Advances in Medical Sciences 64 (2019) 280–284

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Original research article

Can hepatokines be regarded as novel non-invasive serum biomarkers of intrahepatic lipid content in obese children?

Marta Flisiak-Jackiewicz[a,*], Anna Bobrus-Chociej[a], Natalia Wasilewska[a], Eugeniusz Tarasow[b], Malgorzata Wojtkowska[c], Dariusz Marek Lebensztejn[a]

[a] Department of Pediatrics, Gastroenterology, Hepatology, Nutrition and Allergology, Medical University of Bialystok, Bialystok, Poland
[b] Department of Radiology, Medical University of Bialystok, Bialystok, Poland
[c] Department of Radiology, University Teaching Children's Hospital, Bialystok, Poland

ARTICLE INFO

Keywords:
Fibroblast growth factor-21
Selenoprotein P1
Sex hormone-binding globulin
Fatty liver
Children

ABSTRACT

Purpose: Hepatokines are proteins produced by the liver and involved in regulating glucose and lipid metabolism. However, their role as the biomarkers of intrahepatic lipid content is not clear. The aim of the study was to evaluate the serum concentration of selected hepatokines: fibroblast growth factor-21 (FGF-21), selenoprotein P (SELENOP) and sex hormone-binding globulin (SHBG) in obese children.

Patients and methods: The cross-sectional study included 86 obese children with suspected liver disease. Nonalcoholic fatty liver disease (NAFLD) was diagnosed in children with liver steatosis in ultrasound with elevated alanine aminotransferase (ALT) serum activity and excluded other liver diseases. The total intrahepatic lipid content (TILC) was assessed by magnetic resonance proton spectroscopy (^{1}H-MRS).

Results: The concentration of FGF-21 and SELENOP was significantly higher and SHBG significantly lower in children with NAFLD compared to controls. Only FGF-21 level was significantly higher in NAFLD children than in obese patients without NAFLD. The significant positive correlation of FGF-21 with ALT, gamma glutamyltransferase (GGT), triglycerides, homeostatic model assessment–insulin resistance (HOMA-IR), the degree of liver steatosis in ultrasound and TILC in ^{1}H-MRS were found. The ability of serum FGF-21 to diagnose severe liver steatosis was significant.

Conclusions: FGF-21 can be considered as a suitable biomarker in predicting TILC and fatty liver in obese children.

1. Introduction

Nowadays nonalcoholic fatty liver disease (NAFLD) is regarded as the main cause of chronic liver pathology in children [1]. It is thought to be a hepatic manifestation of metabolic syndrome being closely connected to visceral obesity, insulin resistance, dyslipidemia and increased cardiovascular risk [2]. Recently, there has been a growing interest in the role of organokines – proteins of paracrine and endocrine activities – in pathogenesis of metabolic syndrome, diabetes type 2, cardiovascular diseases as well as NAFLD. Organokines consist of adipokines (produced mainly by fat tissue), miokines (produced mainly by skeletal muscles) and hepatokines (produced exclusively or mainly by liver) [3–5]. It has been proven that liver is able to influence the metabolism of lipids and carbohydrates by releasing hepatokines into circulating blood and NAFLD's onset and progression may be the result of their impaired production. Moreover, the hepatokines could be regarded as markers of liver pathology progression [6]. However, their role as the biomarkers of intrahepatic lipid content is not clear. In our previous preliminary study [7] we confirmed increased concentration of one of the hepatokines - fetuine A, in children with NAFLD compared to control but we found no correlation of this glycoprotein with intensity of hepatic steatosis in ultrasound or total intrahepatic lipid content (TILC) in proton magnetic resonance spectroscopy (^{1}HMRS). Therefore, the aim of the present study was to assess the serum concentration of selected hepatokines such as fibroblast growth factor-21 (FGF-21), selenoprotein P (SELENOP) and sex hormone-binding globulin (SHBG) in obese children as potential biomarkers of ectopic fat accumulation in the liver. These three hepatokines were selected to the study, because according to current knowledge they seem to have the greatest impact on the pathogenesis of NAFLD.

