ISSN 2181-1008
DOI 10.26739/2181-1008

ЖУРНАЛ

гепато-гастроэнтерологических исследований

Ежеквартальный научно-практический журнал

№3.2 (том II) 2021

ISSN 2181-1008 (Online)

Научно-практический журнал
Издается с 2020 года
Выходит 1 раз в квартал

Журнал зарегистрирован в Узбекском агентстве по печати и информации

Адрес редакции: 140100, Узбекистан, г. Самарканд, ул. А. Темура 18.
Тел.: +998662333034, +998915497971
E-mail: **hepato_gastroenterology@mail.ru.**

JOURNAL OF HEPATO-GASTROENTEROLOGY RESEARCH
ЖУРНАЛ ГЕПАТО-ГАСТРОЭНТЕРОЛОГИЧЕСКИХ ИССЛЕДОВАНИЙ

Belyx N. A,
MD, PhD, Dr Med Sci, Associate Professor,
Head of the Department of Faculty and Polyclinic Pediatrics with the Course of Pediatric of Postgraduate Education
Ryazan State Medical University, Ryazan, Russian Federation
Buloxova E,
Professor of the Department of Child Diseases and Hospital Pediatrics
Ryazan State Medical University, Ryazan, Russian Federation

ASSESSMENT OF THE RELATIONSHIP BETWEEN LIPID AND CARBOHYDRATE METABOLISM INDICATORS AND VITAMIN D STATUS IN CHILDREN WITH DIFFERENT BODY MASS INDEX

ANNOTATION

Overweight children represent a particularly vulnerable group for vitamin D deficiency. was to study the relationship between lipid and carbohydrate metabolism indicators and VD status in children, depending on the body mass index (BMI). A cross-sectional (one-step) study carried out on a sample of 154 children with different weight of 8-10 years old (girls - 74, boys - 80). There were identified three groups of research participants: group 1 - 44 obese, 2 group - 58 overweight, 3 group - 52 children with normal body weight. For all children, the serum 25(OH)D, parathyroid hormone (PTH), calcium (Ca), phosphorus (P), alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol (CS), triglycerides (TG), beta-lipoproteins (ß-LP), glucose, insulin determined, and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) calculated. VD deficiency in obese children was found almost 2.3 times more often than in overweight ($p = 0.002$) and 2.8 times more often than in children with normal body weight ($p = 0.001$). Indicators of lipid and carbohydrate metabolism were within physiological limits. However, in obese children they significantly exceeded the indicator of healthy children ($p < 0.05$). Children with VD deficiency (25(OH)D<20 ng/ml) had statistically significantly higher medians of serum PTH, TC, TG, ALT, AST, glucose, insulin, HOMA-IR and lower serum P and Ca compared with children with optimal VD status ($p < 0.05$). The medians of serum ALT, AST, TC, ß-LP, TG, glucose, insulin and HOMA-IR in obese children with VD deficiency was statistically significantly higher compared in healthy children with VD deficiency and optimal VD status. VD deficiency is an important predictor of obesity complications and it exacerbates the risk of cardiometabolic disorders in children who are obese in the early school years.

Key words: children, obesity, vitamin D, vitamin D status, cardiometabolic disorders.

Белых Н.А,
доктор медицинских наук, доктор медицинских наук, доцент,
Заведующий кафедрой факультетской и поликлинической педиатрии с курсом педиатрии последипломного образования
Рязанский государственный медицинский университет, Рязань, Российская Федерация
Булохова Е,
доцент кафедры детских болезней и госпитальной педиатрии
Рязанский государственный медицинский университет, Рязань, Российская Федерация

ОЦЕНКА ВЗАИМОСВЯЗИ ПОКАЗАТЕЛЕЙ ЛИПИДНОГО И УГЛЕВОДНОГО ПРОФИЛЯ С УРОВНЕМ ОБЕСПЕЧЕННОСТИ ОРГАНИЗМА ВИТАМИНОМ D У ДЕТЕЙ В ЗАВИСИМОСТИ ОТ ИНДЕКСА МАССЫ ТЕЛА

АННОТАЦИЯ

Дети с избыточной массой тела (МТ) представляют особо уязвимую группу по гиповитаминозу D. Поперечное (одномоментное) исследование проведено на выборке 154 детей с разными весоростовыми показателями в возрасте 8-10 лет (девочек - 74, мальчиков - 80). Выделено 3 группы участников исследования: 1

