da društvene mreže, odnosno mobilne aplikacije olakšavaju bavljenje fizičkom aktivnošću. Na osnovu dobijenih rezultata može se zaključiti da promocija fizičke aktivnosti u kućnim uslovima preko društvenih mreža i mobilnih aplikacija može pružiti neprocenjivi doprinos održavanju fizičke aktkivnosti na globalnom nivou tokom pandemija kao što je KOVID-19.

Ključne reči: fizička aktivnost, mobilne aplikacije, društvene mreže, KOVID-19, pandemija, vanredno stanje

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RESEARCH ARTICLE

Recovering quality of life in outpatients with psychosis spectrum disorders and its association with the symptom domains

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Summary

Quality of life (QoL) as a measure of subjective well-being is an important indicator in the everyday functioning of patients with psychosis spectrum disorders (PSD). The aim of this study was to explore the association between QoL and five symptom domains in outpatients with PSD. Our hypothesis was that negative and affective symptom domains would be associated with lower QoL.

Socio-demographic and clinical data were collected from 68 participants who met the prerequisite for the current study – adult outpatients diagnosed with F20.x-29 (according to ICD-10), qualified by the attending physicians as stable. Their symptoms were assessed using the expanded version of the Brief Psychiatric Rating Scale (BPRS-E) on the basis of which five symptom domains were quantified: positive symptoms, negative symptoms, affective symptoms (anxiety/depression), activation and disorganization. QoL was measured with the ten-point Recovering Quality of Life (ReQol) scale.

Mean age (SD) of the sample was 43.3 (11.0) years, and 60.3% of participants were male. ReQoL mean (SD) score was 25.4 (8.4) and BPRS-E mean total score was 1.9 (0.5). Regarding the BPRS-E and QoL score differences between males and females, educational level or marital status were not observed. Linear regression analyses showed that two out ot five symptom domains were significantly associated with ReQoL: Affective domain (β coeff.=-.717, p<.001) and Negative symptom domain (β coeff.=-.299, p=.001).

The present study of real-world clinically stable patients with PSD demonstrated that affective symptoms (depression/anxiety) had the strongest negative association with QoL in comparison with other symptom domains. This information could be useful for clinicians who should try to alleviate distress in order to improve the PSD treatment outcome.

Keywords: Quality of Life, Psychotic Disorders, Symptom domains, Outpatients

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INTRODUCTION

Psychotic spectrum disorders (PSD) are multifactorial complex conditions with a huge impact on quality of life (QoL) (1). QoL can be defined as a person's sense of well-being and satisfaction with his/her life circumstances, as well as a person's health status and access to resources and opportunities (2). Personal recovery and QoL are especially important in clinically stable outpatients striving towards employment and stable work, socialization, as well as taking charge of their own health and preventing future episodes of mental health deterioration (2). Symptoms of patients diagnosed with schizophrenia and other psychosis spectrum disorders, in particular positive symptoms (perceptual and thought disorders), can be minimized by medication ("clinical recovery"), but their QoL seems to be lower than the QoL of the general population ("personal recovery") and this could be due to several different factors.

Several sociodemographic factors such as age, gender, marital status, and education level were associated with QoL in patients with schizophrenia in previous studies (3). Higher rates of QoL were consistently reported in females compared to male patients with schizophrenia (4). According to Meesters et al, 2010 (5), sociodemographic factors could explain up to 20% of the variance in QoL while the intensity of the clinical symptoms could explain around 50% of it. When patients with schizophrenia, schizoaffective and bipolar disorder were compared, the schizoaffective disorder was associated with the largest losses of QoL (6) and most of the losses in this and other studies (5) were explained by the current depressive symptom levels. Depressive symptoms correlated with QoL in several studies, but not in all (7). Moreover, reports were also showing significant associations between negative symptoms and QoL (4).

Typically, the assessment of symptoms in patients with PSD includes the Positive and Negative Symptoms Scale (PANSS), which measures negative, positive and general symptom domains (8) and additional scales (for example, Calgary Depression Scale for Schizophrenia or other specific scales (9)) would be necessary to address depressive symptoms. However, there are scales such as the BPRS-E (10,11) which could be easily used to get comprehensive information on the major symptom dimensions in PSD including affective symptoms. The BPRS-E was developed to assess the severity of symptoms in patients with psychosis and it is also a sensitive measure of symptom reduction following clinical remission (11). Moreover, this scale was also explored outside the psychosis spectrum. For example, Zanello et al (2013) showed that the 24-item BPRS could be a useful measure of symptom severity and change in symptom status in unipolar depression (12). A recent study performed on a sample of outpatients with psychosis from the Western Balkans which investigated the fitting of the three competing BPRS-E factor models derived in the literature suggested acceptable to good reliability of the five BPRS-E factors/groups of symptoms: Affect, Negative symptoms, Positive symptoms, Activation, and Disorganisation (13).

Understanding the relationship between the different symptom domains with QoL is important because interventions that focus on psychotic symptoms alone may fail to improve subjective QoL (4). Thus, the present study aimed to explore clinically stable outpatients with psychotic disorders to analyze the associations between QoL, socio-demographic characteristics and the five above mentioned symptom domains. Our hypothesis was that negative and affective domains, as assessed by BPRS-E, would be associated with lower QoL. If this hypothesis holds, it means that busy psychiatric services and clinicians could be provided by a simple-to-administer reliable instrument such as BPRS-E to identify patients whose symptoms need further improvement towards recovery.

MATERIALS AND METHODS

The present study was a cross-sectional observational study performed at two psychiatric institutions (the Clinic for Psychiatry, University Clinical Center of Serbia in Belgrade, and the Special Hospital for Psychiatric Diseases "Dr Slavoljub Bakalović" in Vrsac, Serbia) during 2019/2020. The patients included in this study were involved in the large multicentric IMPULSE study which explored the implementation of the psychosocial intervention DIALOG+ for patients with PSD in low-middle income countries from Southeast Europe (for more information about the IMPULSE see Jovanovic et al, 2020; Grant agreement no.779334)) (14).

The inclusion criteria were the same as those for the IMPULSE study: outpatients with the primary diagnosis of PSD (ICD-10 codes F20-29), aged 18–65, with at least one psychiatric hospital admission during their lifetime (this means the diagnosis had been confirmed under comprehensive clinical evaluation), and the capacity and will to provide informed consent. Patients who had an organic brain disorder or severe cognitive deficits were excluded, as well as those who had been considered unstable by the treating clinician.

The information about gender, age, marital status (i.e. married, single, divorced/separated, and widow/widower) and education (i.e. below the level of elementary school, elementary school graduate, high school graduate, university, or college graduate) have been collected, as well as the information about the diagnosis and the number of psychiatric hospitalizations.

The study was conducted in accordance with the Declaration of Helsinki and its design was approved by the Medical Ethics Committee of the Faculty of Medi-

cine University of Belgrade, as well as by the relevant professional boards. All participants provided informed consent before the initiation of the study.

Instruments of measurement

Symptoms were assessed using the Brief Psychiatry Rating Scale-Expanded (BPRS-E) with 24 items (10,11). It was applied to assess psychopathological symptoms in the participants of this study. Trained research assistants interviewed patients and used rated guidelines to provide the scoring. Each symptom was rated on a 7-point Likert scale indicating the symptom severity ranging from "0 - not present" to "7 - extremely severe"(Cronbach's alpha = .797). A higher score indicated more severe symptomatology. For additional information about particular symptom domains, five BPRS-E domains were calculated according to the factor analyses provided by Blazhevska Stoilkovska et al. (submitted): positive symptoms (hallucinations, unusual thought content, suspiciousness, grandiosity), negative symptoms (blunted affect, emotional withdrawal, motor retardation), affective symptoms (anxiety, guilt, depression, suicidality), activation (excitement, motor hyperactivity, elevated mood, distractibility) and disorganization (conceptual disorganization, disorientation, self-neglect, mannerisms and posturing).

Patients were also assessed using the Recovering Quality of Life (ReQoL) scale (2), a generic psychometric self-evaluation. The non-somatic domains of QoL are the most relevant for psychiatric patients and therefore should be the main core (15). This scale measures rather non-physical domains of health-related QoL than pain or disability. It is composed of 10 questions ranging from "never" to "always" and it contains a mixture of positive and negative items. ReQoL had excellent acceptability and feasibility in clinical practice as well as good reliability and construct validity. The positively and negatively worded items score 0–4, where zero on the scale represents the poorest quality of life and four the highest (Cronbach's alpha = .874). ReQoL-10 score up to 24 is considered as falling within the clinical range (2).

STATISTICAL ANALYSIS

All statistical analyses were performed by the SPSS version 20.0 statistical software.

Descriptive statistical values were used to summarize participants' demographic and clinical characteristics (minimum and maximum values, medians and means/standard deviations). Initially, all data were tested for normality and accordingly analyzed using the appropriate parametric or non-parametric tests. Univariable relations were investigated by ANOVAs for associations between categorical and continuous variables, and by correlations between continuous variables (Pearson's correlation). Multivariable associations between QoL (dependent variable) and all potential variables were investigated in linear regression analyses with potential predictors of QoL - the first block consisted of socio-demographic variables whereas the second block contained the symptom domains. All p-values less than 0.05 were considered significant.