* Corresponding author at: Department of Pediatrics, Gastroenterology, Hepatology, Nutrition and Allergology, Medical University of Bialystok, Waszyngtona 17, 15-247 Bialystok, Poland.
E-mail address: m_flisiak@op.pl (M. Flisiak-Jackiewicz).

https://doi.org/10.1016/j.advms.2019.02.005
Received 4 July 2018; Accepted 28 February 2019
Available online 25 March 2019

2. Patients and methods

2.1. Patients

This cross-sectional study included a group of 86 consecutive obese children (65 boys and 21 girls) aged from 8 to 17 years old (median 12 years old) admitted to Department of Pediatrics, Gastroenterology, Hepatology, Nutrition and Allergology (Medical University of Bialystok, Poland) in the years 2011-2014 due to suspected liver pathology (hepatomegaly and/or elevated alanine aminotransferase (ALT) and/or fatty liver features in ultrasound examination).

Viral infection (hepatitis C virus - HCV, hepatitis B virus - HBV and cytomegalovirus - CMV), autoimmune hepatitis, metabolic liver diseases (Wilson disease, alpha-1-antitrypsin deficiency), cystic fibrosis and drug-induced liver injury (DILI) were excluded in all children. Children with diabetes were also excluded from this study.

All subjects underwent physical examinations with anthropometric measurements (body mass index - BMI and waist circumference). Routine blood chemistry analyses including: ALT, gamma glutamyltransferase (GGT), total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, glucose and insulin, were performed using standard methods. Homeostatic model assessment–insulin resistance (HOMA-IR) was calculated according to the formula described by Matthews et al. [8].

2.2. Methods

Fasting serum hepatokines concentration was assessed using the commercial ELISA kits (Human Fibroblast Growth Factor and Human Sex Hormone Binding Globulin - BioVender, Brno, Czech Republic and Human Selenoprotein P1– Cloud-Clone Corp. Houston, TX, USA). The control group comprised 24 non-obese children without any somatic organ pathology. Blood samples were immediately centrifuged and stored in −80 °C until further processing. The intra- and inter-assay CVs of FGF-21 ranged from 3.0 to 4.1% and 3.6 to 3.9%, respectively. The intra- and inter-assay CVs of SHBG ranged from 3.0 to 8.6% and 7.2 to 11.6%, respectively. The intra- and inter-assay CVs of SELENOP were < 10% and < 12%, respectively. All assays were conducted according to the manufacturer's instructions.

Liver ultrasound examination was performed with General Electric Voluson E8, convex probe 3-5 MHz; the intensity of steatosis was assessed using a four-grade scale (0–3) as outlined by Saverymuttu et al. [9]. Severe liver steatosis was defined as a score > 2. Steatosis grade was assessed in a blinded fashion by the same radiologist without knowledge of the patients' laboratory or clinical data.

The proton spectroscopy of the liver was performed using a 1.5 T system (Picker Eclipse, Picker International Inc., Highland Heights, OH, USA). The examinations were conducted with the whole body coil using the sequence of PRESS 35 (point-resolved spectroscopy sequence) (TE 35 ms, TR 1500 ms, nex 192). Water suppression was performed by the use of the MOIST (Multiply Optimized Insensitive Suppression Train) method. A voxel of 3 × 3 x 3 cm (27 cm3) was selected in the region of the right liver lobe on the basis of T2-weighted pictures in the frontal and transverse planes. The voxel was localized in such a way as to avoid large vessels and bile ducts. Spectroscopy was conducted in fasting state. On the basis of obtained spectra, we evaluated the particular metabolite contents, in relative units (RU), according to the pattern: Metabolite/H2O = area of the metabolite x 1000/ area of non-suppressed water. The spectral evaluation included signals of functional groups of the lipid compounds: methyl (Lip 1), methylene (Lip 2), and α-methylenes for the double bond (Lip 3). Based on the measurements, total lipids (TL) were calculated by summing up the content of individual lipid bands - Lip 1, 2 and 3 [10].

2.3. Ethical issues

Informed consent was obtained from all patients' parents. The protocol was approved by the Bioethical Committee of the Medical University of Bialystok, Poland (approval no: R-I-002/88/2014, R-I-002/381/2015).

2.4. Statistical analysis

The serum concentrations of hepatokines, other biochemical tests and anthropometric parameters were expressed as median; 25–75 quartile. The statistical analysis was performed with the Mann-Whitney two-sample test for nonparametric data. The relationship between biochemical tests was analyzed by the Spearman rank-correlation test for non-parametric data. The tests were considered statistically significant at $p < 0.05$. Logistic regression analysis was performed using IBM SPSS Statistics 20.0. Analysis of the receiver operating characteristics (ROC) was used to calculate the power of the assays to detect liver steatosis. The comparison of the area under curve (AUC) was performed using a two-tailed p-test, which compares the AUC to the diagonal line of no information (AUC 0.5).