группа - 44 ребенка с ожирением, 2 группа – 58 детей с избыточной массой тела, 3 группа – 52 человека с нормальной массой тела. Всем детям определяли в сыворотке крови уровень 25(OH)D, паратгормона (ПТГ), кальция (Са), фосфора (Р), общего холестерина (ХС), триглицеридов (ТГ), бета-липопротеидов (ß-ЛП), глюкозы, инсулина, активность АЛТ, АСТ, а также рассчитывали индекс инсулинорезистентности (HOMA-IR). Дефицит витамина D у детей с ожирением встречался почти в 2,3 раза чаще, чем у детей с избыточной массой тела (p=0,002) и в 2,8 раза чаще, чем у детей с нормальной массой тела (p=0,001). Показатели липидного и углеводного обменов находились в физиологических пределах. Однако у детей с ожирением они значимо превышали показатель здоровых детей (p<0,05). Дети с дефицитом VD имели статистически значимо более высокие медианы ПТГ, ХС, ТГ, глюкозы, инсулина, активности АЛТ, АСТ, HOMA-IR и более низкую концентрацию Р и Са по сравнению с детьми, имеющими оптимальный VD статус (p<0,05). Медианы АЛТ, АСТ, ХС, ß-ЛП, ТГ, глюкозы и HOMA-IR у детей с ожирением и дефицитом VD были статистически значимо выше, чем у здоровых детей с дефицитом VD и с оптимальной концентрацией 25(OH)D в сыворотке крови. Дефицит витамина D является важным предиктором формирования осложнений ожирения и усугубляет риск развития кардиометаболических расстройств у детей, страдающих ожирением в младшем школьном возрасте.

Ключевые слова: дети, ожирение, витамин D, дефицит витамина D, кардиометаболические расстройства.

The growing prevalence of obesity in the child population is one of the problems of modern health care. According to World Health Organization (WHO, 2018) forecasts, the number of obese children by the end of 2025 may exceed 70 million only in the age group from 0 to 5 years old [1]. Childhood obesity has serious lifelong consequences. In the short term, such children are accompanied by psychological disorders (depression, anxiety and low self-esteem, a number of emotional and behavioral disorders), they are more likely to suffer from asthma, diseases of the musculoskeletal system [2]. In the future, they have an increased risk of metabolic disorders and cardiovascular pathology, such as arterial hypertension, dyslipidemia, atherosclerosis [3]. In the long term, childhood obesity increases of the risk of developing cardiovascular diseases, diabetes mellitus, some types of cancer and diseases of the musculoskeletal system, which can lead to disability and premature death [4].

In parallel with obesity, the problem of low vitamin D (VD) status in child and adolescent population is becoming more and more urgent. At present, hypovitaminosis D among the child population recorded in many countries of the world, including the Russian Federation [5-7].

For a long time, the regulation of calcium and phosphorus homeostasis considered the main effect of VD. However, in recent years, VD viewing as a hormone that has receptors in most body tissues and performs many “non-classical” effects. Non-skeleton effects of VD include of regulation of cell proliferation and cell differentiation, inhibition of renin and angiogenesis synthesis, contributing of insulin production, activation of macrophage formation, etc. [8]. Overweight children represent a particularly vulnerable group for vitamin D deficiency, which, in recent years, has been associated with health risks similar to obesity [9]. Therefore, according to Mirhosseini N. et al. (2018), VD deficiency may play an important role in the development of cardiovascular diseases [10]. There is also an opinion about of the positive effect of VD subsidy on metabolism in adults with chronic cardiovascular disease. Schroten N. et al. (2013) observed a decrease in plasma renin activity in 101 patients with stable heart failure after 6 weeks of taking 2000 IU VD [11]. The VINDICATE study group (Vitamin D treating patients with chronic heart failure) noted a significant improvement in cardiac function in 229 patients with chronic heart failure after taking VD 4000 IU daily for 1 year [12]. In contrast, several metaanalyzes and systematic reviews have not found a positive effect of VD on the course of cardiovascular disease. Ford J. et al. (2014), for example, expressed insufficient data to support the use of VD as a supplement to reduce the incidence of cardiovascular disease [13]. In their systematic review, Wang L. et al. (2010) noted a statistically insignificant decrease in the incidence of cardiovascular diseases when taking moderate doses of VD. Mao P. et al. (2013) also found that neither VD supplementation nor calcium supplementation affected the incidence of myocardial infarction or stroke [14]. However, most modern studies substantiate the negative effect of low serum 25(OH) D levels on the state of the cardiovascular system, and associate this primarily with the role of micronutrients in the regulation of the renin-angiotensin-aldosterone system (RAAS). Thus, the renin gene has a VD sensitive element that has a regulatory effect on the transcription and production of renin, which, in turn, acting on angiotensin, triggers a number of processes that promote the formation of angiotensin II, which acts as a vasoconstrictor [15].

