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Broj. 2122/10-1
Podgorica, 25.12.2020. godine

Univerzitet Crne Gore
Odbor za doktorske studije

Poštovani,

U skladu sa članom 33 Pravila doktorskih studija, dostavljamo Odluku Vijeća Medicinskog fakulteta i Izvještaj mentora prof. dr Milice Martinović o radu doktoranda dr med Marine Jakšić Kavarić.

S poštovanjem,

MEDICINSKI FAKULTET
D E K A N,
Prof. dr Miodrag Radunović

UNIVERZITET CRNE GORE
MEDICINSKI FAKULTET
Broj: 2122/10
Podgorica, 24.12.2020. godine

Na osnovu člana 64 Statuta Univerziteta Crne Gore (Bilten UCG br:337/15 i 447/18) člana 33 stav 2 Pravila doktorskih studija broj: 08-583 od 26.02.2015. godine, a u vezi sa godišnjim izvještajem mentora o napredovanju doktoranda broj: 2085 od 16.12.2020. godine i Izvještaja komisije za doktorske studije broj: 2085/1 od 18.12.2020. godine, Vijeće Medicinskog fakulteta na elektronskoj sjednici održanoj dana 23-24.12.2020. godine, donijelo je

O D L U K U

1. Usvaja se Drugi godišnji izvještaj mentora, prof. dr Milice Martinović o radu doktoranda dr med Marine Jakšić Kavarić, na sprovedenom istraživanju i postignutim rezultatima, na izradi doktorske disertacije, sa objavljenim rezultatima rada na izradi doktorske disertacije.
2. Drugi godišnji izvještaj mentora o napredovanju doktoranda broj: 2085 od 16.12.2020. godine čini sastavni dio ove odluke.
3. Izvještaj se dostavlja Centru za doktorske studije – Odboru na saglasnost.

VIJEĆE MEDICINSKOG FAKULTETA
PREDSJEDAVAJUĆI,

Prof. dr Miodrag Radunović, dekan

Primljeno	16. 12. 2020
Org. jed.	Broj
med	2085

UCG

DRUGI GODIŠNJI IZVJEŠTAJ MENTORA O NAPREDOVANJU DOKTORANDA

Akademska godina za koju se podnosi izvještaj	2020/2021		
OPŠTI PODACI O DOKTORANDU			
Titula, ime, ime roditelja, prezime	dr Marina (Željko) Jakšić-Kavarić		
Fakultet	Medicinski fakultet, Podgorica, Univerzitet Crne Gore		
Studijski program	Medicina		
Broj indeksa	25/10		
MENTOR/MENTORI			
Prvi mentor	Prof. dr Milica Martinović	Medicinski fakultet,CG	Patološka fiziologija
Drugi mentor	/	/	/

EVALUACIJA DOKTORANDA*					
Koliko ste zadovoljni kvalitetom održanih susreta sa doktorandom?	☐1	☐2	☐3	☐4	☑5
(Ako je prethodni odgovor „1" ili „2" dati obrazloženje i prijedloge za poboljšanje					
Da li je definisan plan rada sa doktorandom?	☑DA	☐NE			
Da li je doktorand ostvario napredak prema predviđenom planu rada?	☑DA	☐NE			
(Ako je prethodni odgovor „ne" dati obrazloženje i prijedloge za poboljšanje)					
Kvalitet napretka doktorandovog istraživačkog rada u periodu između dva izvještaja je:	☐1	☐2	☐3	☐4	☑5
(Ako je prethodni odgovor „1" ili „2" dati obrazloženje i prijedloge za poboljšanje)					
Dati ocjenu doktorandove spremnosti za konsultacije.	☐1	☐2	☐3	☐4	☑5
Dati ocjenu planiranja i izvršavanja godišnjih istraživačkih aktivnosti i stručnog usavršavanja doktoranda.	☐1	☐2	☐3	☐4	☑5
Dati ocjenu napretka u savladavanju metodologije naučno-istraživačkog rada.	☐1	☐2	☐3	☐4	☑5
Dati ocjenu o aktivnostima sprovedenim na pisanju i objavljivanju naučnih radova.	☐1	☐2	☐3	☐4	☑5
Dati ocjenu doktorandovog generalnog odnosa prema studijama.	☐1	☐2	☐3	☐4	☑5
Dati ocjenu ukupnog kvaliteta doktorandovog rada.	☐1	☐2	☐3	☐4	☑5
(Ako je prethodni odgovor „1" ili „2" dati obrazloženje i prijedloge za poboljšanje)					
SAGLASNOST ZA NASTAVAK STUDIJA					