3. Results

3.1. Serum concentration of FGF-21, SELENOP and SHBG

Table 1 shows baseline characteristics of examined children. Seventy two children (83.7%) had liver steatosis in ultrasound examination; 34 of them also had an increased serum ALT activity (NAFLD group).

The serum levels of FGF-21 (190.35; 59.2-309.8 pg/ml) and SELENOP (19449.5; 13327-28058 pg/ml) were significantly higher and SHBG significantly lower (42.6; 26.7-58.8 nmol/l) in NAFLD children than in lean controls (346; 23.9-69.2 pg/ml, 5411; 1618-15135 pg/ml, 117.8; 68.95-149.9 nmol/l, respectively) ($p = 0.000003$; $p = 0.000011$; $p = 0.000002$, respectively).

Children with diagnosed NAFLD had higher levels of FGF-21 ($p = 0.046$) as well as BMI, waist circumference values, ALT and GGT activity, HOMA-IR and intensity of the hepatic steatosis in ultrasound examination and intrahepatic lipid content in 1HMRS (Table 2).

Table 1
The baseline characteristics of examined patients (n = 86).

Data of the patients	Median	25-75 quartile
Age (years)	12	11-15
BMI (kg/m^2)	27.8	26-32
Waist (cm)	94	90-105
ALT (IU/l)	35	23-57
GGT (IU/l)	21	16-30
Total cholesterol (mg/dl)	176.5	146-191
HDL-cholesterol (mg/dl)	46.5	39-54
LDL-cholesterol (mg/dl)	98.5	79-121
Triglycerides (mg/dl)	107.5	83-121
Glucose (mg/dl)	92	85-96
Insulin (μIU/ml)	14.85	11.2-19.5
HOMA-IR	3.5	2.5-4.5
Ultrasound grade	1	1-2
Lipids ^{1}HMRS (R.U.)	107.1	58.3-175
FGF-21 (pg/ml)	114.2	44.7-248.4
SELENOP (pg/ml)	21421	11566-28058
SHBG (nmol/l)	48.55	32.7-62.9

BMI - body mass index, ALT - alanine aminotransferase, GGT - gamma glutamyltransferase, HDL-cholesterol - high-density lipoprotein cholesterol, LDL-cholesterol - low-density lipoprotein cholesterol, HOMA-IR - homeostatic model assessment–insulin resistance, ^{1}HMRS - proton magnetic resonance spectroscopy, R.U. - relative units, FGF-21 - fibroblast growth factor-21, SELENOP - selenoprotein P, SHBG - sex hormone-binding globulin.

Table 2
The comparative characteristics of NAFLD children and non-NAFLD obese patients.

Data of the patients	NAFLD patients (n = 34) Median; 25-75 quartile	Non-NAFLD obese patients (n = 52) Median; 25-75 quartile	P
Age (years)	14; 12-16	12; 10-14	0.026
BMI (kg/m^2)	28.2; 26.6-33.3	26.95; 25.4-30.5	0.03
Waist (cm)	99; 94-107	92; 86-102	0.003
ALT (IU/l)	63; 51-101	25.5; 18-35.5	< 0.001
GGT (IU/l)	30.5; 22-45	18; 14-23	< 0.001
Total cholesterol (mg/dl)	180.5; 156-216	175; 143-188.5	NS
HDL-cholesterol (mg/dl)	44.5; 40-51	50; 39-54.5	NS
LDL-cholesterol (mg/dl)	100; 80-143	98.5; 77.5-116	NS
Triglycerides (mg/dl)	145.5; 85-173	106; 80-136.5	NS (0.08)
Glucose (mg/dl)	93; 85-99	91; 86-95.5	NS
Insulin (μIU/ml)	17-12.8-21	13.75; 10-17.7	NS
HOMA-IR	3.85; 2.79-4.77	3.14; 2.06-3.91	0.025
Ultrasound grade	2; 1-2	1; 0-1	< 0.001
Lipids ^{1}HMRS (R.U.)	158.4; 106.2-210	78.75; 39.2-134	< 0.001
FGF-21 (pg/ml)	190.35; 59.21-309.8	83.2; 41.8-174.75	0.046
SELENOP (pg/ml)	19449.5; 13327-28058	21629; 10369.5-27976	NS
SHBG (nmol/l)	42.6; 26.7-58.8	50.15; 40.4-64.4	NS

BMI - body mass index, ALT - alanine aminotransferase, GGT - gamma glutamyltransferase, HDL-cholesterol - high-density lipoprotein cholesterol, LDL-cholesterol - low-density lipoprotein cholesterol, HOMA-IR - homeostatic model assessment–insulin resistance, ^{1}HMRS - proton magnetic resonance spectroscopy, R.U. - relative units, FGF-21 - fibroblast growth factor-21, SELENOP - selenoprotein P, SHBG - sex hormone-binding globulin.