There are few data on the role of VD deficiency as a risk factor for the onset and progression of cardiovascular disorders in primary school children. In this regard, the study of this problem is interesting, especially among obese children, who form a risk group for the development of chronic pathology.

Aim: to study of the relationship between lipid and carbohydrate metabolism indicators and VD status in children, depending on the body mass index (BMI).

Materials and methods. A cross-sectional (one-step) study carried out on a sample of 154 children with different weight and height indicators. Among the surveyed children there were 74 girls (48.0%) and 80 boys (52.0%) of primary school age (the average age – 9.4±0.7 years). All children permanently live in Ryazan.

Study inclusion criteria: absence of acute or exacerbation of chronic diseases at the time of inclusion in the study; lack of intake of vitamin and mineral complexes for at least 6 months. Before inclusion in the study, the absence of chronic diseases of the kidneys, liver, gastrointestinal tract, as well as the signed informed consent of the child's parent to his participation in the study.

The studies carried out on the bases of the City Child Polyclinic No. 1, Regional Child Hospital and Central Research Laboratory of the RyazSMU. The local

ethics committee of the RyazGMU approved the study protocol. The parents had appropriate information about their participation in the study and their informed consent obtained.

Trained health workers in accordance with a standardized protocol developed by WHO [16] performed anthropometric measurements during a preventive medical examination. The physical growth assessed using the WHO AnthroPlus (2009) [17]. There were calculated the following parameters: Weight-for-Age Z-score (WAZ), body mass-to-age index (BMI-for-Age Z-score, BAZ). The interpretation of the obtained Z-score values carried out according to the following criteria: malnutrition - with <–2 SDS, under nutrition from -2<SDS<-1, norm - -1<SDS<+1, overweight - +1<SDS<+2, obesity - with SDS> +2 [18].

According to the anthropometry data, there were formed 3 groups: 1st group - obese children (n=44, 22 girls and 22 boys), 2nd group - overweight children (n=58, 18 girls, 40 boys), 3rd group – healthy children (n=52, 34 girls, 18 boys).

Serum 25(OH)D level, parathyroid hormone (PTH), glucose, insulin, triglycerides (TG), transaminase activity (alanine aminotransferase, ALT and aspartate aminotransferase, AST), β-lipoprotein (β-LP) level, cholesterol (CS), calcium (Ca), phosphorus (P) were tested in all children. A procedural nurse in a manipulation room located in the Regional Child Hospital carried out blood sampling on an empty stomach, from the ulnar vein. Serum 25(OH)D was evaluated by the enzyme-linked immunoabsorbent assay (DIAsource 25OH Vitamin D Total ELISA Kit, Diasource, Spain) and values <20 ng/ml were considered deficient, 20-30 ng/ml insufficient, and >30 ng/ml - sufficient [19]. The PTH content by the method of immunoradiometric analysis (IRMA PTH kits, IMMUNOTECH, Czech Republic) and insulin by the immunochemiluminescent method on a Roche Cobas e8000 602 analyzer (Roche Cobas, Switzerland) was determined. The serum Ca, P, β-LP, TG, CS, glucose, ALT, AST on a Mindray BS-400 biochemical analyzer (Mindray, China) was measured. The insulin resistance index (HOMA-IR) was calculated (normally below 3.2 U) [20].

The STATISTICA 12 software package used for statistical analysis. Continuous variables presented as medians with an interquartile range (25-75 percentiles). The analysis of the normal distribution of the values of the studied features performed using the Shapiro-Wilk test. When comparing continuous variables across groups, the Kruskal-Wallis test used (for paired comparisons, the Mann-Whitney test). The degree of relationships assessed by calculating the pairwise Spearman correlation coefficients (r). The χ^2 test used to determine the relationship between the two categorical variables. $p< 0.05$ was considered significant**.**

Results. VD deficiency occurred in 76 (49.4%) of the examined children, deficiency - in 30 (19.5%), and normal provision was found only in 48 (31.1%) children. Obese children have VD deficiency in 2.3 times more often than overweight (p=0.002) and in 2.8 times more often than healthy (p=0.001) (Fig.1). The normal provision of VD in overweight children detected almost 2 times less often than in healthy children. Among the surveyed group 1, normal concentration of 25 (OH) D in the blood serum not detected in any child. There were no statistically significant gender differences among the assessed groups (p> 0.05).