*Ocjene su: 1 – nedovoljan, 2 – dovoljan, 3 – dobar, 4 – vrlo dobar, 5 – odličan

Može li doktorand nastaviti studije?	☑ Da ☐ Da, uz određene uslove ☐ Ne
(Ako je prethodno dat odgovor pod „b)" ili „c)" dati obrazloženje i prijedloge za poboljšanje)	
Napomene	
Iz doktorske disertacije pod nazivom "Inflamacija, oksidativni stres i metabolički sindrom kod predgojazne i gojazne djece u Crnoj Gori" do sada je publikovan jedan a prihvaćeni za publikaciju dva rada u prestižnim biomedicinskim časopisima indeksiranim u SCI, SCIE citatnim bazama podataka (u prilogu). U fokusu sva tri objavljena ili za objavljivanje prihvaćena rada nalaze se istraživanja biomarkera i apsolutno inovativnog patofiziološkog supstrata gojaznosti u dječijem uzrastu, što je prepoznato i od strane stručne naučno-medicinske javnosti. U tom smislu, doktorska disertacija, kao i dio publikovanih rezultata koji su proistekli iz nje, doprinose jasnijem naučnom uvidu u kompleksne patofiziološke procese jednog od najrasprostranjenijih metaboličkih oboljenja pedijatrijskog, ali i adultnog doba - gojaznosti. Doktorandica je, uz pomoć mentora, učestvovala u svim fazama izrade publikovanih radova.	
IZJAVA MENTORA	
Izjava mentora o vremenskom periodu i realizaciji polaznih istraživanja (popunjava se samo za prvi izvještaj mentora)	
U Podgorici, 16.12.2020.god.	Ime i prezime mentora Prof. dr Milica Martinović

Prilog dokumenta sadrži:

- Objavljeni rezultati rada na izradi doktorske disertacije (za drugi izvještaj mentora)

Objavljeni rezultati rada na izradi doktorske disertacije:

1. Jaksic M, Martinovic M, Gligorovic-Barhanovic N, Vujacic A, Djurovic D, Nedovic-Vukovic M. Association between inflammation, oxidative stress, vitamin D, copper and zinc with pre-obesity and obesity in school children from the city of Podgorica, Montenegro. J Pediatr Endocrinol Metab. 2019 Sep 25;32(9):951-957. doi: 10.1515/jpem-2019-0086. PMID: 31444965 *(SCI, SCIE, IF 1.34)*

2. Jaksic M, Martinovic M, Gligorovic-Barhanovic N, Antunovic T, Nedovic-Vukovic M. Relationship between Insulin-Like Growth Factor-1, Insulin Resistance and Metabolic Profile with Pre-Obesity and Obesity in Children. J Pediatr Endocrinol Metab. Accepted for publication; Dec 2020 *(SCI, SCIE, IF 1.34)*

3. Martinovic M, Belojevic G, Jaksic M, Kavaric N, Klisic A. Cardiometabolic risk among Montenegrin Urban Children in Relation to Obesity and Gender. Acta Clin Croat. Accepted for publication; July 2018 *(SCIE, IF 0.53)*

U Podgorici,

16.12.2020.god

Dr Marina Jakšić-Kavarić, doktorand

VIJEĆU MEDICINSKOG FAKULTETA

PREDMET: Izvještaj Komisije za doktorske studije

Komisija za doktorske studije Medicinskog fakulteta na sjednici održanoj dana 18.12.2020. godine, razmotrila je Drugi godišnji **izvještaj mentora prof. dr Milice Martinović** o napredovanju studenta – **doktoranda dr med Marine Jakšić Kavarić** (Izvještaj broj: 2085 od 16.12.2020. godine) i zaključila da je u skladu sa svim navedenim elementima u Vodiču za doktorske studije Univerziteta Crne Gore, pa predlaže dalji nastavak po predvidjenom protokolu.

KOMISIJA ZA DOKTORSKE STUDIJE

Prof. dr Filip Vukmirović

Marina Jaksic*, Milica Martinovic, Najdana Gligorovic-Barhanovic, Aleksandar Vujacic, Dijana Djurovic and Mirjana Nedovic-Vukovic

Association between inflammation, oxidative stress, vitamin D, copper and zinc with pre-obesity and obesity in school children from the city of Podgorica, Montenegro

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Abstract

Background: Childhood obesity is a serious health condition with increasing rates worldwide. The aim of this study was to investigate the association between inflammation, oxidative stress, vitamin D, copper and zinc in pre-obese and obese children compared to controls.