Table 3
The comparative characteristics of subgroups of children with mild and severe steatosis in ultrasound.

Data of the patients	Mild steatosis in US (n = 64) Median; 25-75 quartile	Severe steatosis in US (n = 8) Median; 25-75 quartile	P
Age (years)	12; 11-14	15; 11.75-17	NS
BMI (kg/m^2)	27.6; 26.1-32	30.2; 26.8-35.7	NS
Waist (cm)	95.5; 91.25-104.75	105; 94-113.5	NS
ALT (IU/l)	36; 25-56	89; 71.5-111	< 0.001
GGT (IU/l)	21; 16-29.5	39.5; 30.5-54.5	0.003
Total cholesterol (mg/dl)	177.5; 150.5-194.5	179; 156-190	NS
HDL-cholesterol (mg/dl)	47.5; 39-54	41.5; 34-48	NS
LDL-cholesterol (mg/dl)	100.5; 81.5-124	100; 75.5-115.5	NS
Triglycerides (mg/dl)	107.5; 84-152.5	164; 122.5-199	NS (0.05)
Glucose (mg/dl)	91; 85-95	101; 95-103.5	0.001
Insulin (μIU/ml)	14.6-11-20	17.1; 13.65-27.5	NS
HOMA-IR	3.38; 2.4-4.4	5.17; 3.75-8.3	< 0.001
Lipids ^{1}HMRS (R.U.)	110.2; 74.5-180	187; 162.8-228.5	0.01
FGF-21 (pg/ml)	90; 43.7-215.5	263; 224.25-402.55	0.005
SELENOP (pg/ml)	20506; 11605.5-28455	24401.5; 11712.5-28832	NS
SHBG (nmol/l)	49.85; 33.1-65.05	37; 20.2-51.9	NS (0.075)

BMI - body mass index, ALT - alanine aminotransferase, GGT - gamma glutamyltransferase, HDL-cholesterol - high-density lipoprotein cholesterol, LDL-cholesterol - low-density lipoprotein cholesterol, HOMA-IR - homeostatic model assessment–insulin resistance, ^{1}HMRS - proton magnetic resonance spectroscopy, R.U. - relative units, FGF-21 - fibroblast growth factor-21, SELENOP - selenoprotein P, SHBG - sex hormone-binding globulin.

Eight children had severe liver steatosis (grade 3) and 64 had mild steatosis according to the Saverymuttu scale. The concentration of FGF-21 was significantly higher in children with severe liver steatosis compared to patients with mild steatosis (p = 0.005) (Table 3).

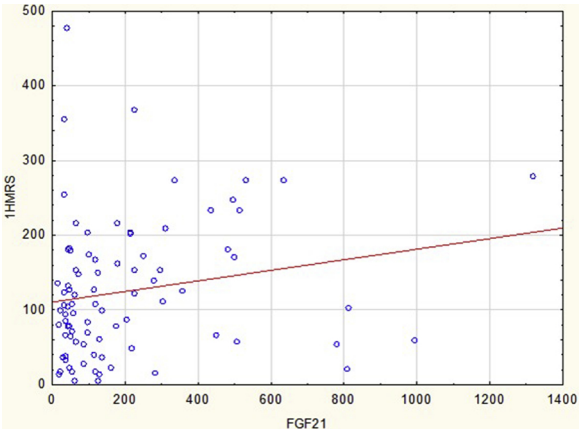

Fig. 1. The correlation between FGF-21 and total intrahepatic lipid content assessed by magnetic resonance proton spectroscopy (r = 0.22, p = 0.04).

There was a significant positive correlation of FGF-21 with: ALT (r = 0.23, p = 0.03), GGT (r = 0.27, p = 0.01), triglycerides (r = 0.39, p < 0.001), HOMA-IR (r = 0.32, p = 0.002), the intensity of hepatic steatosis in ultrasound (r = 0.23, p = 0.03) and intrahepatic lipid content in 1HMRS (r = 0.22, p = 0.04) (Fig. 1). SELENOP negatively correlated with age (r = -0.24, p = 0.03) and SHBG negatively correlated with age (r = -0.22, p = 0.04) and HOMA-IR (r = -0.31, p = 0.004).