RESULTS

Our sample consisted of 68 adult patients, whose mean age was 43.3±11.0 and out of which 60.3% were male. Other socio-demographic and clinical characteristics of the participants are shown in **Table 1**. Diagnoses (according to ICD-10 criteria) are listed in **Table 1**. Most of the participants had schizophrenia or unspecified psychosis that was not caused by a substance or any known physiological condition. The mean number of hospitalizations was 4.7±3.4 (median: 4.0; range:1-15)

The mean total BPRS-E score was 1.9±0.5. Of the five symptom dimensions, BPRS Affective domain was scored by mean 2.4±1.0, Negative symptoms by mean 2.1±0.9, Disorganization was rated mean 1.7±0.7, Positive symptoms were scored 1.6±0.8 and Activation was scored 1.6±0.6. The mean of the total ReQol-10 score was 25.4±8.4. The lowest score was found in relation to the items: "I felt confident about myself" (1.7±1.2), "I felt hopeful about my future" (1.9±1.2) and "I felt happy" (2.1±1.1).

In terms of the BPRS-E and QoL scores, differences between males and females, educational level or marital status were not observed. Also, no differences in the symptom intensity or QoL were found between the diagnostic subgroups. Age and number of hospitalizations did not correlate with the aforementioned outcomes.

The first block of the variables (socio-demographic variables) explained 7.1% of the variance associated with QoL (R2= .071; adjusted R2=.012), while the second block which consisted of all symptom domains explained over 60% of the variance (R2 =.662; adjusted R2=.609).

In the final structure of the regression function, the only significant predictors of QoL were Affective and Negative symptom domains. The participants with more pronounced affective (depression/anxiety) and negative symptoms had lower scores on ReQoL - see **Table 2**.

DISCUSSION

Our research involved real-world outpatients to explore how five different symptom domains measured by one single instrument correlated with QoL. We found that the affective domain of the BPRS-E scale, which includes depression, anxiety, and guilt, had the strongest impact on QoL, followed by the negative dimension (blunted

Table 1. Symptom domains and quality of life by socio-demographic and clinical characteristics

Sociodemographic data		**BPRS-E total score, Mean±SD 1.9±0.5**		**ReQoL total score, Mean±SD 25.4±8.4**	
	Mean±SD				
Age#	43.3±11.0	*r=.109; p=.377*		*r=-.028; p=.824*	
Sex	n (%)		Between group differences		Between group differences
Male	60.3	1.8±0.5	p=.959	25.9±8.3	P=.529
Female	39.7	1.9±0.4		24.6±8.7	
Education	n (%)				
Elementary School or Less	4 (5.9)	1.9±0.4	p=.805	30.0±7.2	p=.527
High School	54 (79.4)	1.9±0.5		25.1±8.7	
University/College	10 (14.7)	1.8±0.5		25.4±8.4	
Marital Status	n (%)				
Married	8 (11.8)	1.7±0.3	p=.367	30.1±5.0	p=.178
Single	52 (76.5)	1.9±0.4		24.4±8.7	
Separated/Divorced, Widow(er)	8 (11.8)	2.0±0.8		26.8±8.1	
Clinical characteristics					
Diagnosis (ICD-10)	n (%)		Between group differences		Between group differences
Schizophrenia- F20	25 (31.3)	2.0±0.5	p=.171	25.8±8.6	p=.746
Schizoaffective disorder – F25	11 (13.8)	1.7±0.4		26.0±6.0	
Unspecified psychosis not due to a substance or known physiological condition- F29	22 (32.4)	1.8±0.4		25.9±9.0	
Other: F21, F22 and F23	10 (14.7)	1.9±0.5		25.4±8.4	
Number of hospitalizations#	4.7±3.4	*r=0.53; p=.667*		*r=-0.85; p=.505*	
#Pearson's correlations					

BPRS - Brief Psychiatric Rating Scale; ReQoL - Recovery Quality of Life

affect, emotional withdrawal, motor retardation). Thus, the hypothesis of this study was confirmed. Socio-demographic factors such as female gender or age, educational level or marital status did not significantly influence QoL in this study. In line with the previous research, the socio-demographic group of variables accounted for QoL variance only to a small extent. However, the symptoms have explained QoL variance to a very large extent in our study and it was in line with the earlier findings (5,16).

Table 2. Multivariable relationships between quality of life (ReQoL) and five symptom domains

BPRS-E symptom domains	β coeff.	p value
Affective	-.717	>.001*
Negative	-.299	.001*
Positive	.035	.705
Activation	-.083	.332
Disorganized	.145	.119

BPRS - Brief Psychiatric Rating Scale; ReQoL - Recovery Quality of Life

In our study, we found that especially anxiety-depression symptoms and negative symptoms measured by BPRS-E determine worse self-evaluation of QoL. These results are in line with what was reported by other authors even though they used different instruments to measure QoL. For example, in comparison with WHO-QoL-BREF used by Gallupi et al. (16) which included 26 items, a 10-item self-rated ReQoL used in the present study is much shorter. Besides being very easy to complete, it is also straightforward to score, quick to interpret and has advantages over similar scales such as EQ-5D-5L (which has an emphasis on pain and disability) or MANSA (which could be strongly associated with depressive symptoms) (15). As mentioned before, busy psychiatric services and clinicians need a simple-to-administer and reliable instrument to identify patients whose symptoms need further improvement.

To enable better daily life for clinically stable PSD outpatients, physicians should try to detect and treat depressive symptoms which seem to have a huge impact on QoL. Challenges to treating depression in PSD include

an additional diagnostic procedure and pharmacological and non-pharmacological management of the symptoms. In a patient with PSD, a clinician should investigate organic factors such as drug misuse, as well as endocrine and other medical problems, as this might be causal or at least contributory to the depressive/anxiety symptoms (17). CBT could be an effective adjunct to medications, however non-pharmacological approach to depressive/anxiety symptoms in psychosis is less explored in comparison to the medication. Drug therapy of affective symptoms in PSD is relying mainly on the results of small-scale trials and reviews. Certain second-generation antipsychotics (quetiapine, lurasidone, amisulpride, aripiprazole, olanzapine, clozapine) could be superior to other antipsychotics in the reduction of depressive symptoms and clozapine could be the therapy of choice in the management of patients at risk from suicide (18). The adjunctive therapy with antidepressants is still debated. Systematic review and meta-analysis (19) suggested small beneficial effects of adjunctive antidepressants, as patients taking add-on antidepressants had more adverse events such as abdominal pain, constipation, dizziness, and dry mouth. On the other hand, long term benzodiazepines adjunctive to antipsychotic drugs could be associated with cognitive impairments (20) and other severe adverse events (21), therefore its prolonged administration needs special caution. Finally, transcranial magnetic stimulation and electroconvulsive therapy could be considered, but they are only indicated when several previous therapeutic approaches proved to be ineffective.

Negative symptoms are an area of unmet therapeutic need in psychotic patients (22). Symptoms such as alogia, asociality, anhedonia, blunted affect or avolition have been associated with a limited response to pharmacotherapies and poor functional outcomes (23). Relatively new drugs such as cariprazine and amisulpride have shown some evidence of their efficacy towards negative symptoms (24, 25). In addition, psychoeducation and psychosocial interventions should be important components in helping patients and their families to cope with the disturbing aspects of avolition, anhedonia and social withdrawal.

There are several limitations of our study. Firstly, the clinical stability of our patients was confirmed by the treating clinician, instead of using scales to confirm the remission. However, the clinical judgment was in line with the level of QoL, i.e ReQoL mean score in our sample was above 24 (up to 24 is considered falling within the clinical range). Secondly, our findings are based on the cross-sectional design of a relatively small and convenient sample of psychosis spectrum patients, which could be considered a limitation to finding how socio-demographic factors could influence QoL or exploring further different types of PSD. Future research needs to include a larger sample and longitudinal design to further explore if several conditions included in PSD have specific associations between symptom domains and QoL in outpatients. Finally, we have not evaluated the possible effects of pharmacotherapy on symptoms or QoL, nor the patients' perception of their treatment. Our recommendation is that future studies also focus on these clinically highly relevant topics, as suggested by the recent study which used machine learning methods to explore QoL in schizophrenia (26).

CONCLUSION

The emergence of the recovery movement in several European countries increased interest in the QoL assessment. The present study of real-world patients with PSD demonstrated that affective and negative psychotic symptoms had the strongest negative impact on QoL. This information could be useful for clinicians who should try to alleviate distress in order to improve the PSD treatment outcome. The better insight into the QoL of our patients, the more we can do to provide them with a seamless journey to recovery.

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Conflict of interest

None to declare.

Author Contributions

NJ, NM - funding acquisition, project administration, supervision
NM, NJ - conceptualization, methodology
SAP, IR, SJ, BS, MZ - investigation, resources
NM, SJ, KS, TT - writing the first and original draft
NM, IR directly accessed and verified the underlying data reported in the manuscript.
All authors - revisions of the manuscript
All of the authors provided important intellectual content and approved of the final version of the manuscript.

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Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and its design was approved by the Medical Ethics Committee of the Faculty of Medicine University of Belgrade (No:2650/VI-3; date 26.06.2018.), as well as by the professional boards of the Clinic of Psychiatry, University Clinical Centre of Serbia (No:350; date 09.05.2018.) and Special Hospital for Psychiatric Diseases "Dr Slavoljub Bakalović" in Vrsac, Serbia (No:01-36/1; date 15.01.2019.).

