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Effect of vitamin D and B_{12} levels on hepatosteatosis in overweight and obese children

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Abstract. ***Background.*** *The childhood non-alcoholic hepatosteatosis leads to significant morbidity and mortality in adulthood. In recent years, vitamin D and B_{12} deficiency has been controversially associated with non-alcoholic fatty liver disease. Therefore, we aimed to evaluate the relationship of vitamin levels and insulin resistance (IR) with non-alcoholic hepatosteatosis in obese and overweight children.* ***Material and methods.*** *A total of 167 overweight and obese children aged 5–18 years were enrolled in this prospective study. The anthropometric measurements including body weight, height, body mass index (BMI) (weight/height², kg/m²) were recorded. Children and adolescents with ≥ 95th percentile of BMI for their age and gender were diagnosed with obesity, and BMI between the 85th and 94th percentiles was classified as overweight. Children and adolescents classified into two groups according to the presence of hepatosteatosis: normal liver and hepatosteatosis group. Additionally, hepatosteatosis grading was performed by ultrasonographic evaluation. Participants' demographic characteristics, physical examination, imaging and laboratory findings including serum levels of vitamin B_{12}, 25(OH)D analysis and insulin resistance index were documented and compared between groups.* ***Results****. One hundred and sixty-seven patients included in this study were: 103 (61.7 %) males, 64 (38.3 %) females, and the mean age of total participants was 11.48 ± 2.99 years. According to BMI-Z score, 26.3 % of individuals were defined as overweight and 73.7 % were obese. Hepatosteatosis was determined in 70.7 % (n = 118) of our cases and it was significantly higher in male patients (79.6 %) than in females (p = 0.001). Mean IR was statistically higher in non-alcoholic fatty liver disease group (11.15 ± 13.39) than in normal liver group (6.95 ± 6.20) (p = 0.029). Moreover, there were statistically significant differences found in IR levels according to severity of hepatosteatosis (p = 0.013). In addition, vitamin D and B_{12} deficiencies were not significantly associated with hepatosteatosis or severity of hepatosteatosis (p > 0.05). Also, no statistically significant differences were found in mean levels of vitamin D, vitamin B_{12} and IR between obese and overweight children.* ***Conclusions****. Our findings support the published data that vitamin D and B_{12} deficiencies do not contribute to the pathology of hepatosteatosis. In addition, insulin resistance has been demonstrated to be a risk factor for non-alcoholic fatty liver and hepatosteatosis severity.*

Keywords: *hepatosteatosis; non-alcoholic fatty liver disease; childhood obesity; vitamin B_{12} deficiency; vitamin D deficiency, insulin resistance*

Introduction

The Centers for Disease Control and Prevention (CDC) reported (2015) a 2-fold increase in prevalence of childhood obesity and a 4-fold increase in adolescent obesity within the last 30 years [1]. Nonalcoholic fatty liver disease (NAFLD) is the most frequently reported chronic pediatric liver disease in children and adolescents. NAFLD prevalence appears to be increasing parallel to childhood obesity in recent years and it was reported in approximately 60 % of overweight children [2].

Although the pathophysiological mechanism of hepatocellular injury remains unclear, insulin resistance (IR) and metabolic syndrome are documented as risk factors in NAFLD. Long-term exposure to childhood-

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onset NAFLD is associated with significantly increased morbidity and mortality in adulthood due to severe hepatocellular damage and fibrosis [3]. Such that childhood NAFLD has been strongly associated with cirrhosis, hepatocellular carcinoma, end-stage liver disease and cardiovascular diseases in adults [4]. Although USG and serologic screening based on liver transaminases (AST, ALT, GGT) and inflammation markers (CRP) are frequently used, liver biopsy is the gold standard method in the diagnosis of hepatosteatosis which is often asymptomatic in childhood [3].

