PARAMETERS OF CARBOHYDRATE METABOLISM IN CHILDREN WITH NON-ALCOHOLIC FATTY PANCREAS

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Abstract: *The aim of the study is to establish the features of carbohydrate metabolism in children with nonalcoholic fatty pancreas disease. Materials and methods: We observed 77 children aged 7-17 years old. The pancreatic steatosis was evaluated by ultrasonography with quantitative evaluation of the ultrasonic attenuation coefficient of the pancreas using the Ultima Expert apparatus Radmir, Ukraine). Children were divided into 3 groups: 1st group - 42 children with pancreatic steatosis and obesity/overweight; 2nd group - 25 obese/overweight children without pancreatic steatosis; 3rd group - 10 children with normal weight. The blood serum insulin level was determined by immunoassay, followed by the calculation of the HOMA1-IR, HOMA-2. Results: Patients with pancreatic steatosis had significantly higher HOMA1-IR, HOMA-2 level compared to children without steatosis p<0,05). The average coefficient of ultrasound attenuation during pancreatic steatometry was significantly higher in patients with pancreatic steatosis and negatively correlated with cell sensitivity to insulin r=-0,26; p<0,05). Conclusion: The study of the HOMA1-IR, HOMA-2 index showed an increase in the secretory function of β-cells in children with pancreatic steatosis, along with a decrease in cellular sensitivity to insulin.*

INTRODUCTION

Overweight and obesity can lead to ectopic fat accumulation involving such organs as the liver, skeletal muscles, heart and pancreas.(1)

Visceral fat and ectopic fat deposits play an important role in the pathogenesis of obesity-related metabolic effects: recent studies have showed that the presence of steatosis of the internal organs is a better predictor of cardiovascular risk than the body mass index (BMI).(2) In addition, non-alcoholic fatty liver disease (NAFLD) is associated with insulin resistance, type 2 diabetes, metabolic syndrome, atherosclerosis and high risk of cardiovascular events.(3)

Recently, much attention has been paid to the ectopic fat deposition in the pancreas (pancreatic steatosis), which after exception of the secondary etiology of steatosis is explained by the term "non-alcoholic fatty pancreas disease" (NAFPD).(4) Steatosis of the pancreas can promote the development of chronic pancreatitis and pancreatic cancer, aggravate the course of acute pancreatitis.(5) In addition, there is evidence that pancreatic steatosis plays an important role in the pathogenesis of glucose metabolism disorders.(6)

Understanding the importance of early diagnosis of carbohydrate metabolism disorders in children and identification of a high-risk group for pre-diabetes, we think that it is important to study the influence of pancreatic steatosis on the development of the corresponding disorders.

PURPOSE

The purpose of our work was to establish the characteristics of carbohydrate metabolism in children with non-alcoholic fatty pancreatic disease; to study the effect of pancreatic fat on the development of insulin resistance and glucose metabolism disorders.

MATERIALS AND METHODS

We examined 77 children aged 7 to 17 years, the average age of the subjects was (11,90±2,83) years. All patients and their parents had given their agreement to participation in the study. Among the examined children, obesity and overweight were diagnosed in 67 children (87,01%), 10 (12,99%) children had a normal weight and so, made up a control group. Sonographic signs of pancreatic steatosis were diagnosed in 42 children (61,76%), 25 children (36,76%) with obesity and overweight did not have signs of steatosis. The assessment of trophic status was carried out according to the WHO recommendations in accordance with the percentile tables of BMI values for age and sex.(7). Diagnosis of abdominal obesity in children was carried out in accordance with the recommendations of the International Diabetes Federation (IDF).(8) Ultrasound examination of the abdomen was performed according to the generally accepted technique using Toshiba Xario apparatus (Japan). The pancreatic steatosis was diagnosed by echographic examination in a pairwise comparison of the echogenicity of the pancreas, kidney and retroperitoneal fat. The presence of liver steatosis was established in accordance with the characteristic of ultrasound signs as an increase in the echogenicity of the liver compared with the echogenicity of the kidneys, the distal attenuation of the ultrasound, the erasure of the vascular pattern of the liver. For the purpose of pancreatic steatosis diagnosing, steatometry of the pancreas was performed - a quantitative evaluation of the ultrasonic attenuation coefficient during sonography of the pancreas, was carried out using the Ultima Expert (Radmir, Ukraine). With turning on the function of steatometry, study was carried out to obtain repeated values of the ultrasonic attenuation coefficient, 5 measurements were performed in each section of the gland with the determination of the mean value of ultrasound attenuation