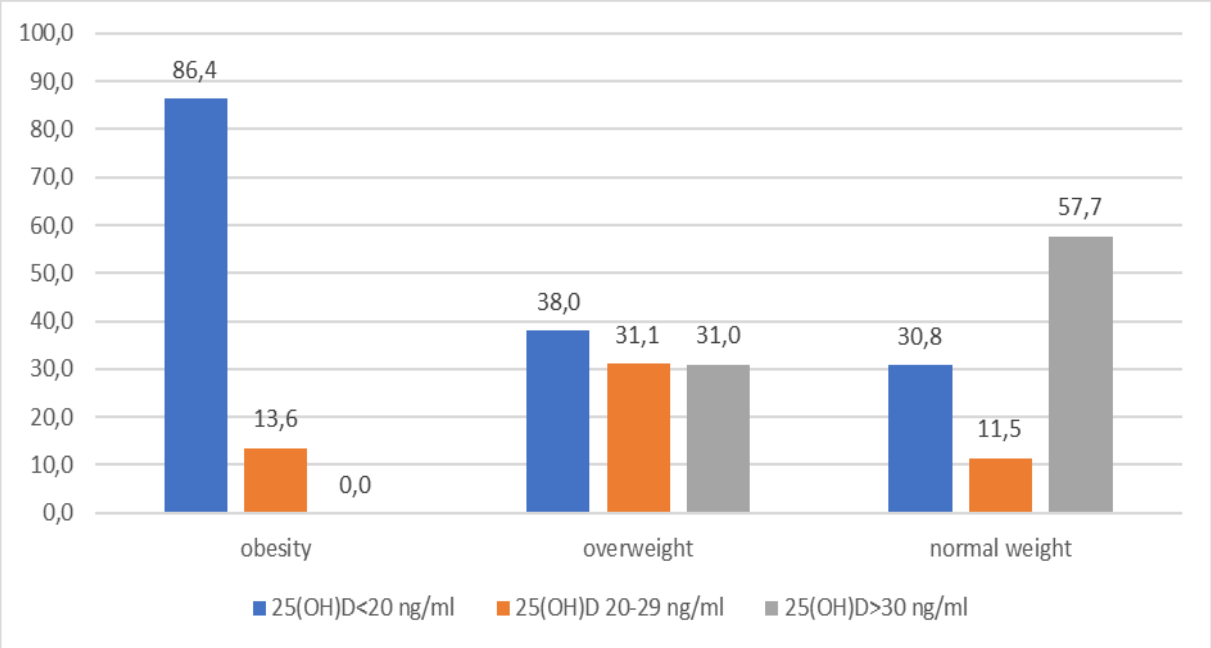

Figure 1. Vitamin D status in participants depending on BMI (%)

The median values of mineral, lipid and carbohydrate metabolism compared depending on BMI in the compared groups (Table 1). Serum PTH level was within the reference values; statistically significant differences between the groups were no found (p>0.05). The median of serum Ca in was normal - 2.46 [2.36; 2.54] mmol/L. Me Ca in obesity child was statistically significantly lower than in 2nd and 3rd groups (p<0.05). Was revealed that with an increase of BMI, the serum Ca level significantly decreased (r=0.51, p<0.05), and in 7 (32.0%) participants with the highest BMI was found of hypocalcaemia (p=0.014). Serum P in all children was within the physiological norm. However, in the 1st and 2nd group the serum P was statistically significantly lower

than in 3rd group (p<0.05). A negative correlation between BMI and P level was found (r=-0.51, p<0.05). Serum ALT, AST, CHS, TG, β-LP, glucose and insulin was within physiological limits. However, the median ALT activity in children in 1st group was 1.8 times higher than in 2nd group (p<0.001) and was more than 2.5 times lower than in healthy children (p<0.001). Moreover, in obese boys, this indicator was higher compared to girls in this group (p = 0.003). The median serum AST activity in obese children also exceeded the value in the overweight children (p<0.001) and normal BMI (p<0.001). Serum CS, TG and β-LP had a direct moderate correlation with BMI (p<0.05), and the medians of these indicators in obese children significantly exceeded the values in overweight and healthy children (p<0.005).