Vitamins D and B_{12} deficiency or insufficiency have been significantly associated with obesity, overweight, type 2 diabetes mellitus, metabolic syndrome, IR and cardiovascular disease in recent years [5–7]. It is well known that immunomodulatory and anti-inflammatory characteristics of vitamin D inhibits hepatic inflammation and fibrosis [8]. Moreover, low serum concentrations of 25-hydroxyvitamin D have been significantly associated with NAFLD and with or without non-alcoholic steatohepatitis (NASH) [9]. Similarly, vitamin B_{12} deficiency triggered hyperhomocysteinemia is significantly associated with NAFLD [10]. Furthermore, even the severity of hepatosteatosis was associated with vitamin D and B_{12} deficiency levels [10, 11]. On the contrary, there are published data concluded that vitamin deficiencies play no role in the etiopathology of hepatosteatosis [12]. Thus, the findings related to the vitamin deficiencies and hepatosteatosis seems to be controversial.

The purpose was to evaluate the relationship between vitamin levels and IR with non-alcoholic hepatosteatosis in obese and overweight children.

Materials and methods

This prospective study was performed with the Institutional Review Board protocol approval 04/03/2019 and number 2019/113 in Istanbul Training and Research Hospital, Department of Gastroenterology, Hepatology and Nutrition, between March 2019 — June 2019.

A total number of 167 overweight and obese children aged between 5–18 years old, were enrolled in present study. Children were enrolled in the study after obtainment of written informed consent from their family. The anthropometric measurements including body weight, height, BMI (weight/height^2, kg/m^2) were recorded. Body weight, height and BMI percentile were determined by using the growth curves of Turkish children [13]. Children and adolescents with a $\geq 95^{th}$ percentile of BMI for their age and gender were diagnosed with obesity, and BMIs between the 85^{th} to 94^{th} percentiles were classified as overweight.

Children and adolescents classified into two groups according to the presence of hepatosteatosis; absent hepatosteatosis group and hepatosteatosis group. Hepatosteatosis assessment performed by liver ultrasonography (Acuson S2000 Ultrasound system, Siemens, Germany). Additionally, hepatosteatosis grading was performed as follows:

Grade 0: Normal parenchymal liver echotexture.

Grade 1: Slightly increased liver echogenicity with normal visualization of vessel walls.

Grade 2: Moderately increased liver echotexture with impaired visualization of the vessel walls.

Grade 3: Severe increased liver echogenicity with poor visualization of the liver, portal vein borders and the diaphragm [14].

The serum levels of vitamin B_{12} and 25(OH)D analysis were performed using an immunodiagnostic system (Siemens, Advia Centaur xp, Germany) at a normality level of 220 pg/ml and 29.0 ng/ml, respectively. Biochemical analysis performed from serum samples by electro-chemiluminescence immunoassay analyzer (Beckman Coulter Unicel DXI 800). Haematological parameters were analysed using a haematology analyser (Cell-Dyne 3700, Abbott, Abbott Park, IL, USA). The insulin resistance index calculated according to the homeostasis model assessment of insulin resistance (HOMA-IR) formula; HOMA-IR = fasting serum insulin (microunits per milliliter) × fasting glucose (millimoles per liter)/22.5 [15]. Participants' demographic characteristics, physical examination, imaging and laboratory findings were documented and compared between groups.

Statistical analysis. All the data were analyzed with SPSS (Statistical Package for the Social Sciences) software for Windows (v21.0; IBM, Armonk, NY, USA). Individual and aggregate data were summarized using descriptive statistics including mean, standart deviations, medians (min-max), frequency distributions and percentages. Normality of data distribution was verified by Kolmogorov-Smirnov test. Comparison of the variables with normal distribution was made with Student t test. The variables which were not normally distributed, the Mann Whitney and Kruskal Wallis tests were conducted to compare between groups. Evaluation of categorical variables was performed by Chi-Square test. P-values of < 0.05 were considered statistically significant.

Results

The 167 patients included in this study were 103 (61.7 %) male, 64 (38.3 %) female and the mean age of total participants was 11.48 ± 2.99 (ranged = 3.36–17.92) years. Mean BMI-Z score was 2.36 ± 0.60 (ranged = 1,02–4,47). According to BMI-Z score, 26.3 % (n = 44) of the cases were defined as overweight (BMI-Z score = 1–2), and 73.7 % (n = 123) were obese (BMI-Z score > 2). Of the patients 36.5 % had comorbid diseases. The most common comorbid disease reported in our patients was gastritis with a percentage of 26.2 % and followed by esophageal reflux (13.1 %), constipation (11.5 %), and ADHD (8.2 %), respectively (table 1).