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coefficient (UAC). A transient liver elastography (Fibroscan 502 Touch) was also used to diagnose hepatic steatosis with the definition of a controlled attenuation parameter (CAP). All patients were examined to exclude secondary steatosis of the liver and pancreas (excluding viral, autoimmune hepatitis, drug-induced liver and pancreas pathology). According to presence of obesity/overweight and pancreatic steatosis, children were divided into the following groups: 1st group - 42 children with existing steatosis of the pancreas and obesity/overweight, 2nd group - 25 obese/overweight children with no signs of pancreatic steatosis, group 3 - 10 children with normal weight who had no signs of pancreatic steatosis.

The serum insulin content was determined by an enzyme immunoassay using the "DRG International, inc". (Germany) kit. The homeostasis model assessment (HOMA1-IR) was calculated by the formula:(1)

HOMA1-IR = (Fasting glucose (mmol/l) x Fasting insulin (μU/ml)) / 22,5.(1)

As a normative value of the HOMA1-IR level, it was taken 75 percentile for the general population, which is considered as 2,78 (11).

The HOMA-2 (updated homeostasis model assessment) index was calculated using the computer program "HOMA Calculator" © Diabetes Trial Unit - University of Oxford, with the determination of insulin sensitivity (% S) and beta-cell function (% B). The normal value was 100%.

An oral glucose tolerance test (OGTT) was performed with a standard load at 1,75 mg/kg dry glucose, but not more than 75 g; we measured fasting plasma, as well as 60 and 120 minutes after loading with glucose.

Nonparametric statistics methods were used for specifying quantitative characteristics, the data were presented as a median and the boundaries of the interquartile segment (25; 75%), for qualitative characteristics - in the form of relative indicators. The significance of the differences was evaluated with the Mann-Whitney U-criterion. When comparing qualitative indicators, the reliability of the differences was estimated with the exact Fisher criterion. Correlation analysis was performed with the calculation of the rank correlation coefficient P.Spearmen-R and Pearson (depending on the expressed data scale). Significance of differences were considered when $p<0,05$. The tendency was determined at $p<0,10$. Statistical processing of the results of the research was carried out using the methods of variation statistics implemented by the standard package of applied programs Statistica 7.0.

RESULTS

Anthropometric data

Groups 1 and 2 did not differ by age and gender, but children of the 3rd group were older than children of the 1st group $p<0,05$). In the analysis of anthropometric data it was established that the growth Z-score did not differ significantly in groups $p>0,1$ (table no. 1). BMI Z-score, waist circumference (WC) and percentile of WC were significantly higher in the 1st group than in the 2nd and 3rd groups $p<0,05$). The incidence of obesity and abdominal obesity was significantly higher in patients in group 1 compared with group 2 $p<0,05$).

Table no. 1. Anthropometric and demographic data (median range)

Parameter	1 gr n=42	2 gr n= 25	3 gr n=10	p1	p2	p3
Height sm)	154,0 (145,0; 165,0)	156,0 (140,0; 168,0)	168,0 (156,0; 173,0)	0,64	0,190	0,14
Weight kg)	55,0 (50,0; 75,0)	59,0 (42,0; 70,0)	51,0 (43,0; 59,0)	0,21	0,038	0,18
BMI kg/m2)	24,76 (22,6; 27,6)	23,73 (21,4; 25,2)	18,33 (17,7; 19,0)	0,028	0,00002	0,0005
BMI z-score	2,25 (2,03; 2,94)	1,97 (1,79; 2,08)	0,95 (0,90; 0,99)	0,0003	0,00002	0,00004
Height z-score	1,13 (0,21; 2,09)	0,91 (0,66; 1,77)	0,78 (0,41; 0,85)	0,94	0,16	0,26
Age years)	11,5 (10,0; 13,0)	11,50 (9,0; 15,0)	14,0 (10,0; 16,00)	0,98	0,03	0,11
Male sex, n %)	27 64,2)	12 48)	5 50)	0,15	0,31	0,60
WC sm)	86,0 (81,0; 93,0)	78,0 (71,0; 84,0)	63,5 (59,0; 65,0)	0,0005	0,0001	0,00004
WC percentile	96,69 (92,6; 100,46)	88,03 (76,25; 91,73)	10,07 (10,0; 25,5)	0,0001	0,000001	0,005
Obesity, abs. n %)	32 76,19)	11 26,19)	0	0,017	-	-
Overweight, abs. %)	10 23,81)	14 56,0)	0	0,017	-	-
Abdominal obesity, abs. %)	36 85,7)	10 40,0)	0	0,006	-	-