Methods: The study involved 202 children aged 7–15 years (63.9% boys), randomly chosen from 10 elementary schools in Podgorica, Montenegro. Participants were divided into three groups according to their nutritional status (International Obesity Task Force [IOTF] criteria): normal-weight (42.1%), pre-obese (40.6%) and obese (17.3%). Serum biochemical analyses were performed (C-reactive protein [CRP], retinol-binding protein [RBP], total antioxidant status [TAS], total vitamin D [VD], copper and zinc).

Results: Serum TAS and CRP concentrations were higher in pre-obese and obese children compared to controls ($p < 0.001$). Serum VD concentrations were lower in pre-obese and obese children compared to their normal-weight peers ($p = 0.027$ and $p = 0.054$, respectively). Copper, zinc and RBP concentrations did not differ significantly among the groups ($p > 0.05$). In pre-obese and obese children, a positive correlation was found between CRP and copper ($r = 0.305$, $p = 0.011$ and $r = 0.440$, $p = 0.013$, respectively), and TAS and RBP ($r = 0.528$, $p < 0.001$ and $r = 0.434$, $p = 0.015$, respectively). Standard regression analyses showed that CRP and TAS increase ($p < 0.001$) whereas VD decreases ($p = 0.011$) with the body mass index (BMI).

Conclusions: We show that pre-obesity and obesity in childhood are positively associated with oxidative stress and inflammation, and inversely associated with VD status. Copper and zinc concentrations were not associated with excess fat in children.

Keywords: inflammation; obesity; oligoelements; oxidative stress; vitamin D.

Introduction

Obesity is defined as an abnormal or excessive fat accumulation that presents a risk to health [1]. It is estimated that 20% of the world's adult population will be obese by 2030 [2]. A recent national study of childhood obesity in Montenegro showed that pre-obesity/obesity may be expected in one out of four Montenegrin school children; the prevalence has increased by 35% in the last 10 years [3]. Excess adipose tissue in children and adults is often accompanied by low-grade inflammation and oxidative stress [4]. Numerous studies have demonstrated an association between the body mass index (BMI) and large waist circumference (WC) with high concentrations of inflammation markers such as C-reactive protein (CRP) [5, 6] and proinflammatory adipokines such as retinol-binding protein (RBP) [7]. Inflammatory markers have been shown to stimulate vascular atherosclerotic lesions and may also affect metabolism by negatively influencing insulin sensitivity causing insulin resistance [6]. Furthermore, hypertrophic fat tissue generates reactive oxygen species which are an underlying cause of oxidative stress and additional proinflammatory cytokine release [8]. According to some authors, obesity is associated with reduced serum vitamin D concentrations. The possible explanation for this association might be increased storage and sequestration of vitamin D in enlarged adipose tissue [4, 9]. Vitamin D deficiency may contribute to the pathogenesis of obesity, metabolic syndrome (MS) and type 2 diabetes. Several *in vitro* studies have shown that vitamin D exerts an anti-inflammatory action on human adipocytes

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by decreasing inflammatory cytokine expression [10]. The anti-inflammatory and anti-oxidative effects of vitamin D have been described in numerous studies [11, 12]. Copper and zinc protect against inflammation and oxidative stress, and the deficiency of these oligoelements might play an important role in the development of cardiometabolic complications of obesity [13]. Studies have also shown that an adequate adipose tissue zinc status is required for normal leptin synthesis and appetite regulation [14]. It is also involved in insulin storage and secretion, which implicates the role of this microelement deficiency in the development of type-2 diabetes mellitus [15]. Copper, similar to zinc, is a component of antioxidant enzymes such as Cu/Zn superoxide dismutase, which protects the body against the action of free radicals [16], but in certain conditions, copper can act as a pro-oxidant, which makes its biological role and significance more complex [17]. Some investigations suggest that copper deficiency may be associated with atherogenic dyslipidemia and hepatic steatosis. Furthermore, in rodent models, copper restriction leads to hypertension, elevated triglycerides and total cholesterol [18].

The objectives of this study were to:

- evaluate the difference in serum concentrations of biomarkers of inflammation and antioxidant defense in pre-obese and obese children, compared to their normal-weight peers;
- examine the correlation between the biomarkers of inflammation and antioxidant defense in pre-obese and obese children; and
- examine the relationship between children's BMI and the biomarkers of inflammation and antioxidant defense.

Materials and methods

The data used in this study were collected as a part of the national survey of school children obesity in Montenegro (2013–2015) entitled the "Research on Obesity and Poverty of Children in Montenegro – Clinical, Pathophysiological, Biochemical and Preventive Aspects". Details of data collection have been explained elsewhere [3]. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Montenegro (Decision No. 3399, dated 24 December 2013).