Hepatomegaly was the most frequent physical finding (72.5 %, n = 121), followed by hepatosplenomegaly (25.1 %, n = 42). Additionally, hepatosteatosis was determined in 70.7 % (n = 118) of our cases. Hepatosteatosis was significantly higher in male patients (79.6 %) than females (56.3 %) (p = 0.001). Of the patients 81 had (68.6 %) grade 1 hepatosteatosis, 34 had (28.8 %) grade 2 hepatosteatosis and 3 had (2.6 %) grade 3 hepatosteatosis (table 1). Hepatosteatosis was detected in 70.5 % (n = 31) of overweight patients and 70.7 % (n = 87) of obese patients (p = 0.972).

According to the evaluation of laboratory findings; mean levels of hemoglobin, ferritin, AST, ALT, GGT and triglyceride were statistically higher in NAFLD group than normal liver group (p-values = 0.002, 0.010, 0, 0, 0 and 0.008, respectively). Similarly, mean HDL was statistically lower in NAFLD group than normal liver group (p = 0,017).

In addition, mean IR was significantly higher in NAFLD group (11.15 ± 13.39) than normal liver group (6.95 ± 6.20) (p = 0.029). Vitamin D deficiency (< 20 ng/ml) and insufficiency (20–30 ng/ml) were found in 66.3 % (n = 108) and 23.9 % (n = 39) of all patients. Additionally, vitamin B_{12} deficiency (< 220 pg/ml) was detected in 37.0 % (n = 61) of patients. Vitamin D and B_{12} deficiencies were not significantly associated with hepatosteatosis (p-values = 0.958 and 0.153, respectively) (table 2).

Moreover, there were statistically significant differences found in IR levels according to severity of hepatosteatosis (p = 0.013). Mean IR was significantly increased particularly in grade 2 hepatosteatosis. In addition, vitamin D and B_{12} deficiencies were not significantly associated with severity of hepatosteatosis (table 3). There were also no

Table 1. Clinical characteristics of cases

Parameter	Clinical Variables	n (%)
Gender	Female Male	64 (38.3) 103 (61.7)
BMI-Z Score	Overweight (1–2) Obese (> 2)	44 (26.3) 123 (73.7)
USG	Hepatomegaly Hepatosplenomegaly	121 (72.5) 42 (25.1)
Hepatosteatosis	Absent Present	49 (29.3) 118 (70.7)
Hepatosteatosis severity	Grade 1 Grade 2 Grade 3	81 (68.6) 34 (28.8) 3 (2.5)
Comorbid Diseases	Gastritis Reflux Constipation ADHD Others	16 (26.2) 8 (13.1) 7 (11.5) 5 (8.2) 25 (41.0)

Table 2. Comparison of clinical features and laboratory outcomes between groups

Parameter	Normal liver group (Mean ± SD)	NAFLD group (Mean ± SD)	*P*-value
BMI Z Score	2.33 ± 0.51	2.38 ± 0.63	0.618
HBA1c (%)	5.39 ± 0.30	5.45 ± 0.36	0.467
Glucose (mg/dL)	89.98 ± 7.36	90.79 ± 7.57	0.523
HOMA-IR	6.95 ± 6.20	11.15 ± 13.39	0.029*
Hemoglobin (g/dL)	12.82 ± 1.02	13.36 ± 1.02	0.002*
Ferritin (mg/L)	27.29 ± 16.55	37.70 ± 23.68	0.010*
Vitamin B_{12} (pg/mL)	306.71 ± 137.70	278.58 ± 164.20	0.153
Vitamin D (ng/ml)	19.33 ± 10.16	19.22 ± 10.58	0.958
AST (U/L)	23.67 ± 7.16	33.46 ± 17.95	0*
ALT (U/dL)	18.99 ± 10.25	44.80 ± 35.14	0*
GGT (U/L)	14.77 ± 4.96	25.22 ± 16.60	0*
LDL (mg/dl)	102.72 ± 53.30	102.42 ± 33.00	0.347
HDL (mg/dL)	48.34 ± 10.60	44.91 ± 12.00	0.017*
Triglyceride (mg/dl)	101.77 ± 76.80	122.76 ± 63.34	0.008*

Notes: here and the table 3:* — p < 0.05 statistically significant; SD — Standard Deviation.