p1 – significance of differences between groups 1 and 2;
p2 – significance of differences between groups 1 та 3;
p3 – significance of differences between groups 2 та 3.

Sonological study data

The presence of liver steatosis was detected in more than half of the 1st group children and in the tenth part of the 2nd group children (table no. 2). Average ultrasound attenuation coefficient of the pancreas acquired maximum values in children with pancreatic steatosis, level of UAC was also significantly higher in children of the 1st group $p<0,05$ (table no. 2).

Table no. 2. Data of sonological study (median range)

Parameter	1 gr n=42	2 gr n= 25	3 gr n=10	p1	p2	p3
UAC, dB/sm	2,57 (2,31; 2,75)	2,25 (1,99; 2,38)	1,82 (1,44; 1,87)	0,0003	0,00006	0,0011
CAP, dB/m	232,5 (198,5; 264,0)	196,0 (167,0; 215,0)	166,0 (157,0; 192,0)	0,0014	0,00029	0,09
Presence of liver steatosis according to ultrasound study, n %)	25 59,5%)	3 12,0%)	0	0,001	-	-

p1 – significance of differences between groups 1 and 2;
p2 – significance of differences between groups 1 та 3;
p3 – significance of differences between groups 2 та 3.

Indicators of carbohydrate metabolism in children of the studied groups.

The increase in HOMA-IR level was observed in 38 children 90,47%) in the 1st group and in 16 64%) children of the 2nd group. Fasting glucose levels and glycosylated hemoglobin levels did not reveal significant differences in the studied groups (table no. 3).

Table no.3. Parameters of carbohydrate metabolism (median range)

Parameter	1 group n=42	2 group n= 25	3 group n=10	p1	p2	p3
Insulin, mcU/ml	22,8 (15,4; 28,0)	13,96 (9,08; 18,4)	9,15 (7,25; 11,8)	0,004	0,00014	0,056
HOMA1-IR	4,86 (3,11; 6,16)	3,56 (1,9; 3,8)	1,86 (1,60; 3,73;)	0,004	0,00005	0,055
HOMA-2	2,95 (1,9; 3,45)	1,8 (1,25;2,4)	1,2 (0,9; 1,55)	0,055	0,00012	0,056
Glycosylated hemoglobine, %	3,98 (3,14; 4,90)	3,58 (3,02; 4,94)	3,38 (2,9; 4,21)	0,59	0,056	0,50
Fasting plasma glucose level, mmol/l	4,6 (4,1; 4,8)	4,7 (4,1; 4,9)	4,3 (4,1; 4,6);	0,58	0,57	0,30
% B	228,75 (142,85; 260,0)	135,25 (100,05; 181,30)	119,95 (92,75; 144,8)	0,006	0,007	0,38

% S	34,10 (28,9; 52,05)	55,25 (42,30; 82,55)	85,0 (92,75; 144,80)	0,003	0,0001	0,06

p1 – significance of differences between groups 1 and 2;
p2 – significance of differences between groups 1 та 3;
p3 – significance of differences between groups 2 та 3.

Patients with steatosis had significantly higher median values of insulin and HOMA-IR compared to children without steatosis both with obesity and normal weight (p<0,05) (table no. 3). Comparison of these parameters in children with obesity without steatosis and children with normal weight did not show significant differences, however, there was a tendency to increase the level of insulin and HOMA-IR in children with obesity and overweight (p=0,055).