Table 1.

Indicators of mineral, lipid and carbohydrate metabolism depending on the body mass index of children

Indicator	Reference values	Group 1 BMI-for-Age Z-score >+2 SDS (n=22)	Group 2 BMI-for-Age +1< Z-score<+2 SDS (n=29)	Group 3 BMI-for-Age -1<Z-score<+1 SDS (n=26)	P_{k-w} 1-2	P_{k-w} 1-3	P_{k-w} 2-3
25(OH)D, ng/ml	>30 ng/ml	12,5 [5,7; 19,1]	23,6 [11,3; 34,5]	32,6 [15,9; 44,4]	0,014	0,001	0,080
PTH, pg/ml	10,0–65,0	28,3 [23,2; 38,3]	25,1 [20,9; 32,6]	27,2 [19,9; 33,5]	0,210	0,562	0,227
Ca, mmol/l	2,3–2,8	2,3 [2,2; 2,4]	2,5 [2,4; 2,5]	2,5 [2,5; 2,7]	0,031	0,000	0,021
P, mmol/l	1,1–2,0	1,2 [1,1; 1,2]	1,2 [1,2; 1,3]	1,3 [1,2; 1,5]	0,011	0,001	0,362
ALT, U/l	< 40,0	35,0 [32,0; 38,0]	20,0 [18,0; 24,0]	13,0 [11,0; 16,0]	0,000	0,000	0,000
AST, U/l	< 40,0	34,0 [32,0; 36,0]	22,0 [20,0; 26,0]	21,0 [17,0; 25,0]	0,000	0,000	0,851
CS, mmol/l	2,8-5,5	4,8 [4,4; 5,2]	4,4 [4,0; 4,5]	3,9 [3,8; 4,4]	0,003	0,001	0,018
ß-LP, U/l	35,0-55,0	45,0 [40,0; 50,0]	40,0 [37,0; 42,0]	35,0 [32,0; 36,0]	0,021	0,000	0,000
TG, mmol/l	0,3-1,5	1,4 [1,3; 1,5]	0,7 [0,5; 0,9]	0,5 [0,5; 0,7]	0,000	0,000	0,020
Glucose, mmol/l	3,4-6,1	4,3 [4,1; 4,5]	4,1 [3,8; 4,4]	3,6 [3,4; 3,7]	0,152	0,000	0,000
Insulin, μU / ml	3,0-20,0	15,5 [14,9; 16,0]	10,8 [9,0; 13,3]	7,8 [5,0; 9,9]	0,000	0,000	0,010
HOMA-IR	<3,2	2,9 [2,8; 3,2]	2,0 [1,7; 2,5]	1,3 [0,8; 1,5]	0,000	0,000	0,000

Note: BMI - body mass index;

HOMA-IR increased with increasing BMI. At the same time, in 5 (23.0%) obese children HOMA-IR exceeded the permissible normal values (p=0.057), despite the normal isolated levels of glucose and insulin.

Children with VD deficiency had a higher BMI. PTH, CS, TG, glucose, insulin, the activity of ALT and AST, as well as HOMA-IR in them exceeded those in children with normal VD status (p<0.05), but the serum P and Ca was lower (p<0.05) (Table 2).

Children with insufficient VD status have statistically significantly higher BMI, TG, ALT, AST, HOMA-IR and a reduced level of Ca compared with children optimally provided with vitamin D (p <0.05). There were no statistically significant differences in the level of β-LP between the groups (p> 0.05). PTH and TG in children with VD deficiency was 1.3 times (p<0.05) higher than in children with insufficient VD status. At decrease serum 25(OH)D increase PTH, Ca, P, β-LP, TG, glucose, insulin, activity ALT, AST and HOMA-IR (Table 3). Thus, these changes indicate that vitamin D deficiency in children 8-10 years old is a risk factor for cardiometabolic disorders at an older age.

The medians of ALT, AST, CS, ß-LP, TG, glucose, insulin, and HOMA-IR in obese children with VD deficiency were statistically significantly higher than in healthy children with VD deficiency and a sufficient VD status.