Table 3. Comparison of vitamin D, vitamin B_{12} and IR levels according to the hepatosteatosis severity

Parameter	Normal liver group (Mean ± SD)	NAFLD group			*P*-value
		Grade 1 (Mean ± SD)	Grade 2 (Mean ± SD)	Grade 3 (Mean ± SD)	
Vitamin D (ng/ml)	19.33 ± 10.16	18.80 ± 10.44	20.15 ± 11.09	20.20 ± 11.93	0.907
Vitamin B_{12} (pg/mL)	306.71 ± 137.70	280.94 ± 179.50	280.42 ± 130.80	195.66 ± 28.74	0.281
HOMA-IR	6.95 ± 6.20	9.77 ± 12.85	14.35 ± 14.68	11.57 ± 7.97	0.013*

Table 4. Comparison of vitamin D, vitamin B_{12} and IR levels according to the BMI Z Score

Parameter	Overweight (Mean ± SD)	Obese (Mean ± SD)	*P*-value
Vitamin D (ng/ml)	18.21 ± 10.20	19.62 ± 10.52	0.439
Vitamin B_{12} (pg/mL)	262.70 ± 132.60	295.21 ± 164.10	0.089
HOMA-IR	7.85 ± 6.99	10.63 ± 13.10	0.330

statistically significant differences found in mean levels of vitamin D, vitamin B_{12} and IR between obese and overweight children (table 4).

Discussion

Despite the increasing prevalence of NAFLD in children and adolescents, there are estimated to be a large number of undiagnosed children due to the asymptomatic characteristics of the disease, the absence of standardized guidelines, invasive and expensive diagnostic procedures. Additionally, NAFLD primarily affects male gender [3]. J.A. Welsh et al. reported 3 times higher male prevalence in a study consisting of 14 918 children diagnosed with NAFLD in 20 years period [16]. V. Nobili et al. documented the male percentage of 64 % in 73 children with NAFLD [11]. Similarly, children included in our study were 61.7 % male and 38.3 % female. Furthermore, hepatosteatosis was significantly higher (79.6 %) in male children.

Vitamin D deficiency or insufficiency has been significantly associated with increased BMI scores in published data. In addition, it is well known that obesity increases the risk of NAFLD. Therefore, the relationship between hepatosteatosis and childhood vitamin deficiencies has become an increasingly popular field of study in recent years with controversial findings [17]. G. Targher et al. reported significantly lower levels of 25(OH)D in histopathologically confirmed NAFLD children (n = 60) than healthy (n = 60) controls [18]. Similarly, in a meta-analysis consisting of 59 studies and 13 524 patients (5896 NAFLD and 7628 controls), researchers documented significantly lower serum 25(OH)D levels in NAFLD patients. Additionally, they noted a 1.26-fold (OR 1.26, 95% CI 1.15 to 1.38) increase in the prevalence of NAFLD associated with vitamin D deficiency. Thus, researchers concluded that vitamin D deficiency may play a role in the pathogenesis of NAFLD and NASH [19]. On the contrary, F. Dursun et al. has not significantly associated serum vitamin D deficiency or insufficiency with hepatosteatosis in 110 obese children [20]. Supportively, K. Katz et al. identified overweight and male gender as risk factors for hepatosteatosis, but not vitamin D deficiency in a study included 1630 adolescents [21]. In accordance with these data, vitamin D deficiency or insufficiency were not significantly associated with hepatosteatosis or severity of hepatosteatosis in present study.

Although decrease in serum B_{12} levels has been documented in acute hepatitis, cirrhosis and hepatocellular carcinoma, the relationship between vitamin B deficiency and NAFLD currently is not clear. There is limited number of published data with debated results evaluating vitamin B deficiency in NAFLD-patients. In a study, M. Koplay et al. compared 45 NAFLD patients with 30 healthy controls and reported statistically increased ALT, decreased B_{12} and folate concentrations in the patient group. Researchers also highlighted significantly reduced vitamin B_{12} levels particularly in grade 2 and 3 hepatosteatosis [10]. A decrease in serum B_{12} levels in NAFLD patients was also demonstrated by F.F. Bolukbas et al. in a study comparing 129 patients diagnosed with NAFLD to 50 healthy controls [22]. On the other hand, S.A. Polyzos et al. have associated B_{12} deficiency with neither NAFLD nor severity of fibrosis in patients with histopathologically confirmed NAFLD. In the same study, significantly increased serum ALT, AST, IR, triglyceride and decreased HDL levels were also documented in NAFLD patients [23]. Similarly, S. Hirsch et al. have not associated B_{12} levels with NAFLD or liver damage in a study consisting of 43 obese women [24]. Supportively in our study, vitamin B_{12} deficiency or insufficiency were not significantly associated with hepatosteatosis or severity of hepatosteatosis.