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KLINIČKI SINDROMI POREMEĆAJA IZ SPEKTRA PSIHOZA I NJIHOVA POVEZANOST SA KVALITETOM ŽIVOTA TOKOM OPORAVKA

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Sažetak

Kvalitet života (QoL) se može definisati kao percepcija lične dobrobiti i blagostanja i važan je pokazatelj funkcionalnosti osoba sa poremećajima iz spektra psihoza (PSD). Cilj aktuelnog istraživanja koje se odnosi na vanbolničke pacijente sa PSD je da se ispita postoji li povezanost QoL sa jačinom pojedinih grupa simptoma posmatranih kroz pet sindroma. Hipoteza rada je da će QoL biti niži kod osoba sa izraženijim negativnim i afektivnim sindromom.

Uključeno je 68 ispitanika, od kojih su prikupljeni socio-demografski i klinički podaci i koji su bili dispanzerski pacijenti sa dijagnozama F20.x-29 (MKB-10) u stabilnoj fazi osnovnog poremećaja. Simptomi su procenjeni korišćenjem kratke psihijatrijske skale procene (BPRS-E), a zatim su računate vrednosti za pet sindoma: pozitivni, negativni, afektivni (anksiozno/depresivni spektar), sindrom aktivacije i sindrom dezorganizacije. Za ispitivanje QoL korišćena je skala sa 10 stavki (ReQoL) kojom se meri kvaliteta života tokom oporavka pacijenata.

Ispitanici su u proseku (SD) bili stari 43.3 (11.0) godine (60.3% muškog pola). ReQoL je u proseku (SD) iznosio 25.4 (8.4), dok je na BPRS-E zabeležena srednja vrednost (SD) od 1.9 (0.5). Socio-demografski parametri (pol, obrazovni nivo ili bračni status) nisu bili povezani sa BPRS-E ili QoL. S druge strane, od kliničkih parametara linearnom regresijom je pokazano da su dva od pet sindroma bila značajno povezana sa QoL: afektivni sindrom (β coeff.=-.717, p<.001) i negativni sindrom (β coeff.=-.299, p=.001).

Aktuelno ispitivanje klinički stabilnih vanbolničkih pacijenata sa poremećajima iz spektra psihoza ukazalo je da afektivni simptomi (anksiozno/depresivni spektar) imaju najjači uticaj na QoL. Ova informacija je korisna kliničarima jer ukazuje gde treba usmeriti napore da bi se poboljšao ishod lečenja osoba sa poremećajima iz spektra psihoza.

Ključne reči: Kvalitet života, Psihoza, Sindrom, Vanbolnički pacijenti

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REVIEW

Neurophysiology of stress – from historical to modern approach

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Summary

Stress is present in our everyday lives and it is considered to be the driving force of evolution. Anxiety, chronic worries and panic attacks are the most common consequences of long-term and exhausting stress. The most significant fundamental contribution that is crucial for the development of the modern concept of stress was made by Claude Bernard who proposed the theory that the body was constantly maintaining a stable and well-balanced internal environment or "*milieu interieur*". Maintaining the internal environment constant was defined as homeostasis by Cannon who proposed two maintenance mechanisms - through negative feedback from the autonomic nervous system and through sensory organs.

Hans Selye proposed stress as non-specific strain on the body, caused by an altered body function which is followed by the release of stress hormones. He named this process the general adaptation syndrome which had three stages: alarm reaction, initial phase exhibiting "fight or flight" response; resistance, when body is getting used to being stressed, and exhaustion, when resistance to stress is gradually decreased and collapses. Hans Selye was the first to coin the term "heterostasis" representing the procedure by which a new stable state was achieved by the activation of physiological adaptive mechanisms.

Lazarus highlighted emotions as an important factor in behavior in response to stress and provided a description of various reactions to stressors. He emphasized the process of cognitive assessment as a mediator in dealing with stressors - how a person imagines or evaluates an event in order to understand stress reactions in people. Eustress, considered to be positive stress leads to toned emotions, motivation and focused energy, while distress, negative stress, occurs after prolonged stress that exceeds our ability to deal with it. Distress causes anxiety or withdrawal (depression and anxiety), and is accompanied by unpleasant feelings and reduced work ability leading to mental and physical illnesses.

Keywords: neurophysiology, stress, history, hormones

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Stress is a non-specific reaction of the body to any request. Stress in health and disease is medically, sociologically, philosophically the most important topic for humanity that I can imagine.

Hans Selye (1907–1982)

INTRODUCTION

Stress is present in our everyday lives and it is considered to be the driving force of evolution. The term stress did not exist in physiology literature 100 years ago, unlike most popular definitions that describe purely psychological reactions to stress. Before the term stress began to be used as a psychological term, it had been used to describe different types of physical exertion. The word stress is derived from the Latin words "*strictus*", meaning tight or narrow and "*stringere*", the verb meaning to tighten (1).

Up to 80% of patients' visits to physicians are due to stress-related health issues (2). In other words, anxiety, together with chronic worries and panic attacks, is the most common consequence of long-term and exhausting stress **(Figure 1)**. Almost all scientific discussions in biological and social sciences, including chemistry, genetics, endocrinology, neuroscience, epidemiology, psychiatry, psychology, etc., recognize a common history of stress in physiology (3).

STRESS RESEARCH BEFORE HANS SELYE

Claude Bernard (1865 -1961)

French physiologist Claude Bernard, one of the world's greatest physiologists and the father of experimental medicine, made the most significant contribution which is crucial for the development of the modern concept of stress. Additionally, he explained how cells and tissues in multicellular organisms can be protected from stress. One of the most significant contributions was Bernard's theory that the body was constantly working to maintain a stable and well-balanced internal environment or "*milieu interieur*". In any stressful situation, the organism is tending to go back to its homeostatic state in order to coordinate physiological processes (4).

Walter Bradford Cannon (1871–1945)

An American physiologist (Harvard Medical School) accepted the Bernard's idea and expanded the theory (5). Cannon defined the process of maintaining the internal environment constant as "homeostasis" and proposed two maintenance mechanisms: through negative feedback via the autonomic nervous system activation and through sensory organs (6). The term homeostasis originated from the Greek roots *homoios* (similar) and *stasis* (stable). Walter Cannon created the term "fight-or-flight" to describe an animal's reaction to a threat, which is called an acute stress response. In fact, the adaptive response to stressors triggers the activation of excitement and the sympathetic nervous system which leads to increased secretion of catecholamine (adrenaline) preparing the animal to fight the threat or save its life (i.e. flee) (7). He focused his own research on the specific and mutual relationship between stress and changes in the mind and body.

Yerkes-Dodson (Robert M. Yerkes and John Dillingham Dodson, 1908)

Yerkes-Dodson's law refers to the relationship between increased levels of arousal (used as a synonym for stress) and physiological and mental responses. Dodson's law is represented by the inverse U-shaped curve for the optimal level of stress necessary to fight or give up the inten-

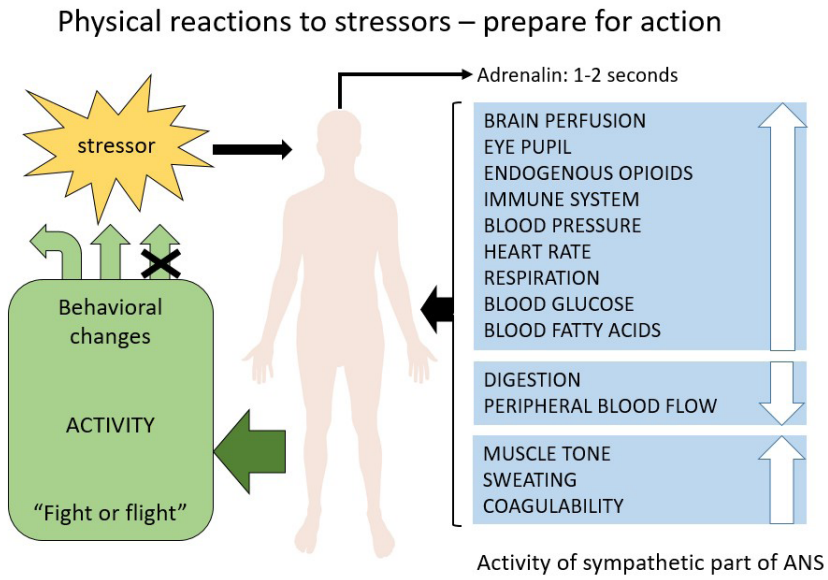

Figure 1. Stress represents physical and emotional adaptive response to internal and external stimuli

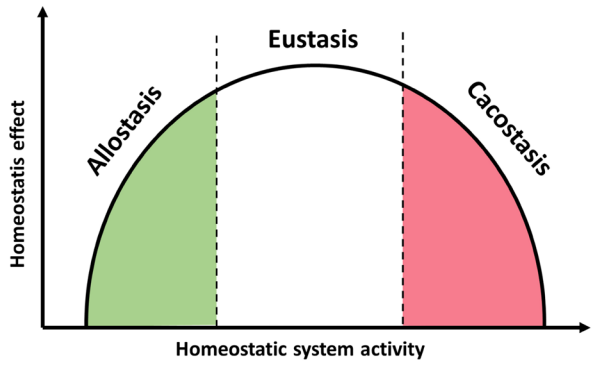

Figure 2. Yerkes-Dodson law (Inverted U-shaped curve): The relationship between stress level and task performance

tion. There is an optimal level of stress for each type of task that supports maximum effectiveness. This point (level) depends on individual characteristics, the type of stressor, the nature of the task itself, perception, etc. In most areas of life, it is necessary to have adequate energy, discipline and motivation. The relationship between these factors is linear only up to a certain point, because when the stress level becomes too high, the activity level (the effect) decreases (8) **(Figure 2)**.