The sample consisted of 202 children aged 7–15 years, 129 boys (63.9%) and 73 (36.1%) girls, randomly chosen from 10 elementary schools from Podgorica, Montenegro, within a representative national sample of children [3]. Informed consent was obtained from all children and their parents. The survey response rate was 100% (202 survey invitation letters delivered).

Anthropometric measurements were obtained for the 202 randomly selected children. Children were weighed on a digital scale accurate to 0.1 kg (SECA, model SE 808, Hamburg, Germany). A stadiometer was used for body height measurements accurate to 0.5 cm (GIMA, code 27328, Gessate, Milan, Italy). BMI was calculated by using the formula: body weight in kilograms divided by the squared height in meters. WC was measured midway between the lowest border of the rib cage and the upper border of the iliac crest, at the end of normal expiration, using an un-stretched tape-meter, and the measurements were recorded to the nearest 0.1 cm. The waist-to-height ratio (WtHR) was calculated by dividing WC by height in cm. An Omron HEM 907 XL (Kyoto, Japan) oscillometric monitor was used for the measurement of blood pressure. The measurement was performed at school in the afternoon, in a quiet room, in a sitting position, after a rest of 5 min. Three measurements with a 1-min interval were performed using an appropriately sized cuff. Mean values of the systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated. Prehypertension in children is defined as an average SBP and/or DBP that is in at least the 90th percentile, but less than the 95th percentile, for sex, age and height. Hypertension in children is defined as an average SBP and/or DBP that is greater than or equal to the 95th percentile for sex, age and height [19]. We formed three groups of children according to their nutritional status: (1) normal-weight (n = 85/42.1%); (2) pre-obese (82/40.6%); and (3) obese (n = 35/17.3%).

Nutritional status was assessed according to the International Obesity Task Force (IOTF) criteria. IOTF provides BMI cut-points by age and sex for thinness, overweight and obesity for children and adolescents aged 2–18. The cut-points correspond to an adult BMI of 16.5 (thinness grade 1), BMI of 17 (thinness grade 2), BMI of 18.5 (thinness grade 3), BMI of 25 (pre-obese) or BMI of 30 (obesity) [20].

Pre-obese/obese children were diagnosed as having MS when they had any three or more of the five following criteria: WtHR ≥0.5, fasting glycemia ≥5.5 mmol/L, triglycerides ≥1.7 mmol/L, high-density lipoprotein cholesterol (HDL-c) <0.90 mmol/L and presence of hypertension. WtHR values of 0.5 and higher point to central obesity which is associated with an increased risk of MS in children [21, 22].

Biochemical analyses

Blood samples were taken in the morning at the departments within primary health care centers. Laboratory analyses were performed at the Center for Laboratory Diagnostics (Clinical Center of Montenegro and Primary Health Care Center in Podgorica). Serum CRP (mg/L) was measured using the spectrophotometric device Roche Cobas 6000 (Mannheim, Germany). For a general overview of the antioxidants in children's serum, we used an automated total antioxidant status (TAS) test (Randox, London, UK). The spectrophotometric measurement of TAS was performed using an Architect c4000 (Abbott, Chicago, IL, USA). An automated total vitamin D (VD) immunoassay was used for the determination of both vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) in children's serum. Vitamin D (nmol/L) was measured using immunochemistry (Roche Cobas 6000, Mannheim, Germany). Serum RBP (g/L) was measured using turbidimetry (Dade Behring BN II Nephelometer, Siemens, Marburg, Germany). Serum copper and zinc (μmol/L) were determined by inductively coupled plasma-optical emission spectrometry (ICP-OES) (Spectro Arcos, Kleve, Germany).

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corporation, Armonk, NY, USA). The Shapiro-Wilk test was used for testing the normality of variable distribution. Analysis of variance (ANOVA) and the Kruskal-Wallis

test were used for the assessment of differences between the three investigated groups. The results are presented as means and standard deviations (SD) for normally distributed variables or medians and interquartile ranges for non-normally distributed variables. We used the least significant difference (LSD) and the Mann-Whitney test for post-hoc testing. Depending on variable distribution, Pearson's or Spearman's correlation coefficients (r) were calculated to evaluate the correlations between oxidative and inflammatory biochemical parameters. The chi-square (χ^2) test was used for categorical variables. Standard linear regression was used for the assessment of oxidative and inflammatory parameters depending on the BMI values. A p-value <0.05 was considered as statistically significant.

Results

The three groups of studied children were similar in age but significantly different concerning the anthropometrics ($p < 0.01$). The characteristics of the studied children are shown in Table 1.