The discussion. Vitamin D deficiency is quite common in childhood and is more common among obese children. The data obtained coincide with the results of studies of previous years [21, 22]. It is believed that the relationship of anthropometric and biochemical markers of cardiovascular risks with the high prevalence of vitamin D deficiency is indirect, because this is a consequence of a sedentary lifestyle, decreased activity, stay indoors and poor nutrition, which lead to the progressive accumulation of fat mass. So, in the works of Skinner A. et al. (2015) and Durá-Travé T. et al. (2017) it was obesity rather than insufficient VD provision that positively correlated with dyslipidemia [23, 24]. Nevertheless, various authors describe the existence of strong correlations between low VD-status and various components of the lipid metabolism [25, 26].

Table 2.

Anthropometric and biochemical parameters depending on vitamin D status

Indicator	Serum 25(OH)D			P_{k-w} 1-2	P_{k-w} 1-3	P_{k-w} 2-3
	< 20 ng/ml (n=76)	20–29 ng/ml (n=30)	> 30 ng/ml (n=48)			
BMI z-score	2,0 [1,01; 2,9]	1,4 [1,0; 1,9]	0,8 [-0,3; 1,0]	0,150	0,000	0,001
PTH, pg/ml	32,1 [25,5; 39,3]	24,5 [20,1; 36,2]	23,2 [18,3; 29,0]	0,041	0,009	0,649
Ca, mmol/l	2,4 [2,3; 2,5]	2,5 [2,4; 2,6]	2,7 [2,5; 2,7]	0,001	0,000	0,129
P, mmol/l	1,2 [1,1; 1,2]	1,3 [1,2; 1,3]	1,7 [1,7; 1,8]	0,006	0,000	0,000
ALT, U/l	28 [19; 36]	24 [18; 30]	14 [11,5; 18]	0,407	0,000	0,001
AST, U/l	29 [22; 34]	25 [22; 31]	20 [18; 24]	0,272	0,000	0,007
TC, mmol/l	4,4 [3,7; 4,8]	4,3 [3,9; 4,6]	4,1 [3,8; 4,4]	0,963	0,035	0,035
ß-LP, U/l	40 [36; 46]	39 [36; 42]	36 [33; 40]	0,296	0,059	0,217
TG, mmol/l	1,2 [0,5 1,4]	0,9 [0,5; 1,1]	0,6 [0,5; 0,8]	0,041	0,017	0,015
Glucose, mmol/l	4,1 [3,7; 4,4]	4,2 [4; 4,4]	3,6 [3,45; 3,8]	0,696	0,001	0,001
Insulin, μU/ml	14,5 [8,1; 15,6]	13,1 [9,5; 15,0]	9,0 [7,3; 10,4]	0,150	0,000	0,015
HOMA-IR	2,6 [1,5; 2,9]	2,6 [1,8; 2,7]	1,4 [1,2; 1,7]	0,827	0,000	0,002

Note: BMI - body mass index;

Table 3.

Spearman's correlation coefficients between 25(OH)D level and z-score BMI/age and biochemical parameters

Indicator	z-score BMI / age		25(OH)D, ng/ml	
	r	p	r	p
z-score BMI / age	1,000	≥0,05	-0,480	<0,05
25(OH)D, ng/ml	-0,480	<0,05	1,000	≥0,05
PTH, pg/ml	0,122	≥0,05	-0,441	<0,05
Ca, mmol/l	-0,512	<0,05	0,799	<0,05
P, mmol/l	-0,512	<0,05	0,873	<0,05
ALT, U/l	0,816	<0,05	-0,471	<0,05
AST, U/l	0,626	<0,05	-0,427	<0,05
TC, mmol/l	0,448	<0,05	-0,216	≥0,05
ß-LP, U/l	0,616	<0,05	-0,234	<0,05
TG, mmol/l	0,717	<0,05	-0,332	<0,05
Glucose, mmol/l	0,817	<0,05	-0,365	<0,05
Insulin, μU/ml	0,740	<0,05	-0,341	<0,05
HOMA-IR	0,850	<0,05	-0,400	<0,05

Ertugrul D. et al. (2011) suggested that in adults it is dyslipidemia that negatively affects the level of 25(OH)D, and not vice versa, since the use of statins improves the lipid profile and the concentration of 25(OH) D simultaneously [27]. Studies by Song Y. et al. (2013) and Durá-Travé T. et al. (2020) show that low 25(OH)D level are associated with a high prevalence of intolerance glucose and the development of type 2 diabetes [28, 29]. Since VD receptors also founded in the tissue of the pancreas, and Ca plays an important role in the secretion of insulin by ß-cells, it is very likely that VD deficiency increases the risk of carbohydrate metabolic disorders.