Work performance deteriorates when stress levels are too high or too low for a particular task. Having no stress at all causes motivation loss, a decrease in attention and interest for work. On the other hand, in the presence of too much stress, when the optimal point is crossed (across the border), the contribution is reduced and the work is counterproductive (9).

MODERN CONCEPT OF STRESS

Hans Hugo Bruno Selye (1907–1982)

Hans Selye developed the concept of general adaptation syndrome (GAS), which was later called the stress response (10). Known as the "father of stress", Selye began his research while a medical student (1926) because he noticed that many patients with various diseases had the same "non-specific" symptoms that were common responses to stress stimuli. The term "stress" has been accepted in all languages and it describes a "nonspecific neuroendocrine response" (11). Hans Selye published over 1,500 articles and 30 books on the subject of stress.

Selye described stress as nonspecific, since the reaction to stress can be a result of various types of stressors which made him focus on intrinsic, physical aspects of stress. Chronic stress causes excessive production of mediators, chemical substances and hormones, which can lead to gastric and duodenal ulcers and hypertension. Although the hypothesis of GAS later proved to be incorrect, he put stress on the map of the diseases and emphasized that stress had significant effects on the immune system, as well as on the adrenal gland (12).

By studying the physiology and pathology of stress and disease adaptation, he concluded that a certain amount of stress had positive effects, while too much stress led to pathological conditions, increasing autonomic and hormonal activity as well as muscle effort.

According to Selye, the critical task is to identify optimal levels of stimulation in the work environment. GAS has three phases: 1. alarm reaction; 2. adaptation; 3. exhaustion for a given stimulus **(Figure 3)**. After exposure

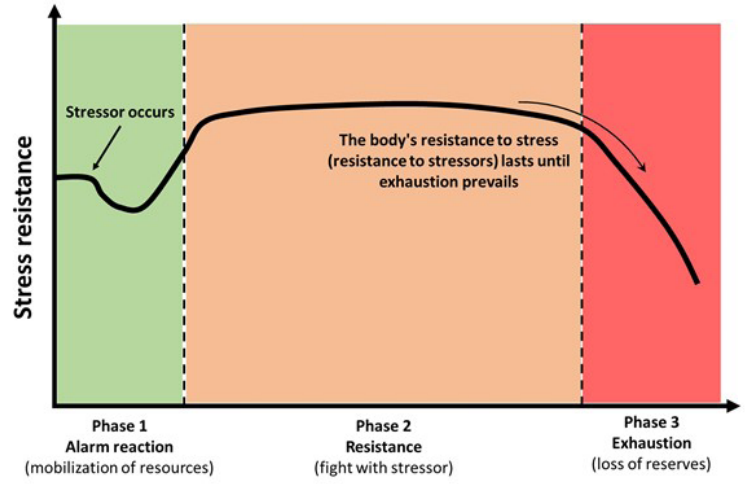

Figure 3. Three phases of Selye's general adaptation syndrome

BIOLOGICAL SYNDROME: STRESS	
Phase	**Neuroendocrine effect**
Alarm reaction	Activation of central nervous system
Resistance	Activation of hypothalamus-hypophysis-adrenal axis
Tissue changes	Adrenal gland hypertrophy, gastric ulcer, atrophy of thymus and lymphoid tissue
Exhaustion	Summation of effects and possible lethal outcome

to stressors, the alarm is initial response to stress which refers to the fight-or-flight effect, when the sympathetic nervous system is activated by a sudden release of hormones. Because no organism can be continuously in an alarm state, a phase of adaptation or resistance follows during which symptoms subside. The third phase or the phase of exhaustion occurs after an even greater and prolonged exposure to stressors, because the adaptability or "adaptive energy" of the organism is limited, and body is no longer able to cope with stress (13).

According to Selye, many stress-induced diseases occur in the resistance phase and according to him, these are "adaptation diseases". These adaptive diseases include headache, insomnia, and increased blood pressure which carries a risk of heart dysfunction. Besides, there is an increased usage of chemical resources and increased immune response that can cause permanent changes in the body as well as kidney disease. Hans Selye was the first to coin the term "heterostasis"(from the Greek *heteros* or other) as the procedure in which a new stable state was achieved by the activation of physiological adaptive mechanisms (14-16).

Heterostasis (cacostasis or allostasis)

Life and vital homeostatic systems (physiological) are programmed and rigorously adjusted during evolution, aiming to preserve a predefined steady state in order to maintain complex dynamic balance (homeostasis or eustasis) (17).

Stress leads to an imbalance of homeostasis or brings the organism into a state of disharmony. The adaptive response to stress is a new level of homeostasis that tends to correct and restore disturbed variables to their physiological range (18, 19).

The tendency to establish endangered homeostasis is called cacostasis or allostasis. Allostasis is homeostasis in the period of coping with stress under changed conditions. Allostasis provides stability and balance through psychological and behavioral changes. Optimal adjustment in the shortest period occurs by increasing hormone levels (20).

Homeostatic mechanisms exert their effects in the form of an inverse U-shaped curve in relation to the intensity of stress (homeostasis imbalance). Based on the homeostatic capacities of individuals homeostasis can be positioned at the following levels:

1. Basal homeostasis (or eustasis) is achieved in the central, optimal range of the curve, the organism returns to basal homeostasis or eustasis **(Figure 4)**.
2. Suboptimal effects of homeostatic mechanisms may occur on both sides of the curve showing insufficient adaptation, allostasis
3. When adaptive responses are inadequate due to excessive, long-term exposure to stressors, the organism falls into cacostasis (improper homeostasis, dyshomeostasis), which can be harmful to the organism. Exposure to stressors (insufficient maternal care, poor family relationships, abuse, etc.) during critical periods of development when sensitivity to stressors is increased, such as periods of prenatal development, infant period, the periods of childhood and adolescence, can have long-lasting effects. Long-term cacostasis can last a lifetime because it is caused by an epigenetic plastic change in nerve cells (at the molecular level) that is induced by stress hormones (corticotropin releasing hormone and cortisol) and thus a weak brain response to stress.
4. The most favorable is hyperstasis or perfect adaptation of the organism, which is a consequence of improved homeostatic capacities based on experience. During the mentioned critical periods when cacostasis can be induced, individuals in a favorable social environment (understanding, care and concern of the mother for the offspring, etc.) develop resistance to stressors that will appear in adulthood by inducing hyperstasis. Epigenetics refers to the connection of man with environmental factors (exposure to psychosocial stress) in critical periods of growth and development that strengthens a child for stress in adulthood (21-23).

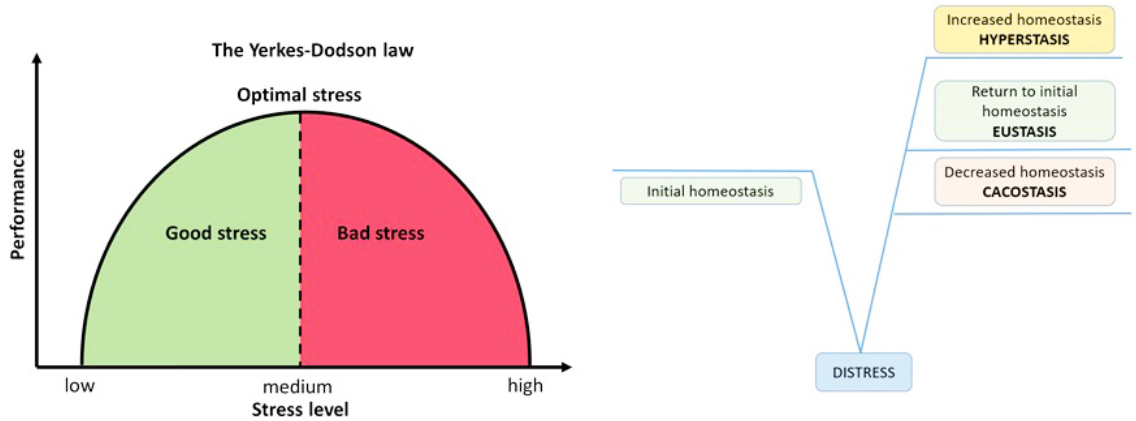

Figure 4. Activity of homeostatic systems: allostasis, eustasis, cacostasis and hyperstasis

Richard Lazarus (1922–2002)

Lazarus R., one of the most influential psychologists in the history of this field, has an important role in the improvement of stress research with an attempt to find a theory that would consider several factors involved in the "stress response". Lazarus (1966) argues that psychological stress occurs in individuals who consider the situation or circumstances as threatening. He emphasizes the process of cognitive assessment as a mediator in dealing with stressors - how a person thinks about or evaluates an event (information processing), in order to understand stress reactions in people (24, 25). The events themselves do not create stress, but the stress itself occurs after a cognitive evaluation and consideration of the event as threatening or negative (psychological stress). The basic assumption was that stress and coping with stress are reciprocal, because if coping is effective, stress is controlled and vice versa when coping is not effective, stress increases and can get out of control. Lazarus emphasized emotions as an important factor in behavioral response to stress and explained various reactions to stressors (26, 27).