It is unclear whether insulin resistance is a cause or a consequence of NAFLD. But IR related-liver fat accumulation is frequently reported and in some studies IR increase is defined as NAFLD feature even in non-obese patients [25]. J.F. Fu et al. divided 861 obese children (aged between: 6–16 years) into 3 groups; 'fatty liver — normal ALT', 'fatty liver — elevated ALT' and 'normal liver — normal ALT'. Researchers have revealed that IR was significantly increased in fatty liver groups [26]. Similarly, in a study conducted with 846 children, K. Tominaga et al. histopathologically confirmed the NAFLD diagnosis in 37 children and concluded that NAFLD was closely associated with metabolic syndrome and IR [27]. In a study conducted by A. Fraser et al. with 5586 adolescents, researchers demonstrated significantly increased serum ALT, CRP, triglyceride and IR levels in children with NAFLD [28]. In accordance with these data, mean serum levels of hemoglobin, ferritin, AST, ALT, GGT, triglyceride were statistically higher and mean HDL was statistically lower in NAFLD group than normal liver group in our study. Additionally, mean IR was statistically higher in NAFLD group than normal liver group. Moreover, it is remarkable that mean IR was significantly increased particularly in grade 2 hepatosteatosis.

Conclusions

Our findings support the published data that vitamin D and B_{12} deficiencies do not contribute to the pathology of hepatosteatosis. It should be considered that vitamin deficiency may occur particularly in obese pediatric population due to the already existing hepatocellular damage and fibrosis. In addition, insulin resistance has been demonstrated to be a risk factor for non-alcoholic fatty liver and hepatosteatosis severity.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Вплив вмісту вітамінів D і B_{12} на частоту стеатогепатозу в дітей із надмірною масою тіла та ожирінням

Резюме. ***Актуальність.*** Неалкогольний стеатогепатоз у дітей призводить до зростання захворюваності та смертності в дорослому віці. Останнім часом опубліковані суперечливі дані стосовно взаємозв'язків між рівнями вітамінів D і B_{12} і частотою неалкогольного стеатогепатозу. ***Мета дослідження:*** оцінити зв'язок між рівнем вітамінів D і B_{12} та інсулінорезистентністю (ІР) і частотою неалкогольного стеатогепатозу в дітей з ожирінням та надмірною масою тіла. ***Матеріали та методи.*** У проспективне дослідження були включені 167 дітей із надмірною масою тіла та ожирінням віком від 5 до 18 років. Визначали антропометричні показники, включаючи масу тіла, зріст, індекс маси тіла (ІМТ) (вага/зріст^2, кг/м^2). У дітей і підлітків з ІМТ ≥ 95-го перцентиля для віку і статі діагностували ожиріння, а ІМТ від 85-го до 94-го перцентиля класифікували як надмірну масу тіла. Діти та підлітки були розподілені на дві групи: зі стеатогепатозом і без порушення функціонального стану печінки. Додатково оцінювали стан печінки за допомогою ультразвукового дослідження. Визначали демографічні характеристики учасників дослідження, проводили загальноклінічний огляд, лабораторні дослідження, включаючи аналізи на виявлення рівня вітаміну B_{12} і 25(OH) D у сироватці крові та визначення індексу ІР. ***Результати.*** Із 167 обстежених 103 (61,7 %) були чоловічої статі, 64 (38,3 %) — жіночої, їх середній вік становив 11,48 ± 2,99 року. Згідно з ІМТ у 26,3 % випадків була визначена надмірна маса тіла, а 73,7 % — ожиріння. Стеатогепатоз діагностований у 70,7 % випадків (n = 118), його частота була вірогідно вищою в пацієнтів чоловічої статі (79,6 %), ніж жіночої (p = 0,001). Середній показник ІР був статистично вищим у групі дітей зі стеатогепатозом (11,15 ± 13,39), ніж у контрольній групі (6,95 ± 6,20) (p = 0,029). Крім того, установлені статистично значущі відмінності рівнів ІР за ступенем вираженості стеатогепатозу (p = 0,013). Не спостерігалося вірогідного взаємозв'язку між дефіцитом вітамінів D та B_{12} і наявністю та тяжкістю стеатогепатозу (p > 0,05). Також не було виявлено статистично значущих відмінностей між середнім вмістом вітамінів D і B_{12} та індексом ІР серед дітей з ожирінням та надмірною масою тіла. ***Висновки.*** Отримані результати підтверджують опубліковані раніше дані про те, що дефіцит вітамінів D та B_{12} не сприяє розвитку стеатогепатозу в дітей із надмірною масою тіла та ожирінням. Інсулінорезистентність є фактором ризику виникнення та прогресування стеатогепатозу.