3.2. Diagnostic value of hepatokines for identification of patients with severe liver steatosis confirmed in ultrasound

In the logistic regression analysis it was demonstrated that only FGF-21 out of the three tested hepatokines, may be useful in the differentiation of obese patients with confirmed severe liver steatosis in ultrasound from patients with mild steatosis (OR-10.461, 95%CI 1.538–71.147, p = 0.016).

This finding was confirmed in ROC analysis. The ability of serum FGF-21 to diagnose severe liver steatosis was significant (AUC = 0.8057, p < 0.001, sensitivity = 100%, specificity = 73.4%, cut-off > 207.8 pg/ml). SELENOP and SHBG did not allow a useful prediction (Fig. 2).

4. Discussion

In our study, we have found significantly higher levels of FGF-21 and SELENOP with simultaneously lower SHBG in children with NAFLD

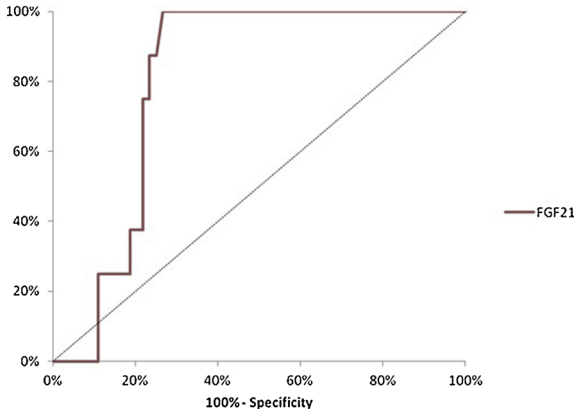

Fig. 2. ROC curve of FGF-21 ability to detect children with advanced liver steatosis in ultrasound.

compared to non-obese controls. We have also found higher FGF-21 levels in children with NAFLD compared to other obese children. According to our knowledge, this is the first and the only study analyzing concurrent levels of three hepatokines in NAFLD patients.

Our obtained results are consistent with data from other published studies, in which significantly higher levels of FGF-21 in adult NAFLD patients were found compared to controls [11–15]. Similar data in children were obtained by Reinehr et al. [16], Giannini et al. [17] and Sodhi et al. [18]. However, a study by Alisi et al. [19] demonstrated lower FGF-21 concentration in the group of children with biopsy-proven NAFLD compared to the control group, although the control group was also obese children and it has only been one study with such observation.

The results obtained by Choi et al. [20] were similar to our findings and demonstrated higher concentration of SELENOP whereas Polyzos et al. [21] and Hua et al. [22] found lower SHBG levels in adult NAFLD patients compared to controls; up till now there has been no such a study in children. According to the recent study by Saito et al. [23] currently available ELISA kits for SELENOP measurement demonstrate variable ranges of blood concentration in healthy adults. Values showed in our study were about 100 times lower compared to those measured using other kits or even more with the same kit but in adult population [23]. There is no clear explanation for this difference.

However, the main aim of our study was to assess the possibility of potential correlation between the concentration of hepatokines and the TILC with the intensity of organ dysfunction. In our studied group of obese children only FGF-21 positively correlated with TILC measured in proton magnetic resonance spectroscopy, which is considered to be a reliable non-invasive diagnostic method. The diagnostic value of the method was confirmed by demonstrating that morphology correlates well with ^{1}HMRS in evaluating hepatic fat content [24]. SELENOP and SHBG concentrations did not correlate with TILC. Only a single hepatokine - FGF-21 has been evaluated in previously studied trials. The serum FGF-21 concentration positively correlated with TILC assessed in ^{1}HMRS [25] as well as in MRI (HFF%) [17]. In addition, Li et al. [12] showed a correlation of this glycoprotein with hepatic triglycerides assessed in liver biopsy. Therefore it can be stated that FGF-21 can be considered as a useful biomarker confirming ectopic lipid accumulation in the liver of children with NAFLD.