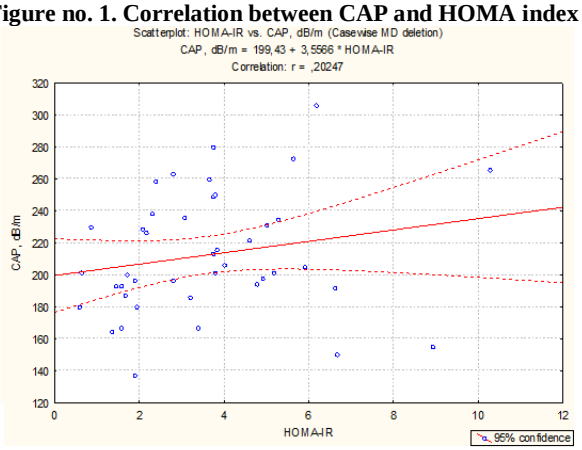
Regarding the level of HOMA-2, it acquired the maximum value in children with steatosis, which was higher in obese children without steatosis than in children with normal weight. % B was significantly higher in patients in group 1 than in the 2nd and 3rd groups. % S among children of the 1st group was significantly lower than the corresponding indicator for the 2nd and 3rd groups (p <0,05).

Table no. 4. Correlation between the parameters of carbohydrate metabolism and anthropometric and sonological data

Parameter	Insulin	HOMA1-IR	HOMA-2	% B	% S	Fasting plasma glucose level. mmol/l	Glucose level 60 min after load, mmol/l	Glucose level 120 min after load, mmol/l
Pancreatic steatosis ultrasound)	0,38*	0,38*	0,46*	0,22	-0,19	0,16	0,24*	0,20
Liver steatosis ultrasound)	0,33*	0,29*	0,38*	0,29*	-0,09	0,02	0,3	0,21
WC percentile	0,33*	0,32*	0,38*	0,17	-0,17	0,13	0,08	0,12
BMI z-score	0,17	0,16	0,24	0,05	-0,10	0,1	0,03	0,14
BMI kg/m2)	0,52*	0,53*	0,52*	0,21	-0,23	0,15	0,20	0,11
WC sm)	0,52*	0,54*	0,54*	0,18	-0,32*	0,20	0,23	0,13
CAP, dB/m	0,30*	0,20*	0,34*	0,20	-0,17	0,24*	0,20	0,07
UAC, dB/sm	0,21	0,20	0,24	0,19	-0,26*	0,09	-0,07	-0,13
Age years)	-0,24	0,25*	0,22	0,01	-0,24	0,25	0,25	0,07

* – significance of differences p<0,05

Figure no. 1. Correlation between CAP and HOMA index



Correlation analysis found that the HOMA1-IR index and HOMA-2 index positively correlated with the presence of ultrasound signs of liver and pancreatic steatosis, the presence of abdominal obesity and age of the subjects (p<0,05) (figures no. 1, 2, table no. 4). Indicator % B showed a positive correlation with the presence of liver steatosis (figure no 1), the index % S, in its turn, revealed a negative correlation with WC and UAC of the pancreas (figure no. 3) (p <0,05).