Ключові слова: стеатогепатоз; діти; ожиріння; дефіцит вітаміну B_{12}; дефіцит вітаміну D; інсулінорезистентність

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Влияние содержания витаминов D и B_{12} на частоту стеатогепатоза у детей с избыточной массой тела и ожирением

Резюме. ***Актуальность.*** Неалкогольный стеатогепатоз у детей приводит к росту заболеваемости и смертности во взрослом возрасте. В последние годы опубликованы противоречивые данные о взаимосвязи между уровнями витаминов D и B_{12} и частотой неалкогольного стеатогепатоза. ***Цель исследования:*** оценить взаимосвязь между уровнем витаминов D и B_{12} и инсулинорезистентностью (ИР) и частотой неалкогольного стеатогепатоза у детей с ожирением и избыточной массой тела. ***Материалы и методы.*** В проспективное исследование были включены 167 детей с избыточной массой тела и ожирением в возрасте от 5 до 18 лет. Определяли антропометрические показатели, включая массу тела, рост, индекс массы тела (ИМТ) (вес/рост^2, кг/м^2). У детей и подростков с ИМТ ≥ 95-го перцентиля для возраста и пола диагностировали ожирение, а ИМТ от 85-го до 94-го перцентиля классифицировали как избыточную массу тела. Дети и подростки были разделены на две группы: со стеатогепатозом и без нарушения функционального состояния печени. Дополнительно оценивали состояние печени с помощью ультразвукового исследования. Определяли демографические характеристики участников исследования, проводили общеклинический обзор, лабораторные исследования, включая анализы на выявление уровня витамина B_{12} и 25(OH)D в сыворотке крови и определение индекса ИР. ***Результаты.*** Из 167 обследованных 103 (61,7 %) были мужского пола, 64 (38,3 %) — женского, их средний возраст составил 11,48 ± 2,99 года. Согласно ИМТ в 26,3 % случаев была выявлена избыточная масса тела, а в 73,7 % — ожирение. Стеатогепатоз диагностирован в 70,7 % случаев (n = 118), его частота была достоверно выше у пациентов мужского пола (79,6 %), чем женского (p = 0,001). Средний показатель ИР был статистически выше в группе детей со стеатогепатозом (11,15 ± 13,39), чем в контрольной группе (6,95 ± 6,20) (p = 0,029). Кроме того, установлены статистически значимые различия уровней ИР по степени выраженности стеатогепатоза (p = 0,013). Не наблюдалось достоверной взаимосвязи между дефицитом витаминов D и B_{12}, наличием и тяжестью стеатогепатоза (p > 0,05). Также не было выявлено статистически значимых различий между средним содержанием витаминов D и B_{12} и индексом ИР среди детей с ожирением и избыточной массой тела. ***Выводы.*** Полученные результаты подтверждают опубликованные ранее данные о том, что дефицит витаминов D и B_{12} не способствует развитию стеатогепатоза у детей с избыточной массой тела и ожирением. Инсулинорезистентность является фактором риска возникновения и прогрессирования стеатогепатоза.

Ключевые слова: стеатогепатоз; дети; ожирение; дефицит витамина B_{12}; дефицит витамина D; инсулинорезистентность