In our study, we also showed significantly higher levels of FGF-21 in children with severe hepatic steatosis compared to children with mild steatosis in ultrasound. It was found that only FGF-21, one out of the three tested hepatokines, may be useful in differentiating obese patients with confirmed severe steatosis from patients with mild steatosis. The studies conducted in adults demonstrated that hepatic FGF-21 mRNA expression correlated with liver steatosis [12]. A slightly different result was obtained by Yan et al. [25]; they observed that FGF-21 levels increased progressively with the increase of intrahepatic liver content (measured in ^{1}HMRS), but when hepatic fat content reached the fourth quartile, FGF-21 tended to decline. The authors of that study suggested that lowering FGF-21 levels in adult patients with severe liver steatosis may be explained by decreased production of this glycoprotein by hepatocytes due to their injury or death caused by lipotoxicity and hepatic inflammation. It appears that the decrease in FGF-21 levels in NAFLD patients may also be associated with disease progression to nonalcoholic steatohepatitis (NASH). Confirmation of this hypothesis may be found in the study by Alisi et al. [19], which showed lower FGF-21 concentrations in children with biopsy-proven NASH compared to children with NAFLD without the morphological features of NASH.

It has been suggested that hepatic expression of FGF-21 is a response to FGF-21 resistance, and that FGF-21 resistance may be a pathogenetic component of NAFLD development and progression to NASH. The increase in FGF-21 levels may be a potential protective factor against lipids and carbohydrates metabolism disorders such as metabolic syndrome or NAFLD [26,27]. It has been shown that FGF-21 directly regulates lipid metabolism and reduces hepatic lipid accumulation in an insulin-independent manner [28–30]. It affects many elements of the "multi-hits theory" of NAFLD e.g. oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress and low-grade chronic inflammation. Moreover, it was suggested that increased FGF-21 may protect against chronic exposure to high levels of free fatty acids which are lipotoxic in muscle tissue, pancreas and liver [31]. This observation was confirmed in animal model studies. It was shown that in diet-induced obese mice, administration of FGF-21 caused a decrease in hepatic steatosis, reduced levels of triglycerides in serum and liver and reversible fatty liver by inhibition of sterol regulatory element-binding transcription factor-1 (SREBP-1), and key transcription factor of lipogenesis [32,33]. Moreover, systematic exercise and caloric restriction in Otsuka Long-Evans Tokushima Fatty (OLETF) rats reduced hepatic expression of FGF-21 mRNA and serum level of FGF-21 which may indicate that such intervention alleviate FGF-21 resistance [34].

In our study, no invasive liver biopsy was performed. Currently according to the ESPGHAN Hepatology Committee liver biopsy is not recommended in screening for NAFLD, but is indicated if advanced disease is suspected or before pharmacological or surgical treatment [35]. The examined children in our study did not meet the criteria necessary for the liver biopsy and the potentially obtained biopsy morphological outcome would not affect the planned therapeutic treatment (life-style modification). It seems that the lack of advanced features of liver disease particularly in children with severe fatty liver disease confirmed in imaging studies which excluded these patients from performing liver biopsy, was confirmed by high FGF-21 levels in this group of children. It can be stated that the results of our study in the pediatric population confirm the conclusion from the study of Yan et al. [25] that serum FGF-21 is a potential biomarker indicating hepatic fat content in adults with mild or moderate NAFLD but not severe liver disease manifestation in the course of NAFLD.

In addition to the lack of liver biopsy results, in the study group of children discussed above, our work has several limitations. Selection bias should be taken under consideration because the patients were from a tertiary center - Hepatology Department (dealing with various liver disorders), so the children enrolled to the study were previously tested for suspected liver disease. The relatively small sample size (especially of children with severe liver steatosis) limits the generalizability of our findings. However, it should be stressed, that studies conducted in children may be more convincing than those in adults because children have far fewer potential confounding factors and the disease process is usually less advanced.

5. Conclusions

FGF-21 can be considered as a suitable biomarker in predicting total intrahepatic lipid content and fatty liver in obese children. The results of the other hepatokines (SELENOP, SHBG) studies suggest that they are less important in the pathogenesis of NAFLD, although further research is required.

Conflict of interests

The authors declare no conflicts of interests.

Financial disclosure

This study was financially supported by grants from the Medical University of Bialystok, Poland. Grant No: 143-43618L, N/ST/ZB/15/001/1143 (153-43770L, N/ST/ZB/16/002/1143).