Positive (eustress) and negative (distress) stress

Eustress is considered to be positive stress because important life changes, such as marriage, the birth of a baby, a demanding job or retirement are not stress-free. Eustress is the stress that enhances physical or mental functions, helps achieving goals, increases excitement, concentration and performance, leading to personal progress as well as to effective avoidance of dangerous situations. The consequences of positive stress are toned emotions, motivation and focused energy (28, 29).

At birth, a child experiences one of the greatest stressful experiences in life. High levels of hormones released during birth affect the newborn's adaptation to life outside the womb. Positive toned emotions in stress by artists (painters, composers, writers) or scientists are inspiring and creative. Positive attitude and good social support are strongly correlated with an increased ability of the immune system to fight pathogens. Optimists have good solutions to problems and use such experiences in dealing with chronic stressors (30, 31).

Distress is negative stress, created by the influence of prolonged stress that exceeds our ability to deal with it by coping or adapting (28). Negative stress causes anxiety or withdrawal (depression and anxiety), and is accompanied by unpleasant feelings, reduced work ability leading to mental and physical illnesses (32). Recent studies indicated that anxiety-related behavior in rats can also been enhanced by a lack of sleep and sleep deprivation, which can be considered as stress (33, 34). Besides, it has been showed that sleep deprivation can even make brain more susceptible to seizures by changing brain production of interleukins (35). In addition, chronic pain syndrome, as a stressful condition, contributes to anxiety-like behavior that significantly correlates with brain biochemical and hippocampal immunohistochemical alterations (36). Stress can be the reason for the onset of a disease, but the disease for whose onset stress is the main reason is called stress disease.

CONCLUSION

It is very complicated to define stress using simple terms - it simply represents a straining force in physical and mental manner. The concept of stress evolved over time depending on the specific period in history.

The modern concept of stress was based on Seyle's principles or arguing against them. The effects of stress are the results of a complex interaction between environmental and genetic factors. Adaptation on everyday challenges and stressful events is individual and it depends on the previous stressful experiences, comorbidities, allostatic states and ability to cope and to maintain interior balance and psychical and emotional homeostasis. In modern age, stress is considered to be an important contributor to diseases, especially to cardiovascular and immune system disorders. New evidence supports the opinion that negative emotions, chronic pain or asleep disorders can lead to a psychiatric pathological condition such as anxiety, depression and emotional distress in general.

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Authors' contributions

OS conceptualized the manuscript. MV, DM, OS, ARM, DH did literature screening. NS, AZ and MV prepared figures. All authors participated in manuscript writing and provided critical intellectual inputs.

Declaration of conflicting interests

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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NEUROFIZIOLOGIJA STRESA – OD ISTORIJSKOG KA SAVREMENOM PRISTUPU

Olivera Stanojlović[1], Nikola Šutulović[1], Dušan Mladenović[2], Aleksa Zubelić[1], Dragan Hrnčić[1], Aleksandra Rašić-Marković[1], Milena Vesković[2]

Sažetak

Stres je prisutan u svakodnevnom životu i smatra se pokretačkom snagom evolucije. Anksioznost, hronične brige, napadi panike najčešće su posledice dugotrajnog i iscrpljujućeg stresa. Najznačajniji fundamentalni doprinos koji je ključan za razvoj savremenog koncepta stresa dao je Klod Bernar predloživši teoriju prema kojoj telo stalno održava stabilno i dobro izbalansirano unutrašnje okruženje ili *„milieu interieur"*. Održavanje konstantne unutrašnje sredine Valter Kanon je definisao kao homeostazu i predložio dva mehanizma održavanja, putem negativne povratne sprege iz autonomnog nervnog sistema i preko čulnih organa.

Hans Seli je opisao stres kao nespecifično opterećenje za telo, uzrokovano izmenjenom funkcijom organa praćenom oslobađanjem hormona stresa. On je to nazvao opšti adaptacioni sindrom koji je imao tri stadijuma: alarmna reakcija, početna faza „bori se ili beži"; otpornost, kada se telo navikava na stres i iscrpljenost kada se otpor prema stresu postepeno smanjuje i kolabira. Hans Seli je prvi skovao termin „heterostaza" koji predstavlja postupak kojim se aktiviranjem fizioloških adaptivnih mehanizama postiže novo stabilno stanje.

Ričard Lazarus je istakao emocije kao važan faktor u ponašanju kao odgovor na stres i opisao različite reakcije na stresore. On naglašava proces kognitivne procene kao posrednika u suočavanju sa stresorima – kako osoba razmišlja ili ocenjuje neki događaj da bi razumeo reakcije na stres kod ljudi. Eustres, koji se smatra pozitivnim stresom, dovodi do toniranih emocija, motivacije i fokusirane energije, dok distres, negativni stres, nastaje nakon dužeg stresa koji prevazilazi našu sposobnost da se nosimo sa njim. Distres izaziva anksioznost ili depresiju, a praćen je neprijatnim osećanjima, smanjenom radnom sposobnošću koja dovodi do psihičkih i fizičkih bolesti.

Ključne reči: neurofiziologija, stres, istorija, hormoni

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RESEARCH ARTICLE

The association of glutathione transferase omega polymorphisms with laboratory inflammatory parameters in COVID-19

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Summary

In a view of important functions of glutathione transferase omega (GSTO) class in redox homeostasis and innate immunity, it was proposed that interindividual differences in COVID-19 clinical manifestations might be affected by *GSTO1* (rs4925) and *GSTO2* (rs156697) polymorphisms.

To assess the potential association of these polymorphisms with biochemical, coagulation and inflammatory laboratory parameters in the group of mild and severe COVID-19 patients.

GSTO1 and *GSTO2* single nucleotide polymorphisms were determined by qPCR in 251 samples of COVID-19 patients. Biochemical, coagulation and inflammatory laboratory parameters of COVID-19 participants were procured from routine laboratory practice on the day of admission.

Polymorphisms of *GSTO1* and *GSTO2* affect laboratory biochemical profile of COVID-19 patients. *GSTO1**C allele was associated with increased levels of C-reactive protein (CRP) (p=0.035), interleukin-6 (IL-6) (p=0.047), D-dimer (p=0.014) and lactate dehydrogenase LDH (p=0.002), whereas *GSTO2**G allele was associated with CRP (p=0.033). COVID-19 patients homozygous for variant *GSTO1**A allele and *GSTO2**G had the highest levels of serum Fe (p=0.019, p=0.052, respectively).

Our findings regarding the influence of *GSTO1* and *GSTO2* polymorphisms on inflammation and coagulation parameters might be of clinical importance. In future, these findings could aid in a more personalized approach for better recognition of patients prone to thrombosis and excessive immune response.

Keywords: COVID-19, polymorphisms, inflammation, coagulation, *GSTO1*, *GSTO2*

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INTRODUCTION

Considering diverse variations in severity, duration and outcomes of coronavirus disease 2019 (COVID-19), defining a genetic predisposition, along with clinical and environmental factors, might be an important step in improving the diagnosis and treatment of high-risk individuals. Due to the established role of oxidative distress in the pathophysiology of COVID-19, it has been proposed that inter-individual differences in patients' clinical manifestations might also be affected by variations in genes encoding detoxifying and antioxidant enzymes, glutathione transferases (GSTs) (1). GSTs are a superfamily of enzymes that catalyze the conjugation of glutathione (GSH) to a wide range of chemical carcinogens, drugs and oxidative stress products. Seven cytosolic GST classes have been identified in humans: alpha, mu, pi, sigma, theta, zeta, and omega class (2).

The omega class GST (GSTO) shares only 20% amino acid sequence identity with the other GST classes (3), with a range of catalytic activities that are unrelated to the functions of other GST classes (4). GSTO display a prominent function in redox regulation, glutathionylation/deglutathionylation cycle and innate immune response (3). Glutathionylation/deglutathionylation is thought to be an important regulation mechanism of protein function implicated in the modulation and control of various signaling pathways (5). Monocytes and macrophages are important elements of the innate immune system and the effect of glutathionylation on macrophage function and inflammation has been currently investigated (6–8). GSTO1-1 with its deglutathionylation activity catalyzes the deglutathionylation of cellular proteins and could have and important role in modulating the glutathionylation of intracellular proteins that participate in specific signaling pathways (4). Recent studies have emphasized the role of GSTO1-1 in the pro-inflammatory response of macrophages to bacterial lipopolysaccharide (LPS) that is mediated through Toll like receptor (TLR4) (9). The application of a small molecule inhibitor of GSTO1-1 weakens the inflammatory response to LPS suggesting that the active GSTO1-1 has a pro-inflammatory role. This further implies that the glutathionylation of a key protein has an important role in the TLR4 pro-inflammatory pathway (10). All these findings brought researchers to the conclusion that GSTO1-1 can exert a pro-inflammatory action in innate immunity.