Conclusions. Obesity is more associated with the risks of impaired lipid and carbohydrate metabolism than VD deficiency. However, insufficient VD status is an important predictor of comorbid pathology and aggravates the risk of cardiometabolic disorders in obese children already at primary school age. Medical professionals, including pediatricians, pediatric endocrinologists, cardiologists, should be aware of the possible consequences of VD deficiency in obese children, as well as timely adjust the VD status when the level of the body's supply with this micronutrient decreases.

References/ Список литературы

1. World Health Organization (WHO). Nutrition: Global Targets 2025. Geneva: WHO; 2018. http://www.who.int/nutrition/global-target-2025. Accessed 2 Mar 2021

2. Kansra A., Lakkunarajah S., Jay M. Childhood and Adolescent Obesity: A Review. Front. Pediatr. 2021; Vol. 8 (581461): 1-16. doi: 10.3389/fped.2020.581461

3. Chung S., Onuzuruike A, Magge S. Cardiometabolic risk in obese children. Ann N Y Acad Sci. 2018; Vol. 1411 (1): 166–183. doi: 10.1111/nyas.13602

4. Cesare M., Sorić M., Bovet P., et al. The epidemiological burden of obesity in childhood: a worldwide

epidemic requiring urgent action. BMC Medicine. 2019; Vol. 17 (212): 1-21. https://doi.org/10.1186/s12916-019-1449-8

5. Zakharova I.N., Klimov L.Ya., Maltsev S.V., et al. Security of vitamin d and correction of its insufficiency in children of early age in the Russian Federation (fragment of the national program). Prakticheskaya medicina [Practical medicine]. 2017; Vol. 5 (106): 22-8. (In Russian)

6. Belykh N.A., Blokhova E.E. Obesity and micronutrient disbalance in children. Science of the young [Eruditio Juvenium]. 2019; Vol. 7 (3): 429-38. (In Russian) doi: 10.23888/HMJ201973429-438

7. Zakharova I.N., Tvorogova T.M., Gromova O.A., et al. Vitamin D Insufficiency in Adolescents: Results of Year-Round Screening in Moscow. Pediatricheskaya farmakologiya [Pediatric pharmacology]. 2015; Vol. 12 (5): 528-531. (In Russian). https://doi.org/10.15690/pf.v12i5.1453

8. Dreval' A.V., Kryukova I.V., Barsukov I.A., et al. Extra-osseous effects of vitamin D (a review). RMJ. 2017; Vol. 1: 53–6. (In Russian)

9. Filatova T.E., Nizov A.A., Davydov V.V. Experience of treatment of male hypertension with obesity, fasting hyperglycemia and deficiency of vitamin D. Rossijskij mediko-biologicheskij vestnik im. akademika I.P. Pavlova [I.P.Pavlov Russian Medical Biological Herald]. 2017; Vol. 25 (1): 69-75. (In Russian) doi: 10.23888/pavlovj2017169-75

10. Mirhosseini N., Rainsbury J., Kimball S. Vitamin D Supplementation, Serum 25(OH)D Concentrations and Cardiovascular Disease Risk Factors: A Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 2018; Vol. 5 (87): 1-35. doi: 10.3389/fcvm.2018.00087

11. Schroten N., Ruifrok W., Kleijn L., et al. Short-term vitamin D3 supplementation lowers plasma renin activity in patients with stable chronic heart failure: An open-label, blinded end point randomized prospective trial (VitD-CHF trial). Am Heart J. 2013; Vol. 166: 357-64.

12. Witte K., Byrom R., Gierula J., et al. Effects of vitamin D on cardiac function in patients with chronic HF: The VINDICATE study. J Am Coll Cardiol. 2016; Vol. 67 (22): 2593-603.