The authors contribution

Study Design: Marta Flisiak-Jackiewicz, Dariusz Marek Lebensztejn

Data Collection: Marta Flisiak-Jackiewicz, Anna Bobrus-Chociej, Eugeniusz Tarasow, Malgorzata Wojtkowska, Dariusz Marek

Lebensztejn

Statistical Analysis: Marta Flisiak-Jackiewicz, Dariusz Marek Lebensztejn

Data Interpretation: Marta Flisiak-Jackiewicz, Natalia Wasilewska, Dariusz Marek Lebensztejn

Manuscript Preparation: M Marta Flisiak-Jackiewicz, Anna Bobrus-Chociej, Natalia Wasilewska, Eugeniusz Tarasow, Malgorzata Wojtkowska, Dariusz Marek Lebensztejn

Literature Search: Marta Flisiak-Jackiewicz, Dariusz Marek Lebensztejn

Funds Collection: Dariusz Marek Lebensztejn

References

[1] Vajro P, Lenta S, Socha P, Dhawan A, McKiernan P, Baumann U, et al. Diagnosis of nonalcoholic fatty liver disease in children and adolescents: position paper of the ESPGHAN Hepatology Committee. J Pediatr Gastroenterol Nutr 2012;54:700–13.

[2] Pacifico L, Nobili V, Anania C, Verdecchia P, Chiesa C. Pediatric nonalcoholic fatty liver disease, metabolic syndrome and cardiovascular risk. World J Gastroenterol 2011;17:3082–91.

[3] Parola M, Marra F. Adipokines and redox signaling: impact on fatty liver disease. Antioxid Redox Signal 2011;15:461–83.

[4] Reschke S, Eckel J. Adipo-myokines: two sides of the same coin – mediators of inflammation and mediators of exercise. Mediators Inflamm 2013. 320724.

[5] Stefan N, Haring H-U. The role of hepatokines in metabolism. Nat Rev Endocrinol 2013;9:144–52.

[6] Lebensztejn DM, Flisiak-Jackiewicz M, Bialokoz-Kalinowska I, Bobrus-Chociej A, Kowalska Irina. Hepatokines and non-alcoholic fatty liver disease. Acta Biochim Pol 2016;63(3):459–67.

[7] Lebensztejn DM, Białokoz-Kalinowska I, Kłusek-Oksiuta M, Tarasow E, Wojtkowska M, Kaczmarski M. Serum fetuin A concentration is elevated in children with non-alcoholic fatty liver disease. Adv Med Sci 2014;59(1):81–4.

[8] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentration in man. Diabetologia 1985;28:412–9.

[9] Saverymuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. Br Med J 1986;292:13–5.

[10] Tarasów E, Siergiejczyk L, Panasiuk A, Kubas B, Dzienis W, Prokopowicz D, et al. MR proton spectroscopy in liver examination of healthy individuals in vivo. Med Sci Monit 2002;8:36–40.

[11] Yilmaz Y, Eren F, Yonal O, Kurt R, Aktas B, Celikel CA, et al. Increased serum FGF21 levels in patients with nonalcoholic fatty liver disease. Eur J Clin Invest 2010;40(10):887–92.

[12] Li H, Fang Q, Gao F, Fan J, Zhou J, Wang X, et al. Fibroblast growth factor 21 levels are increased in nonalcoholic fatty liver disease patients and are correlated with hepatic triglyceride. J Hepatol 2010;53:934–40.

[13] Li H, Dong K, Fang Q, Hou X, Zhou M, Bao Y, et al. High serum level of fibroblast growth factor 21 is an independent predictor of non-alcoholic fatty liver disease: a 3-year prospective study in China. J Hepatol 2013;58(3):557–63. https://doi.org/10.1016/j.jhep.2012.10.029.

[14] Shen J, Chan HL, Wong GL, Choi PC, Chan AW, Chan HY, et al. Non-invasive diagnosis of non-alcoholic steatohepatitis by combined serum biomarkers. J Hepatol 2012;56:1363–70.

[15] Shen Y, Ma X, Zhou J, Pan X, Hao Y, Zhou M, et al. Additive relationship between serum fibroblast growth factor 21 level and coronary artery disease. Cardiovasc Diabetol 2013;12:124.

[16] Reinehr T, Woelfle J, Wunsch R, Roth C. Fibroblast growth factor 21 (FGF-21) and its relation to obesity, metabolic syndrome, and nonalcoholic fatty liver in children: a longitudinal analysis. J Clin Endocrinol Metab 2012;97(6):2143–50.

[17] Giannini C, Feldstein AE, Santoro N, Kim G, Kursawe R, Pierpont B, et al. Circulating levels of FGF-21 in obese youth: associations with liver fat content and markers of liver damage. J Clin Endocrinol Metab 2013;98(7):2993–3000.