GSTO2-2 has very high dehydroascorbate reductase (DHAR) activity compared to GSTO1-1 (4) with an important role in regeneration of dehydroascorbate (11). DHAR activity makes GSTO2-2 an important participant in the regulation of redox homeostasis and immune system functioning. So far, several studies have reported that a high-dose intravenous vitamin C has positive effects in the treatment of moderate to severe COVID-19 patients due to its potential inhibitory effect on SARS-CoV-2 multiplication (12). Genome-wide association studies (GWAS) recognized the significance of *GSTO2* in pulmonary function, but its precise role and function in the lungs remain unclear (13). Mukherjee B. et al. described 31 polymorphisms in *GSTO1* and 66 polymorphisms of *GSTO2* gene (14). Regarding the functional implication of those genetic variations in *GSTO1* and *GSTO2* genes, the most often investigated are single nucleotide polymorphisms (SNPs) of *GSTO1*, rs 4925 and *GSTO2*, rs 156697 (14). A SNP (NCBI SNP ID: rs4925, 419 C to A) of *GSTO1* was reported at nucleotide 419 causing alanine to aspartate substitution in amino acid 140 (A140D, Ala140Asp) of exon 4. SNP of *GSTO2* was found at nucleotide 424 causing an asparagine to aspartate substitution in amino acid 142 (N142D, Asn142Asp) of exon 4 (NCBI SNP ID: rs156697, 424 A to G) (15). It has been shown that GSTO1 rs4925 polymorphism causes a change primarily in deglutathionylase activity (2,4). Regarding *GSTO2* rs156697 polymorphism, a strong association between variant *GSTO2**G allele and lower *GSTO2* gene expression has been shown (14,16). In our recent study comprising COVID-19 patients and healthy controls, the individuals carrying variant *GSTO1**AA and variant *GSTO2**GG genotypes exhibited higher odds of COVID-19 development, contrary to the ones carrying referent alleles ($p = 0.044$, $p = 0.002$, respectively). These findings have been confirmed by haplotype analysis. Carriers of H2 haplotype (*GSTO1**A and *GSTO2**G variant alleles) were at 2-fold increased risk of COVID-19 development ($p = 0.002$) (17).

Since genetic polymorphisms in glutathione transferase omega genes modify COVID-19 risk, inter-individual differences in COVID-19 clinical presentation might also be affected by *GSTO* genetic profile. In this line, the aim of this study was to assess the potential association of genetic polymorphisms in genes encoding *GSTO1* (rs4925) and *GSTO2* (rs156697), with biochemical, coagulation and inflammatory laboratory parameters in the group of mild and severe COVID-19 patients.

MATERIAL AND METHODS

This case-only study recruited 251 patients from the Institute of Infectious and Tropical Diseases, University Clinical Centre of Serbia, between July 2020 and February 2021, diagnosed with COVID-19 by means of positive RT-PCR test, as previously described by Miljanovic et al. in 2021 (18). All patients were stratified according to the COVID-19 National Guidelines, version 9, into those with mild COVID-19 (Stage I) and severe COVID-19 (Stages II, III and IV). The principles of International Conference on Harmonization (ICH) Good Clinical Practice, the "Declaration of Helsinki," and national and international ethical guidelines were respected throughout this study with the authorization received from the Ethics Commit-

tee of the Clinical Centre of Serbia (566/01 from July 13, 2020 and 608/01 from August 7, 2020). Written informed consent was obtained from all study participants. Clinical, demographic and epidemiological data were collected using RedCap® based questionnaire (https://redcap.med.bg.ac.rs/, AntioxIdentification).

All patients had their laboratory analyses and non-contrast chest CT estimated on the day of admission, on the seventh and on the fourteenth day, consecutively.

All laboratory parameters of COVID-19 participants were procured from routine laboratory practice on the day of admission.

Patients' DNA was extracted from EDTA-anticoagulated peripheral blood obtained from the study participants using PureLink™ Genomic DNA Mini Kit (ThermoFisher Scientific, United States). *GSTO1* (rs4925, ID number: C_11309430_30) and *GSTO2* (rs156697, ID number: C_3223136_1_), polymorphisms were determined by TaqMan Drug Metabolism Genotyping assays (Life Technologies, Applied Biosystems, United States) on the Mastercycler ep realplex platform (Eppendorf, Germany).

Statistical data analysis was performed using IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, United States). The obtained results were presented as frequency, percent and mean ± standard deviation (SD). Based on the normality tests, the differences in continuous data were assessed using an appropriate statistical test. Differences between categorical variables were tested for using a $\chi 2$-test. The risk for COVID-19 development and progression was calculated with adjusted odds ratios (OR) and 95% confidence intervals (CI) using logistic regression analysis. All p-values below 0.05 were considered significant.

RESULTS

Baseline characteristics of 82 mild COVID-19 and 169 severe COVID-19 patients are shown in **Table 1**. As presented, these two groups did not differ significantly in terms of gender, diabetes and obesity (p>0.05), although the patients with severe COVID-19 had higher BMI than those with mild form of the disease (p=0.037). The presence of hypertension was associated with higher odds of severe COVID-19 form (OR=3.15, 95%CI: 1.60-6.21, p=0.001). On the other hand, smoking was associated with decreased odds of severe COVID-19 (OR=0.21, 95%CI: 0.09-0.44, p< 0.001).

The distribution of *GSTO1 (rs4925), GSTO2 (rs156697)* genotypes among mild and severe COVID-19 patients is presented in Table 2. There was a significantly higher number of carriers of at least one variant *GSTO1* allele in the group of mild COVID-19 patients in comparison with the severe COVID-19 group of individuals (57.5% vs. 42.9% respectively, p=0.031).

As for *GSTO2* there was no statistical significance between mild and severe COVID-19 groups in terms of genotypes (p=0.050).

Biochemical parameters, obtained from inspected COVID-19 patients upon their admission to hospital,

Table 1. Baseline characteristics of mild and severe COVID-19 patients

	Mild COVID-19 (n=82)	Severe COVID-19 (n=169)	OR[b] (95%CI)[c]	*p*
Age (years)[a]	45.08 ± 11.10	55.08 ± 11.88	/	< 0.001
Gender, n (%)				
Male	42 (51.2)	94 (55.6)	1.00[d]	
Female	40 (48.8)	75 (44.4)	0.84 (0.49-1.42)	0.512
Hypertension, n (%)[c]				
No	42 (72.4)	55 (45.5)	1.00[b]	
Yes	16 (27.6)	66 (54.5)	3.15 (1.60-6.21)	0.001
Obesity, n (%)[c]				
BMI < 30	50 (64.1)	108 (64.7)	1.00[b]	
BMI > 30	28 (35.9)	59 (35.3)	0.98 (0.56-1.71)	0.931
BMI (kg/m^2)[a]	27.80 ± 5.69	29.31 ± 5.01	/	0.037
Smoking, n (%)[c]				
Never	37 (46.8)	94 (57.7)	1.00[b]	
Former	17 (21.5)	56 (34.4)	1.30 (0.67-2.52)	0.442
Ever	25 (31.6)	13 (8.0)	0.21 (0.09-0.44)	< 0.001
Diabetes[c]				
No	74 (90.2)	150 (88.8)	1.00[b]	
Yes	8 (9.8)	19 (11.2)	1.17 (0.49-2.80)	0.722

n, number of patients in each group, [a]mean ± standard deviation, [b]OR, odds ratio, [c]CI, confidence interval, [d]reference group

Table 2. The distribution of *GSTO1* and *GSTO2* genotypes among mild and severe COVID-19 patients

Genotype	Mild COVID-19 n, %	Severe COVID-19 n, %	*P*
GSTO1 (rs4925)			
CC	34 (42.5)	96 (57.1)	
CA	30 (37.5)	46 (27.4)	
AA	16 (20.0)	26 (15.5)	0.096
CA+AA	46 (57.5)	72 (42.9)	**0.031**
GSTO2 (rs156697)			
AA	30 (36.6)	84 (49.7)	
AG	32 (39.0)	54 (32.0)	
GG	20 (24.4)	31 (18.3)	0.143
AG+GG	52 (63.4)	85 (50.3)	0.050

n, number of patients in each group

with regard to assessed *GSTO1* and *GSTO2* genotypes, are presented in **Table 3**. The COVID-19 patients who were carriers of variant *GSTO1**AA genotype, had decreased levels of lactate dehydrogenase (LDH) (p=0.002) and increased levels of iron (Fe) (p=0.019). The presence of *GSTO2**GG genotype was found to be significantly associated with increased activity of alanine aminotransferase (ALT) (p=0.027). The carriers of variant *GSTO2**GG genotype had increased levels of iron in comparison with the carriers of reference *GSTO2**AA genotype with a clear tendency to significance (p=0.052).

The association of *GSTO1* and *GSTO2* polymorphisms with inflammatory laboratory parameters, are presented in **Figures 1 and 2**. The patients who were carriers of variant *GSTO1**AA genotype had significantly decreased levels of CRP and IL-6 in comparison with the carriers of referent *GSTO1**CC genotype (p=0.035, p=0.047 respectively). As for the *GSTO2* polymorphism, the patients who were carriers of variant *GSTO2**GG genotype had lower CRP values in comparison with the patients with referent *GSTO2* genotype (p=0.033). The association of *GSTO1* and *GSTO2* polymorphisms with D-dimer, as a coagulation laboratory parameter, are presented in **Figures 3 and 4**. COVID-19 patients carriers of variant *GSTO1**AA genotype had significantly lower levels of D-dimer in comparison with carriers of of referent *GSTO1**CC genotype (p=0.033). As for *GSTO2* polymorphisms, no association was found with D-dimer levels.