Figure no. 2. Correlation between HOMA-IR and WC percentile

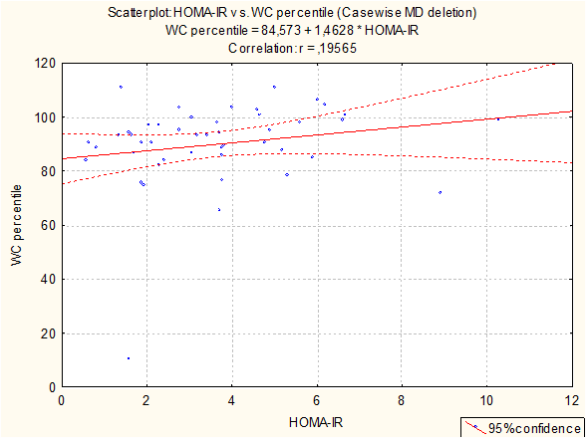
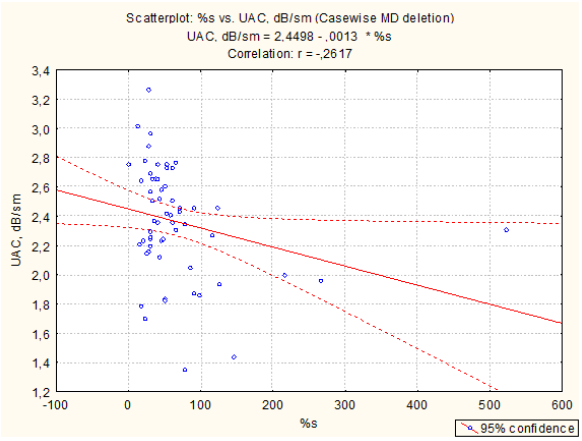


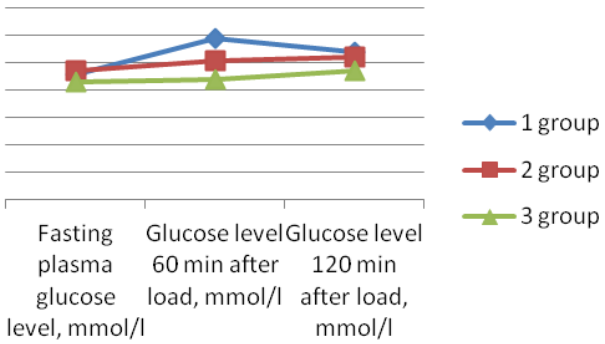
Figure no. 3. Correlation between %S and UAC



Pancreatic steatosis and glucose metabolism

It was found that children with pancreatic steatosis had higher levels of glycemia 60 minutes after loading (p<0,05) (figure no. 4).

Figure no. 4. Data of OTTG in the examined children



The level of fasting and glycemia 120 minutes after loading did not show significant difference between groups. It

was found that fasting glycemia was correlated with the CAP level (table no. 5). The level of glycemia 60 min after load was correlated with the presence of ultrasound symptoms of pancreatic steatosis (table no. 5).

During analysis of the obtained data, it was found that the impaired glucose tolerance was observed in 1 patient in the 1st group, impaired fasting glycemia was diagnosed in 2 patients of the 1st group and was not observed in children of the 2nd and 3rd groups.

Risk factors for Homa-IR elevation

The study found that the risk factors for increasing HOMA-IR as one of the most commonly used tests for diagnosing insulin resistance were liver steatosis and pancreatic steatosis, abdominal obesity ($p<0,05$). In the analysis of the general model, it was found that pancreatic steatosis was an independent factor in increasing insulin resistance index, and the presence of puberty period has shown a tendency for being significant risk factor for increasing HOMA1-IR (table no. 5).

Table no. 5. Risk factors for HOMA1-IR elevation

Factors	Univariative analysis			Multivariative analysis	
	OR 95 CI)	RR 95 CI)	p	OR	p
Pancreatic steatosis ultrasound)	15,2 4,04-15,07)	2,71 1,69-4,35)	0,0004	13,26 2,07-85,10)	0,005
Liver steatosis ultrasound)	7,29 1,84-28,93)	1,85 1,30-2,62)	0,004	2,55 0,32-20,12)	0,36
Obesity	1,64 0,55-4,85)	1,45 1,00-2,08)	0,37	0,26 0,035-1,93)	0,18
Abdominal obesity	3,67 1,20-11,20)	1,91 1,94-2,92)	0,02	1,17 0,21-6,42)	0,85
Male sex	2,16 0,73-6,37)	1,26 0,89-1,08)	0,16	2,0 0,34-11,86)	0,43
Puberty	2,86 0,81-10,07)	1,44 1,01-2,05)	0,096	4,73 0,81-27,66)	0,08