[18] Sodhi K, Bracero L, Feyh A, Nichols A, Srikanthan K, Latif T, et al. Role of serum biomarkers in early detection of non-alcoholic steatohepatitis and fibrosis in West Virginian children. J Clin Cell Immunol 2016;7(1):393.

[19] Alisi A, Ceccarelli S, Panera N, Prono F, Petrini S, De Stefanis C, et al. Association between serum atypical fibroblast growth factors 21 and 19 and pediatric non-alcoholic fatty liver disease. PLoS One 2013;8(6). e67160.

[20] Choi HY, Hwang SY, Lee CH, Hong HC, Yang SJ, Yoo HJ, et al. Increased selenoprotein P levels in subjects with visceral obesity and nonalcoholic fatty liver disease. Diabetes Metab J 2013;37:63–71.

[21] Polyzos S, Kountouras J, Tsatsoulis A, Zafeiriadou E, Katsiki E, Patsiaoura K, et al. Sex steroids and sex hormone-binding globulin in postmenopausal women with nonalcoholic fatty liver disease. Hormones 2013;12(3):405–16.

[22] Hua X, Sun Y, Zhong Y, Feng W, Huang H, Wang W, et al. Low serum sex hormone-binding globulin is associated with nonalcoholic fatty liver disease in type 2 diabetic patients. Clin Endocrinol (Oxf) 2014;80(6):877–83.

[23] Saito Y, Misu H, Takayama H, Takashima S, Usui S, Takamura M, et al. Comparison of human Selenoprotein P determinants in serum between our original methods and commercially available kits. Biol Pharm Bull 2018;41:828–32.

[24] Longo R, Pollesello P, Ricci C, Masutti F, Kvam BJ, et al. Proton MR spectroscopy in quantitative in vivo determination of fat content in human liver steatosis. J Magn Reson Imaging 1995;5:281–5.

[25] Yan H, Xia M, Chang X, Xu Q, Bian H, Zeng M, et al. Circulating fibroblast growth factor 21 levels are closely associated with hepatic fat content: a cross-sectional study. PLoS One 2011;6(9). e24895.

[26] Hui E, Xu A, Yang HB, Lam KSL. Obesity as the common soil of non-alcoholic fatty liver disease and diabetes: role of adipokines. J Diabetes Invest 2013;4(5):413–25.

[27] Liu J, Xu Y, Hu Y, Wang G. The role of fibroblast growth factor 21 in the pathogenesis of non-alcoholic fatty liver disease and implications for therapy. Metabolism 2015;64(3):380–90.

[28] Zhang Y, Lei T, Huang JF, Wang SB, Zhou LL, Yang ZQ, et al. The link between fibroblast growth factor 21 and sterol regulatory element binding protein 1c during lipogenesis in hepatocytes. Mol Cell Endocrinol 2011;342:41–7.

[29] Li K, Li L, Yang M, Liu H, Boden G, Yang G. The effects of fibroblast growth factor-21 knockdown and over-expression on its signaling pathway and glucose-lipid metabolism in vitro. Mol Cell Endocrinol 2012;348:21–6.

[30] Lee J, Hong S-, Park SE, Rhee E-, Park C-, Oh K-, et al. Exendin-4 regulates lipid metabolism and fibroblast growth factor 21 in hepatic steatosis. Metab Clin Exp 2014;63(8):1041–8.

[31] Sypniewska G. Laboratory assessment of cardiometabolic risk in overweight and obese children. Clin Biochem 2015;48(6):370–6.

[32] Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, Maratos-Flier E. Hepatic fibroblast growth factor 21 is regulated by PPAR alpha and is a key mediator of hepatic lipid metabolism in ketotic states. Cell Metab 2007;5:426–37.

[33] Xu J, Lloyd DJ, Stanislaus CHale S, Chen M, Sivits G, et al. Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in diet-induced obese mice. Diabetes 2009;58:250–9.

[34] Fletcher JA, Meers GM, Laughlin GM, Ibdah JA, Thyfault JP, Rector RS. Modulating fibroblast growth factor 21 in hyperphagic OLETF rats with daily exercise and caloric restriction. Appl Physiol Nutr Metab 2012;37:1054–62.

[35] Dezofi A, Baumann U, Dhawan A, Durmaz O, Fischler B, Hadzic N, et al. Liver biopsy in children: position paper of the ESPGHAN Hepatology Committee. J Pediatr Gastroenterol Nutr 2015;60(3):408–20.