Serum TAS and CRP concentrations were significantly higher in pre-obese and obese children compared to controls ($p < 0.001$). Serum vitamin D concentration was lower in pre-obese and obese children compared to normal-weight children ($p = 0.027$ and $p = 0.054$, respectively). However, the difference in vitamin D concentration between obese and normal-weight children was only borderline significant ($p = 0.054$). Serum copper, zinc and RBP concentrations did not differ significantly among the groups ($p > 0.05$) (Table 2).

In pre-obese children, a weak positive correlation was found between CRP and copper ($r = 0.305$, $p = 0.011$), and a moderate positive correlation was found between TAS and RBP ($r = 0.528$, $p < 0.001$) (Table 3).

In obese children, a moderate positive correlation was found between copper and CRP ($r = 0.440$, $p = 0.013$), and TAS and RBP ($r = 0.434$, $p = 0.015$), while a moderate negative correlation was found between copper and RBP ($r = -0.423$, $p = 0.02$) (Table 4).

Standard linear regression was used to evaluate the prediction of the value of inflammatory and antioxidative defense markers, depending on children's BMI. Serum levels of CRP and TAS increased ($p < 0.001$), VD decreased ($p = 0.011$) and RBP slightly changed ($p = 0.001$) with increasing BMI. BMI explains the 9.4% variability of CRP, but if adjusted with copper, this percent increased to 17.6%. BMI also explains the 3.7% and 24.2% variability of vitamin D and antioxidant status without adjustment, respectively. The adjusted model with TAS and triglycerides explains almost 30% the variability of the antioxidant status. Serum values of copper and zinc do not depend on BMI (Table 5).

Table 1: Characteristics of the studied children.

	Normal-weight (n=85)	Pre-obese (n=82)	Obese (n=35)	p-Value
Age, years[a]	10.82±1.62	11.05±1.45	10.83±1.67	0.607
Body weight, kg[b,c]	30.15 [25.65–53.22]	42.60 [35.00–51.50]	50.00 [42.30–62.50]	<0.001
Body height, cm[a]	137.68±10.38	143.62±11.59[d]	144.89±11.59[d]	<0.001
BMI, kg/m^2[b,c]	16.3 [14.97–17.10]	20.70 [19.50–22.80]	24.10 [22.50–27.60]	<0.001
WC, cm[b,c]	57.25 [54.00–61.00]	69.00 [64.00–76.00]	78.00 [69.00–86.00]	<0.001

[a]Data are presented as mean value and standard deviation; [b]Data are presented as median value and interquartile ranges; [c]$p < 0.001$. There was difference between all groups (Mann-Whitney U test); [d]$p < 0.001$ vs. normal weight (LSD post-hoc test). BMI, body mass index; LSD, least significant difference; WC, waist circumference.

Table 2: Biochemical parameters in normal-weight, pre-obese and obese children.

	Normal-weight (n=85)	Pre-obese (n=82)	Obese (n=35)	p-Value
TAS[a,c]	1.50±0.14	1.60±0.12	1.70±0.11	<0.001
CRP[b,c]	0.30 [0.16–0.42]	0.59 [0.26–1.43]	1.03 [0.46–3.07]	<0.001
VD[b]	77.20 [67.70–95.10]	70.10 [56.00–86.60][d]	69.65 [59.30–85.87]	0.046
RBP[b]	0.026 [0.020–0.029]	0.026 [0.022–0.031]	0.028 [0.025–0.031]	0.157
Copper[a]	18.19±3.17	18.83±2.96	18.16±3.27	0.367
Zinc[b]	13.00 [12.10–14.35]	13.05 [11.42–14.42]	13.30 [11.90–13.80]	0.651

[a]Data are presented as mean value and standard deviation; [b]Data are presented as median value and interquartile ranges; [c]$p < 0.001$. There was difference between all groups (LSD post-hoc test for TAS and Mann-Whitney for CRP); [d]$p = 0.027$ vs. normal weight. CRP, C-reactive protein; LSD, least significant difference; RBP, retinol-binding protein; TAS, total antioxidant status; VD, total vitamin D.

Table 3: Correlation between inflammatory and antioxidative defense markers in pre-obese children.

Pre-obese	CRP		VD		RBP	
	r	p-Value	r	p-Value	r	p-Value
TAS	0.110	0.344	0.200	0.086	0.528	0.000
Copper	0.305	0.011	0.102	0.412	−0.216	0.104
Zinc	−0.065	0.598	−0.165	0.182	0.047	0.726

CRP, C-reactive protein; RBP, retinol-binding protein; TAS, total antioxidant status; VD, total vitamin D.