DISCUSSIONS

There is evidence that accumulation of fat in the pancreas can potentially affect insulin-producing β-cells, both directly due to the lipotoxicity associated with the release of free fatty acids, and through the activation of proinflammatory pathways.(1,9,10) Obesity, especially abdominal type, is accompanied by the development of insulin resistance, which is confirmed by the HOMA1-IR increasing along with BMI growth.(11) The content of pancreatic fat, as shown in the study of K.A. Lê, positively correlates with the level of circulating free fatty acids.(12) Huge amount of studies in patients with pancreatic steatosis showed that the content of pancreatic fat negatively correlated with insulin secretion in patients with impaired fasting glucose or impaired glucose tolerance.(13,14) Meanwhile, in patients with normoglycemia a significant association between pancreatic fat content and β-cell function was not confirmed.(14) J. Staaf et al.(1) found that increased pancreatic fat fraction can potentially lead to β-cells stress and insulin processing dysfunction and insulin resistance. The authors came to the conclusion that other deposits like visceral and hepatic fat are more associated with insulin resistance. J. S. Lee, in turn, acknowledged that the HOMA1-IR level increased simultaneously with the increase of the pancreatic steatosis degree; HOMA1-IR level was associated with the presence of pancreatic steatosis after adjusting for age, BMI and lipid profiles, but the relationship between pancreatic steatosis and HOMA1-IR disappeared after further adjustments to the visceral fat distribution, which provides that visceral fat may mediate the association between insulin resistance and pancreatic steatosis development.(15)

Similar conclusions were also obtained in the study by A. P. Rossi et al. (16) who found that insulin resistance was associated with hepatic steatosis instead of pancreatic steatosis in obese adults.

In our work, it has been established that the HOMA1-IR elevation was observed in more than 90% of children with pancreatic steatosis, and in 80,6% of obese/overweight children. Also, in our study it was demonstrated that WC, as a marker of visceral fat distribution, showed a positive correlation with the level of insulin and the corresponding indexes of insulin resistance. At the same time average HOMA1-IR level in children with pancreatic steatosis was significantly higher in comparison to children without steatosis regardless of the presence of excess weight, indicating a strong position of insulin resistance in the pathogenesis of nonalcoholic fatty pancreatic disease. The results of our study revealed that the presence of pancreatic steatosis was associated with 2,7-fold increase in relative risk of HOMA1-IR elevation, while hepatic steatosis and abdominal obesity - in 1,85-fold and 1,91-fold increase in corresponding risk, respectively. In our study, abdominal obesity, liver steatosis, pancreatic steatosis were the risk factors for the HOMA1-IR increasing, however, when analyzing the general model, a significant relationship was maintained with pancreatic steatosis.

It should be noted that transient insulin resistance is a normal component of puberty state. Insulin sensitivity is higher before puberty (stage 1 by Tanner) and reaches its lowest point in prepubertal period (stage 3 by Tanner). In this case, in order to compensate for a short-term decrease in insulin sensitivity in adolescence, insulin secretion increases and is restored after puberty.(17) However, neither the level of testosterone nor estradiol has shown association with insulin resistance. Since the levels of growth hormone (GH) and insulin-1 growth factor (IRF-1) are higher in adolescence than in adolescent and adult years, it is possible that insulin resistance may be related to the GH / IRF axis -1.(18) However, there is evidence that in adolescent obesity, baseline insulin sensitivity is not restored at the end of puberty, and is associated with obesity and with complications such as type 2 diabetes mellitus.(18) In our study in logistic model, puberty showed tendency for being a significant risk factor for increasing HOMA1-IR.

HOMA1-IR is the first described model for assessing insulin resistance. As reported by meta-analysis of 2013 year, HOMA1-IR can be used as a predictor of cardiovascular disease.(19) However, according to several studies, the most accurate representation of the metabolic processes demonstrates the HOMA2-IR model - since it simulates the feedback between insulin and glucose in various body organs.(20) % B reflects the function of β-cell as a percentage of β-cell function comparing to healthy subjects and % S - insulin sensitivity as a percentage of cell sensitivity comparing to healthy subjects. HOMA2-IR is corrected for resistance to peripheral and hepatic glucose, and also includes correction of glucose loss in the kidneys, making it suitable for use in people with hyperglycaemia.(20,11)