DISSCUSSION

In a view of important functions of novel glutathione transferase omega class in redox homeostasis and innate immunity, a potential modifying effect of *GSTO1* and *GSTO2* polymorphisms on individual susceptibility towards COVID-19 clinical presentation was suggested. In this study, the inflammatory, coagulation and biochemical laboratory parameters were analyzed in COVID-19 patients stratified according to polymorphic variants in *GSTO* genes. The data obtained showed that *GSTO* polymorphisms were associated with inflammatory parame-

Table 3. The association of GSTO1 and GSTO2 gene polymorphisms with biochemical parameters

Genotype	ALT (U/L)[a]	AST (U/L)[a]	LDH (U/L)[a]	Fe (μmol/L)[a]	TIBC (μmol/L)[a]	Creatinine (μmol/L)[a]
***GSTO1* (rs4925)**						
CC	54.5±39.4	41.1±25.0	315.7±219.8	6.3±4.1	44.3±10.9	95.7±54.0
CA	46.6±25.4	36.5±23.9	267.3±135.2	6.7±5.5	51.6±53.7	83.2±22.6
AA	53.1±21.4	34.1±14.9	222.8±92.9	8.6±5.3	45.2±7.7	81.2±22.7
P	0.158	0.364	0.002	0.019	0.792	0.152
***GSTO2* (rs156697)**						
AA	52.2±39.5	36.9±21.5	295.1±201.7	6.6±4.5	50.3±38.1	91.0±31.1
AG	46.8±21.9	38.8±23.9	296.1±192.5	5.9±4.1	43.1±10.0	94.5±65.7
GG	59.2±30.2	42.6±23.4	245.8±108.8	8.7±5.9	41.0±7.9	80.3±22.4
P	0.027	0.344	0.175	0.052	0.173	0.241

[a]Mean ±SD; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; TIBC, total iron-binding capacity

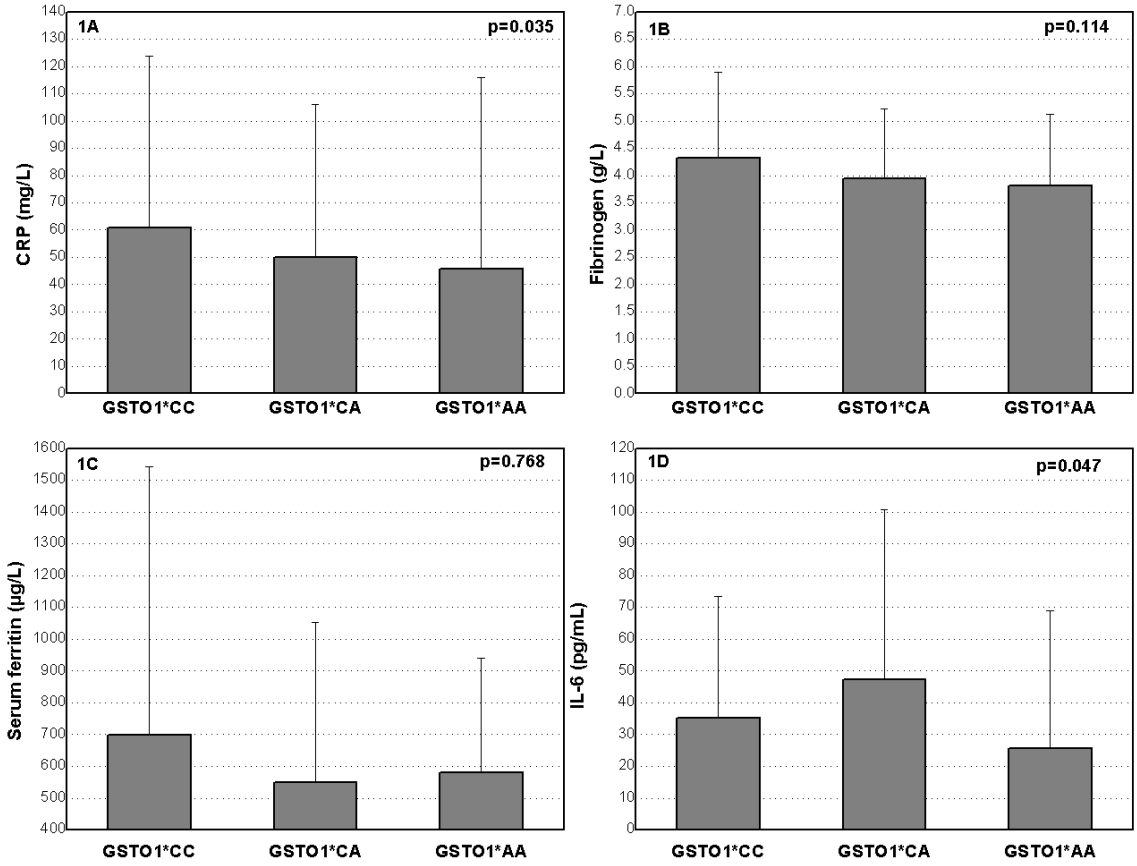

Figure 1. The association of GSTO1 polymorphism with CRP (A), fibrinogen (B), ferritin (C) and IL-6 (D).

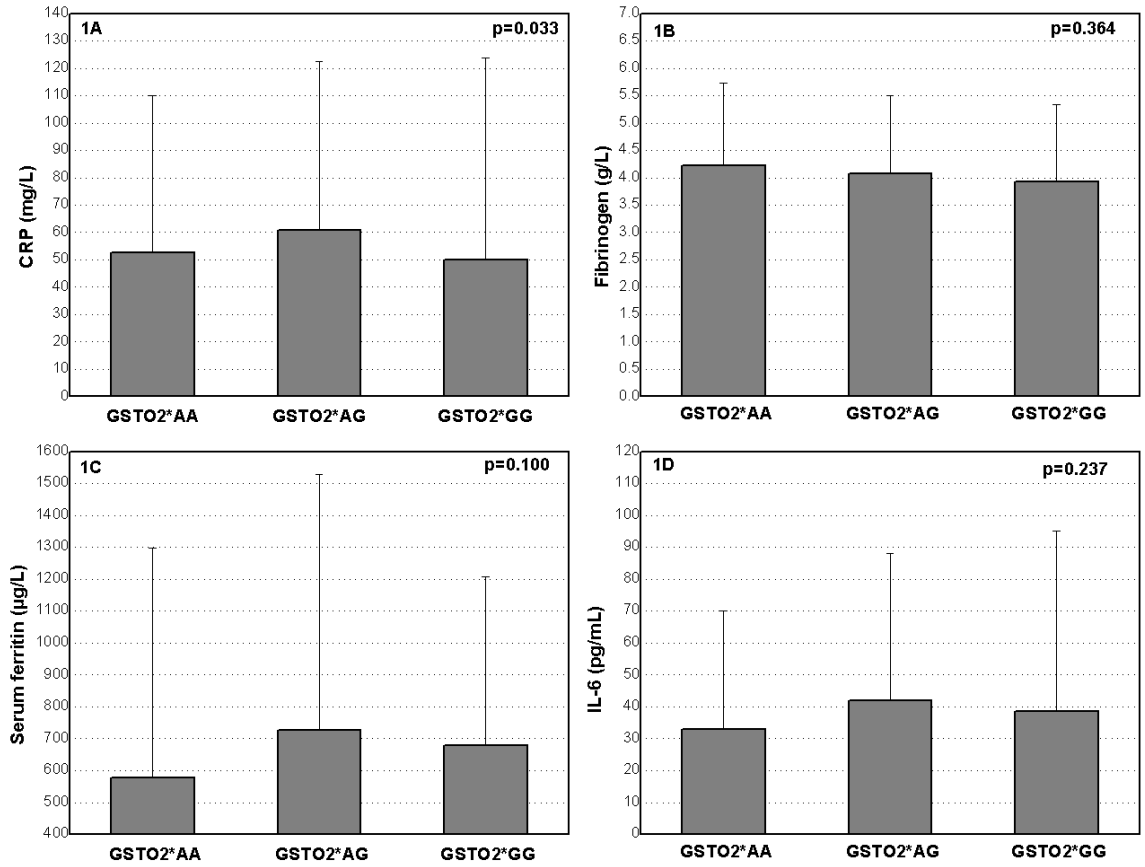

Figure 2. The association of GSTO2 polymorphism with CRP (A), fibrinogen (B), ferritin (C) and IL-6 (D).

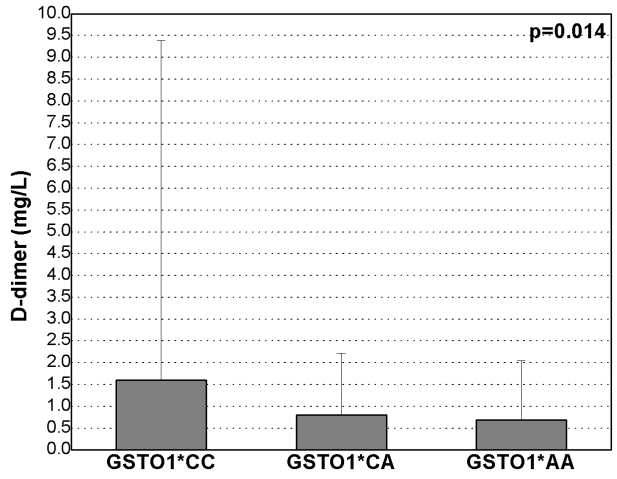

Figure 3. The association of GSTO1 polymorphism with D-dimer.