Table 4: Correlation between inflammatory and antioxidative defense markers in obese children.

Obese	CRP		VD		RBP	
	r	p	r	p	r	p
TAS	0.112	0.541	−0.172	0.347	0.434	0.015
Copper	0.440	0.013	0.133	0.477	−0.423	0.020
Zinc	0.186	0.316	−0.101	0.588	−0.011	0.954

CRP, C-reactive protein; RBP, retinol-binding protein; TAS, total antioxidant status; VD, total vitamin D.

Hyperglycemia was found more in obese children than in controls (p = 0.007). HDL-c did not significantly differ between the three groups (p = 0.216). The concentration of triglycerides was higher in the pre-obese (14.6%) and obese (8.6%) groups compared to normal-weight children (0.0%). There was no significant difference in triglyceride concentrations between the pre-obese and obese group of children. Hypertension was more present in obese children (54.3%) compared to controls (25.9%, p = 0.003) and the pre-obese group (31.1%, p = 0.020). There was no difference in the presence of hypertension between normal-weight and pre-obese children (p = 0.477). MS was present in 11.4% of obese, 9.8% of pre-obese and 0% of normal-weight children (p < 0.001) (Table 6).

Discussion

This study evaluated the inflammation and the antioxidative defense-related biomarkers, as the response induced by oxidative stress, in pre-obese and obese children in Montenegro. In our report, the value of the serum pro-inflammatory marker CRP was higher in obese and pre-obese children compared to their normal-weight peers. A similar elevation of inflammatory markers in obese children was found by Luciardi et al. [23] indicating that the excess fat is strongly associated with low-grade inflammation in white adipose tissue, caused by lipid accumulation in adipocytes, which stimulates the liver to produce systemic proinflammatory markers such as CRP [24]. Additionally, in pre-obese and obese children, CRP was positively related to copper. A significant elevation of serum copper followed by the increase in inflammatory markers and serum zinc decrease were also found in obese children in an Egyptian study, but the exact mechanism of these actions is still unknown [25]. In our report, serum TAS was higher in pre-obese and obese children in comparison to controls. A number of authors found lower total antioxidant capacity in obese prepubescent children [26, 27]. Some studies showed that TAS was raised in visceral obesity showing a positive relation with a number of

Table 5: Unadjusted and adjusted regression coefficients for BMI impact on inflammatory and antioxidative defense markers.

	Adjusted model[a]	Effect of BMI – linear standard regression		
		β [95% CI]	r^2	p-Value
CRP	Unadjusted, n = 196	0.162 [0.090–0.230]	0.094	<0.001
	Copper, n = 176	0.167 [0.096–0.238]	0.176	<0.001
VD	Unadjusted, n = 172	−1.119 [−1.984 to −0.255]	0.037	0.011
TAS	Unadjusted, n = 147	0.018 [0.014–0.023]	0.242	<0.001
	RBP, n = 147	0.011 [0.007–0.015]	0.363	<0.001
RBP	Unadjusted, n = 183	0.000 [0.000–0.001]	0.070	<0.001
	TAS, n = 145	0.000 [0.000–0.001]	0.237	
	Triglycerides, n = 147	0.000 [0.000–0.001]	0.161	
	TAS + triglycerides, n = 145	0.000 [0.000–0.001]	0.294	
Copper	Unadjusted, n = 176	−0.017 [−0.136–0.101]		0.771
Zinc	Unadjusted, n = 176	−0.048 [−0.126–0.029]		0.221

[a]Model was adjusted only for variables which showed correlation coefficient above 0.3 and did not correlate with BMI above 0.7.
β, regression coefficient; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; n, number of observations units included in regression; RBP, retinol-binding protein; TAS, total antioxidant status; VD, total vitamin D.

Table 6: Metabolic syndrome criteria in normal-weight, pre-obese and obese children.

MS criteria	Normal-weight (n=85)	Pre-obese (n=82)	Obese (n=35)	p-Value between all groups
Glycemia > 5.5	11 [12.9%]	20 [24.4%]	12 [34.3%][a]	0.023
HDL-c < 0.9	1 [1.2%]	5 [6.1%]	1 [2.9%]	0.216
Triglycerides	0 [0.0%]	12 [14.6%][b]	3 [8.6%][c]	0.001
Hypertension	21 [25.9%]	23 [31.1%]	19 [54.3%][d,e]	0.011
WtHR[f]	1 [1.2%]	29 [36.7%]	27 [77.1%]	<0.001
MS present[f]	0 [0.0%]	8 [9.8%]	4 [11.4%]	<0.001