Analysing HOMA2-IR levels, we found that this index was significantly higher in patients with pancreatic steatosis, and correlated with the presence of liver steatosis diagnosed by ultrasound and CAP, also pancreatic steatosis according to ultrasound data. Interestingly, secretory activity of β-cells and the level of fasting glucose positively correlated with the presence of liver steatosis (according to ultrasound and CAP, respectively), whereas the insulin sensitivity was negatively associated with pancreatic steatosis (actually UAC) and WC, that suggests different mechanisms of pancreatic and liver steatosis influence on the development of insulin resistance. It is assumed that the ectopic accumulation of fat is organoselective, possibly due to genetic factors. Visceral fat is associated with

liver and pancreatic fat, but the question whether visceral fat is the main cause of fat accumulation in the pancreas remains open.

We also conducted an analysis of the OGTT, since the question whether the NAFPD has an independent effect on glucose metabolism remains controversial. According to A. P. Rossi et al. it was found that even after correcting the logistic model for obesity and NAFLD, pancreatic steatosis was still positively associated with diabetes and prediabetes, but only in male representatives.(16) In the van der N. J. Zijl et al. study, the highest level of pancreatic fat fraction was found in patients with diabetes.(14) In a study by R. Begovatz et al. (21), there was no association between fatty tissue infiltration and the first phase of insulin response after oral glucose load, regardless of the presence of glucose intolerance. These opposite data can be explained by methodological differences (both in the methods of diagnosis of the pancreatic steatosis and methods for evaluating the function of beta cells) or differences in age and ethnic composition of the subjects.

In our work we demonstrated the growth of plasma glucose level after a standard load in children with pancreatic steatosis. Our data also indicated increased secretory activity of beta-cells and decreased insulin sensitivity. Impaired glucose tolerance was observed in one child with pancreatic steatosis, and impaired of fasting glucose in 2 children with pancreatic steatosis, indicating that the majority of children had compensation of β-cell function.

Thus, unlike NAFLD, the pathophysiological mechanisms and the clinical significance of pancreatic steatosis are less known. Previous studies have shown that fatty infiltration of the pancreas contributes to the loss of β-cellular mass and function, which may lead to the development of type 2 diabetes. On the other hand, insulin resistance may increase the accumulation of ectopic fat, increasing the delivery of free fatty acids, and then stimulate anabolic process through hyperinsulinemia.(2,22) According to our study, the growth of glycemia in 60 minutes after loading and decrease (%S) may indicate a dominant role in reducing the cell's sensitivity to insulin as the earliest consequence of pancreatic steatosis. Taking into account the above-mentioned studies and the results of our own study, it can be assumed that metabolic disorders may develop practically simultaneously with NAFPD and NAFLD.

Because of the discrepancy between the results of available studies, whether pancreatic steatosis is a cause of insulin resistance or is only part of metabolic disturbances during visceral obesity,(23,24) remains an open question. As the epidemic of obesity grows, NAFPD becomes a health problem that deserves attention. However, new studies as well as our study have shown that NAFPD should be considered not only as a simple inert fat accumulation, but also as an early marker of insulin resistance. Further research should focus on pathophysiological events in pancreatic steatosis, and thus, revealing the role of NAFPD in the development of metabolic syndrome and glucometabolic disorders.

CONCLUSIONS

1. Children with pancreatic steatosis demonstrated higher insulin and HOMA1-IR levels compared to children without pancreatic steatosis (both with obesity/overweight and normal weight).
2. The study of the HOMA-2 index showed growth of the β-cells secretory function in children with pancreatic steatosis along with a decrease of cellular sensitivity to insulin.
3. Paediatric pancreatic steatosis was characterized by a increase in 60 min glycemia after glucose loading compared to children without steatosis.
4. Steatosis of the pancreas can be considered as a risk factor for insulin resistance development. In children with pancreatic steatosis, abdominal obesity and liver steatosis should be considered additionally among factors having an effect on the development of insulin resistance.
5. The average coefficient of ultrasound attenuation during pancreatic steatometry was significantly higher in patients with pancreatic steatosis and revealed a negative correlation with cell sensitivity to insulin. The obtained results testify the prospect of further use of this diagnostic method.

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