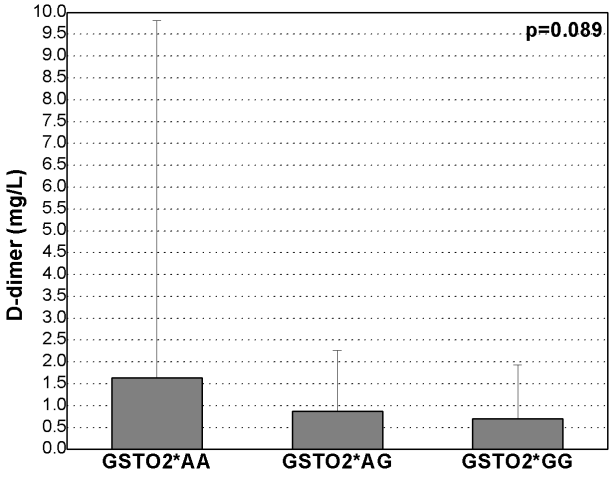

Figure 4. The association of GSTO1 polymorphism with D-dimer.

ters in COVID-19 patients. Indeed, COVID-19 carriers of *GSTO1* referent genotype had significantly higher levels of CRP and IL-6 in comparison to the carriers of at least one variant *GSTO1**A allele. In addition, significant correlations between *GSTO1* polymorphism and serum Fe, D-dimer and LDH were found, whereas *GSTO2* polymorphism was associated with serum Fe level and ALT activity.

It has been well established that patients exhibiting severe form of COVID-19 have significantly lower count of lymphocytes, monocytes and platelets in comparison to the patients with mild COVID-19 (19). Furthermore, significantly increased CRP at admission is frequently associated with severe COVID-19, whereas the predictive value of IL-6 and TNF-α in disease severity and death was assessed in numerous studies (20). In fact, determining the IL-6 level, together with TNF-α, could be considered as a clinical device for identifying patients at increased risk, and those who should be treated with the IL-6R antagonist tocilizumab (21). Furthermore, an increased activity of liver enzymes, alanine ALT and AST, as well as renal parameters, such as blood urea nitrogen and creatinine, along with high D-dimer is characteristic of patients who develop the severe form of the disease represented by multi-organ failure. Additionally, regarding coagulation parameters, patients with severe COVID-19 had statistically significantly higher levels of D-dimer than those with mild to moderate COVID-19. This finding seems important, since increased plasma D-dimer levels, a sensitive fibrin degradation marker indicative of increased coagulation and oxidative distress, also correlate with mortality (22).

Great inter-individual variability among SARS-CoV-2 infected individuals in terms of disease progression and outcome clearly implies a possible effect of host genetic factors (23). Our data suggests that genetic variants in *GSTO1* gene may not only have a modulating effect in the propensity to SARS-CoV-2 infection, but also in determining the intensity of innate immune response. Intriguingly, the novel function of GSTO1-1 in promoting the activation of one of the main innate immune components, NLRP3 inflammasome, has been recently established (24). Namely, it was found that deglutathionylating NIMA related kinase 7 (NEK7) by GSTO1 corresponded to the activation of NLRP3 inflammasome (24,25). This inflammasome is involved in the conversion of pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18 with the consequent release of additional cytokines, such as IL-6 (26). This further implies the importance of the NLRP3 inflammasome in the development of COVID-19 and formation of cytokine storm. In this line, the data on overactivation of NLRP3 inflammasome, as well as its association with acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) in COVID-19 are not unexpected (25–27). In the view of the fact that *GSTO1* polymorphism was proposed to exhibit differential efficiency in activating NLRP3 inflammasome, this potentially contributes to either promoting or attenuating the inflammatory response, as well as to the level of local or systemic tissue injury (24). We found that COVID-19 carriers of referent *GSTO1*CC* genotype had significantly higher levels of LDH, CRP and IL-6 in comparison to the carriers of at least one variant GSTO1*A allele. Since ferritin, CRP and LDH have been shown to be the predictive laboratory biomarkers of COVID-19 severity, it might be speculated that determination of GSTO1 polymorphisms could aid in the identification of high-risk individuals. Moreover, our results are in concordance with findings on the positive correlation between IL-18, CRP, LDH and IL-6, and the inflammasome activation in COVID-19. To date, several FDA-approved therapies that interfere with inflammasome activation signaling have been considered for the treatment of COVID-19, including anakinra, tocilizumab and IFN-β (28).

Interestingly, in our study, COVID-19 patients who were homozygous for variant *GSTO1**A allele and *GSTO2**G had the highest levels of serum Fe. Indeed, our results are in agreement with a recent meta-analysis

on serum levels of Fe metabolism parameters. Namely, in severe COVID-19 patients lower serum Fe levels are related to higher concentrations of hepcidin and ferritin without significant differences in transferrin saturation (29). It is also important to note that increased plasma ferritin stimulates the production of reactive oxygen species further contributing to both dysregulated redox homeostasis and ferroptosis-mediated tissue damage (30,31). In this setting, a possible consequence of *GSTO2* polymorphism is the alteration in its antioxidant activity that may also affect the activity of transcription factor, hypoxia inducible factor alpha, (HIF-1α) important in inducing pro-inflammatory response to COVID-19 (32). In this context, it can be speculated that vitamin C-dependent inhibition of the HIF-1α pathway may provide an additional approach to controlling inflammation (32). Assuming the specific roles of GSTO enzymes in these processes, our results support the hypothesis that GSTO polymorphisms are associated with the propensity for developing severe COVID-19, with special emphasis on the *GSTO1* polymorphism.

Our results on the association between *GSTO1* and *GSTO2* polymorphisms with laboratory parameters of inflammation and coagulation patients may provide some new information in understanding the complex molecular mechanisms in COVID-19, as well as contribute to an early identification of patients who are more prone to a worse course of the disease. Further studies are needed to identify the precise function of *GSTO1* gene variants that may be associated with abnormal immune response in COVID-19 and the potential treatment of GSTO1 inhibitors with anti-inflammatory properties in the patients with the risk of systematic inflammatory response.

Author Contributions

Conceptualization, A.S.-R. and T.S.; methodology, T.D., V.C. and D.J.; software, Z.B.; validation, T.D., V.C. and D.J.; formal analysis, Z.B.; investigation, T.D., V.C. and D.J.; resources, G.S., J.R., I.M., M.A. and M.E.; writing—original draft preparation, A.S.-R., T.S., and T.D.; writing—review and editing, T.S., A.S.-R., M.P.-E., M.M., T.D., V.C., D.J., G.S., J.R., I.M., M.A., M.E. and Z.B.; visualization, T.D., V.C. and D.J.; supervision, A.S.-R. and T.S.; project administration, T.S.; All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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POVEZANOST POLIMORFIZMA GLUTATION TRANSFERAZA OMEGA SA LABORATORIJSKIM POKAZATELJIMA ZAPALJENJA U KOVIDU-19

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Sažetak

S obzirom na važnu ulogu koju glutation transferaze klas omega (*GSTO*) imaju u održavanju redoks ravnoteže i u urođenoj imunosti, može se prepostaviti da polimorfizmi gena *GSTO1* (rs4925) i *GSTO2* (rs156697) imaju potencijalni efekat na razlike koje postoje u kliničkim manifestacijama COVID-19.

Da se ispita potencijalna veza između ovih polimorfizama i biohemijskih, koagulacionih i inflamatornih laboratorijskih parametara u grupi pacijenata koji su imali blaži i teži oblik COVID-19.

Polimorfizmi izmene jednog nukleotida *GSTO1* i *GSTO2* su određivani qPCR metodom kod 251 pacijenta obolelog od COVID-19. Biohemijski, koagulacioni i inflamatorni laboratorijski parametri su određivani kod svih pacijenata tokom rutinske analize na prijemu u bolnicu.

Polimorfizmi *GSTO1* i *GSTO2* koreliraju sa biohemijskim laboratorijskim profilom COVID-19 pacijenata. Dobijene su statistički značajno više vrednosti C-reaktivnog proteina (CRP) (p=0,035), interleukina 6 (IL-6) (p=0,047) laktat dehidrogenaze (LDH) (p=0,002) i D-dimera (p=0,014) kod nosilaca referentnog *GSTO1**C alela u poređenju sa vrednostima ovoh parametara kod pacijenata nosilaca varijantnog *GSTO1**A alela. COVID-19 pacijenti nosioci *GSTO-2**G alela imali su značajno niže vrednosti CRP (p=0,033). Pacijenti koji su bili homozigotni nosioci varijantnog *GSTO1**A alela ili varijantnog *GSTO2**G alela su imali značajno više vrednosti serumskog Fe (p=0,019, p=0,052, redom).

Povezanost *GSTO1* i *GSTO2* polimorfizama sa laboratorijskim parametrima inflamacije i koagulacije imaju potencijalni klinički značaj u identifikaciji onih pacijenata koji su skloniji neadekvatnom imunskom odgovoru na prisustvo virusa ili pojavi tromboze.

Ključne reči: COVID-19, polimorfizmi, inflamacija, koagulacija, *GSTO1*, *GSTO2*

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