[a]p = 0.007 vs. normal weight; [b]p < 0.001 vs. normal weight; [c]p = 0.006 vs. normal weight; [d]p = 0.003 vs. normal weight; [e]p = 0.020 vs. pre-obese; [f]There was difference between all groups. HDL-c, high-density lipoprotein cholesterol; MS, metabolic syndrome; WtHR, waist-to-height ratio.

metabolic risk factors [28]. This may be explained by the stronger activation of antioxidant mechanisms in order to balance oxidation in obese subjects [8]. In addition to this, a significant positive correlation was observed between TAS and RBP in pre-obese and obese subjects. The proinflammatory adipokine RBP has an impact on the development of β-cell dysfunction and insulin resistance, which are markedly associated with oxidative stress [29]. It may also be viewed as an independent marker of many adiposity-related co-morbidity risk factors in children, such as dyslipidemia, abdominal obesity or hypertension [30]. Still, in our study, values of RBP did not significantly differ among the investigated groups. We observed a decrease in VD in pre-obese and obese compared to normal-weight children, which is concordant with studies reporting a reverse association between vitamin D serum concentration and adiposity [9]. Some researchers found that low serum vitamin D was significantly associated with increased inflammatory markers in obese children [31]. However, the associations between serum vitamin D concentrations and biomarkers of inflammation were rarely reported in large-scale cross-sectional studies in school-aged children [11]. Our results are not an exception in that sense. Reports also suggest that vitamin D has both anti-inflammatory [32] and antioxidant activity [33, 34], but the recent review on vitamin D was controversial about the ability of vitamin D to prevent or reduce oxidative stress [35].

We found no statistically significant difference in the values of copper and zinc between normal-weight, pre-obese and obese children. In several studies which examined serum oligoelements in obese children, copper concentrations were higher in obese compared to normal-weight children, whereas serum zinc concentrations were lower compared to non-obese controls [13]. These findings indicate the antioxidant role of copper in fat-stimulated oxidative stress [36].

MS is among the most common comorbidities associated with obesity [37]. In our study, high prevalence of MS was recorded in pre-obese and obese children. Numerous other studies have been reporting the increase of the prevalence of MS worldwide, mainly due to the escalating global epidemic of obesity. It is important to mention that some of the underlying causes of obesity and MS may also include poor lifestyle choices such as low physical activity, sedentary behavior and poor dietary factors. As a final result, the risk of MS greatly increases during adulthood for those children exposed to cardiometabolic risk factors in their early lives [37].

Conclusions

We show that inflammation and accentuated antioxidative defense, as a result of increased oxidative stress, are positively associated with pre-obesity and obesity in childhood, representing a pathological basis of obesity-related diseases in children. Our study also determined an inverse association between vitamin D status and excess adiposity in children. Serum copper was associated with inflammation markers in both pre-obese and obese subjects. Zinc nutritional status in pre-obese and obese individuals was not altered. The worrying presence of MS, which is known to contribute to the onset of cardiovascular diseases even in childhood, was found in a significant number of pre-obese and obese children. Further investigations are needed to clarify the complex association between inflammation, oxidative stress and biomarkers such as copper, zinc and vitamin D in pre-obese/obese children. It is important to ensure the clinical and laboratory follow-up of pre-obese and obese children in order to prevent these subjects from developing cardiometabolic complications as a result of the long-term presence of excess adiposity.

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Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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Dear Dr. Jakšić:

I would like to thank you for submitting your manuscript entitled "Relationship between Insulin-Like Growth Factor-1, Insulin Resistance and Metabolic Profile with Pre-Obesity and Obesity in Children" to the Journal of Pediatric Endocrinology and Metabolism (JPEM). Your manuscript has been reviewed, and it is a pleasure to accept it for publication in JPEM. The comments of the reviewer(s) are included at the bottom of this letter.

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Thank you for your fine contribution. On behalf of the Editors of Journal of Pediatric Endocrinology and Metabolism we look forward to your continued contributions to the Journal.

Kind regards
Dr. Wieland Kiess
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Reviewer(s)' Comments to Author:

Full title: Relationship between Insulin-Like Growth Factor-1, Insulin Resistance and Metabolic Profile with Pre-Obesity and Obesity in Children

Short title: IGF-1, Insulin Resistance and Obesity-Related Metabolic Parameters

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Relationship between Insulin-Like Growth Factor-1, Insulin Resistance and Metabolic Profile with Pre-Obesity and Obesity in Children

Abstract

Introduction: Childhood obesity is a serious medical condition with alarmingly high rates worldwide. There is controversy regarding the relationship between insulin-like growth factor-1 (IGF-1) and pediatric obesity. We investigated the relationship between IGF-1, insulin resistance (IR) and metabolic profile with childhood pre-obesity/obesity.