13. Ford J., MacLennan G., Avenell A., et al. Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. Am J Clin Nutr. 2014; Vol. 100 (3): 746–55. doi: 10.3945/ajcn.113.082602

14. Mao P., Zhang C., Tang L., et al. Effect of calcium or vitamin D supplementation on vascular outcomes: a metaanalysis of randomized controlled trials. Int J Cardiol. 2013; Vol. 169 (2): 106–11. doi: 10.1016/j.ijcard.2013.08.055

15. Kolesnikov A.N., Dubovaya A.V., Udovitchenko Yu.V. Participation of Vitamin D in Pathogenesis of Cardiovascular Diseases. Ros Vestn Perinatol i Pediatr. 2018; Vol. 63 (5): 43–50. (In Russian). doi: 10.21508/1027–4065–2018–63–5–43–50

16. WHO Regional Office for Europe: Copenhagen, Denmark. WHO European Childhood Obesity Surveillance Initiative. Protocol. 2016. [Accessed 2021 Mar 1]. Available from: http://www.euro.who.int/__data/assets/pdf_file/0018/333900/COSI-protocolen.pdf?ua=1.

17. WHO. AnthroPlus for Personal Computers Manual: Software for Assessing Growth of the World's Children and Adolescents; WHO: Geneva, Switzerland, 2009. [Accessed 2020 Nov 1]. Available online: http://www.who.int/entity/growthref/tools/who_anthroplus_manual.pdf.

18. Peterkova V.A., Nagaeva E.V., Shiryaeva T.Yo. Assessment of the physical development of children and adolescents. Normative-methodical and reference materials. Monthly supplement to the journal "Information Bulletin of Health of the Samara Region". 2018; Vol. 194 (1): 1-75. (in Russian)

19. Union of Pediatricians of Russia. National program «Vitamin D deficiency in children and adolescents of the Russian Federation: modern approaches to correction». Moscow: Pediatr", 2018: 96 p. (in Russian)

20. Zil'berman L.I., Kuraeva T.L., Peterkova V.A., the expert board of the Russian Association of Endocrinologists. Federal clinical recommendations on diagnostics and treatment of type 2 diabetes mellitus in the children and adolescents. Problemy endokrinologii [Problems of Endocrinology]. 2014; Vol. 5: 57-68. (in Russian). doi: 10.14341/probl201460557-68

21. Migliaccio1 S., Nisio A., Mele C., et al. Obesity and hypovitaminosis D: causality or casualty? International Journal of Obesity Supplements. 2019; Vol. 9 (1): 20–31. https://doi.org/10.1038/s41367-019-0010-8

22. Beketova N.A., Pavlovskaya E.V., Kodentsova V.M., Vrzhesinskaya O.A., Kosheleva O.V., Sokolnikov A.A., Strokova T.V. Biomarkers of vitamin status in obese school children. Voprosy pitaniia [Problems of Nutrition]. 2019; 88 (4): 66–74. doi: 10.24411/0042-8833-2019-10043 (in Russian)

23. Skinner A., Perrin E., Moss L., et al. Cardiometabolic Risks and Severity of Obesity in Children and Young Adults. N. Engl. J. Med. 2015; Vol. 373 (14): 1307–1317.

24. Durá-Travé T., Gallinas-Victoriano F., Chueca-Guindulain M., et al. Prevalence of hypovitaminosis D and associated factors in obese Spanish children. Nutr. Diabetes. 2017; Vol. 7 (3): 248. doi: 10.1038/nutd.2016.50

25. Okbay Güneş A., Alikaşifoğlu M., Erginoz E., et al. The relationship between cardiometabolic risks and vitamin D levels with the degree of obesity. Turk Pediatri Ars. 2019; Vol.54 (4): 256–263.

26. Mellati A., Sharifi F., Faghihzadeh S., et al. Vitamin D status and its associations with components of metabolic syndrome in healthy children. J. Pediatr. Endocrinol. Metab. 2015; Vol. 28, (5-6): 641–48. doi: 10.1515/jpem-2013-0495

27. Ertugrul D., Yavuz B., Cil H., et al. STATIN-D Study: Comparison of the Influences of Rosuvastatin and Fluvastatin Treatment on the Levels of 25 Hydroxyvitamin D. Cardiovasc. Ther. 2011; Vol. 29, (2): 146–52. doi: 10.1111/j.1755-5922.2010.00141.x

28. Song Y., Wang L., Pittas A., et al. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: A metaanalysis of prospective studies. Diabetes Care. 2013; Vol. 36, (5): 1422–28. doi: 10.2337/dc12-0962

29. Durá-Travé T., Gallinas-Victoriano F., Peñafiel Freire D., et al. Hypovitaminosis D and Cardiometabolic Risk Factors in Adolescents with Severe Obesity. Children. 2020; Vol. 7, (2): 1-11. doi:10.3390/children7020010/