Materials and methods: The study involved 201 children aged 7-15 years, divided in three groups according to their nutritional status (International Obesity Task Force criteria): normal-weight (n=84), pre-obese (n=82), obese (n=35). Laboratory (IGF-1, insulin, fasting blood glucose (FBG), lipid profile, alanine-aminotransferase (ALT), uric acid), anthropometric and body composition parameters were analyzed. Body mass index and IGF-1 standard deviation score (SDS), waist-to-height ratio (WtHR) and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score were calculated.

Results: Pre-obese/obese children had significantly higher IGF-1 SDS, FBG, insulin, HOMA-IR, uric acid, ALT, triglycerides, and lower high-density lipoprotein cholesterol (HDL-c) while obese group had higher WtHR and low-density lipoprotein cholesterol (LDL-c) compared to controls ($p<0.05$). In obese group IGF-1 SDS was positively correlated with fat free mass, muscle mass, total body fat (TBF) ($p<0.01$), and negatively correlated with LDL-c ($p<0.01$). In pre-obese/obese HOMA-IR and insulin were positively correlated with age, TBF ($p<0.01$) and negatively correlated with HDL-c (pre-obese) ($p<0.05$). IGF-1 SDS was higher in insulin-resistant compared to non-insulin resistant group ($p<0.001$). Multivariate regression analysis

showed that IGF-1 (β=0.006; 95% CI: 0.002-0.010), TBF (β=0.38; 95% CI: 0.30-0.46) were predictors of BMI values ($p<0.001$, $r^2=0.710$).

Conclusion: Pre-obesity/obesity and IR were associated with higher IGF-1 SDS values in children. Further studies are required to clarify the role of IGF-1 in pathophysiology of obesity and its comorbidities.

Keywords: Childhood Obesity, Insulin-Like Growth Factor-1, Insulin Resistance, Metabolic Profile

I am writing you about the manuscript No. 2018-076, entitled: "Cardiometabolic risk among Montenegrin urban children in relation to obesity and gender" that was accepted for publication in Acta Clin Croat on 12-07-2018.

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Dear Editorial Team,

CARDIOMETABOLIC RISK AMONG MONTENEGRIN URBAN CHILDREN IN RELATION TO OBESITY AND GENDER

Running Title: Childhood Obesity and Cardiometabolic Risk

Milica Martinovic[1], Goran Belojevic[2], Marina Jaksic[3], Nebojsa Kavaric[4], Aleksandra Klisic[4]

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Abstract

Objective: To investigate the gender role in the relationship between childhood overweight/obesity and cardiometabolic risk (CMR).

Design: A cross-sectional study

Setting: A Primary Health Care Center, Department of Pediatrics, Podgorica, Montenegro

Participants: A random sample of 201 schoolchildren from Podgorica (12/64 % boys) aged 7-12 years comprised three anthropometric sub-samples: 1. Normal weight (n=85/42%); 2. Overweight (81/41%); 3. Obese (35/17%). The exclusion criterion was underweight.

Main Outcome Measures: We determined children's nutritional status according to the criteria of International Obesity Task Force. We used an oscillometric device for the measurement of blood pressure. We assessed the CMR using a sum of z values of five indicators: glycemia, total cholesterol, inverted value of high-density lipoprotein cholesterol, triglycerides and hypertension. We got a cut-off value for a high CMR by adding one standard deviation to the mean z value of CMR for this sample of children.

Results: We found a higher CMR among both overweight and obese (OOb) boys compared to normal weight boys ($p < 0.001$). The effect size of the difference in CMR between OOb girls and normal weight girls was less prominent ($p < 0.05$). A multiple logistic regression revealed independent predictors for a high CMR /OR (95% CI)/: Body Mass Index percentile (per percentile) / 1.05(1.01-1.09)/, glycemia (per mmol/L) /8.38 (1.87-37.67), total cholesterol (per mmol/L) /5.00 (2.26-11.05)/ and hypertension (vs. normal tension) /7.58 (2.52-24.03/.

Conclusions: Both overweight and obesity in childhood are related to a raised CMR and this effect is more prominent among boys compared to girls.

Key Words: child; gender role; hypertension; metabolic syndrome; obesity

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Na osnovu člana 165 stava 1 Zakona o opštem upravnom postupku ("Službeni list RCG", broj 60/03.), člana 115 stava 2 Zakona o visokom obrazovanju ("Službeni list CG", broj 44/14.) i službene evidencije, a po zahtjevu studenta Jakšić Željko Marina, izdaje se

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