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Original article

Reversibility of Hyperglycemic States in Children with Obesity-Diagnostic Pitfalls in the Assessment of Glucose Metabolism in Children and Adolescents with Obesity

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What is already known about this topic?
It is well known that current rate of weight gain in population of children and adolescents is enormous. As the prevalence of obesity increases, so does the occurrence of associated comorbidities. One of them are glucose metabolism disorders. Unfortunately, the data regarding glucose metabolic alterations in children and adolescents with obesity is firstly, limited and secondly, significantly varies depending on the different studies.

What this study adds to the literature?
Therefore, in this study we took an attempt to establish the prevalence of hyperglycemic states and its reversibility in pediatric patients with obesity as well as factors determining the reversibility of prediabetes or progression to diabetes.

Abstract
Objective: Disorders of glucose metabolism in children with obesity are less common than in adults. There is also evidence that they may be transient. The aim of this study was to determine the prevalence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), type 2 diabetes mellitus (DM2) and its reversibility in pediatric patients with obesity and to define the factors determining the reversibility of prediabetes or progression to diabetes.
Methods: Retrospective analysis included 573 patients with obesity (mean BMI Z-score 4.4, 316 girls at mean age 13.5 years old, range 2.9-17.11, all Caucasians).
Results: The normal results of OGTT were present in 90.8 % (n=520) and prediabetes in 9.2% (n=53) (IFG 17%, IGT 88.7%, DM 0%) subjects. Among those who underwent OGTT twice, impaired glucose regulation was present in 9.3% subjects (n=5) (IFG 40%, IGT 80%, DM 0%) at baseline and in 14.8% subject (n=8) (IFG 25%, IGT 50%, DM 25%) at follow-up after lifestyle modification only. After 12-36 months of follow up, in the previous presence of IGT, 60% reverted to NGT, 20% persisted as IFG and 20% as IGT and no one progressed to DM. The risk factors for progression of glucose metabolism disorders were increase of BMI Z-score, and higher insulin levels, and HOMA-IR.
Conclusions: IFG and IGT are common in pediatric patients with obesity, while the progression to DM2 is a rare condition. Disorders of glucose metabolism disorders have reversible character. Every change of BMI Z-score has a significant impact on changes of glucose levels.
Keywords: Childhood obesity, glucose metabolism, type 2 diabetes

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Introduction
According to World Health Organization data, up to 35.5% of boys and 23.1% of girls at school-age in Poland are affected by overweight or obesity[1]. Moreover, current rate of weight gain in population of polish children and adolescents is the greatest in Europe[2]. As the prevalence of obesity increases, so does the occurrence of associated comorbidities. The most important impact on the risk for morbidity and premature death during adulthood has a number of metabolic changes like hypertension, dyslipidemia, atherosclerosis, steatohepatitis and glucose metabolism disorders[3]. Those glucose metabolism disorders are defined as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). The progression from normal glucose tolerance (NGT) to type 2 diabetes (DM2) through impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) also known as prediabetes is well described in obese adult population[4]. Although the underlying pathophysiology of this development is multifactorial, one of the most important factor is the balance between insulin sensitivity and insulin secretion[5]. The data regarding the natural history of glucose metabolic alterations in children and adolescents with obesity is limited[6]. It seems that contrary to the adults, both impaired fasting plasma glucose and after 120' postload glucose measurements as well as the insulin resistance (IR) may be reversible in pediatric population.

Aim
The aim of this study was to determine the prevalence of hyperglycemic states, such as: impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and type 2 diabetes (DM2) and its reversibility in pediatric patients with obesity. In addition, an attempt to define the factors determining the reversibility of prediabetes or progression to diabetes.

Material and Methods
This was a retrospective study performed in the Department of Pediatric and Adolescents Endocrinology, Children's University Hospital in Kraków. The study population consisted of 573 patients (316 girls and 256 boys at mean age 13.5 years old, range 2.9-17.11, all Caucasians) diagnosed and treated from 2000 to 2022. The inclusion criteria for the study were: BMI greater than or equal 95th percentile for age and sex, age below 18 years at the first visit and undergoing 2-h oral glucose tolerance test (OGTT)[7]. 54 patients from all 573 patients (29 girls and 25 boys at mean age 11.11 years old, range 3.7-16.1) underwent oral glucose tolerance test (OGTT) twice within 12-36 month. A week prior

to the oral glucose tolerance tests (OGTTs), patients received a normo-caloric, mixed diet. The oral glucose tolerance tests (OGTTs) were performed after an overnight fast at 08:00 a.m. after admission to the hospital. Two baseline samples were obtained for measurements of plasma glucose, insulin, total cholesterol, LDL and HDL fractions of cholesterol, triglycerides, uric acid and liver enzymes (alanine ALT and aspartate aminotransferase AST). Thereafter, flavored glucose in a dose of 1.75 g per kilogram of body weight (up to a maximum of 75 g) was given orally and blood samples were obtained after 120 minutes for the measurement of plasma glucose and insulin. Glucose concentration was measured by the dry chemistry method with a Vitros 5.1.FF machine (Ortho-Clinical Diagnostics). Insulin levels were measured by an immunoluminometric assay (ADVIA Centaur Siemens). HOMA-IR was calculated using the formula: Fasting insulin level (mU/L) × Fasting glucose level (mmol/L)/22.5. Each time weight, height, BMI, pubertal stage, systolic and diastolic blood pressure (mean of three measurements) were recorded and standardized in all patients. Weight and height were measured using a standardized calibrated scale and blood pressure was measured using an automatic sphygmomanometer. The presence of hypertension was assesed by 'Paediatric office blood pressure calculator' by HyperChildNET COST Action[8]. The diagnostic criteria for impaired fasting glucose (IFG) was a fasting blood glucose of 100–125 mg/dL (5.6–6.9 mmol/L), impaired glucose tolerance (IGT) was defined as a 2-hr plasma glucose level between 140 and 199 mg/dl (7.8–11.0 mmol/L) and diabetes mellitus (DM) as a fasting glucose level of 126 mg/dL (7.0 mmol/L) or higher (two abnormal readings required) or a two-hour plasma glucose level of more than 200 mg/dl (11.1 mmol/L) (one abnormal reading required)[9]. In the duration of follow up the interventions consisted of dietary and psychological guidance in order to achieve sustainable, long-term lifestyle changes. In general, the patients were not put on medications affecting glucose metabolism. To assess the differences between groups, an ANOVA and Kruskal-Wallis tests were used. Calculations were performed using the Statistica 13.0 software. A value of $P < 0.05$ was chosen as the level of significance.

Results

The mean BMI Z-score of the study group was 4.3 (range 2.0-9.9), BMI of the study group was 31.0 (range 18.9-81.3). The normal results of oral glucose tolerance test (OGTT) were present in 90.8 % (n=520). Prediabetes, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) was present in 9.2% subjects (n=53). In this group (34 girls and 19 boys) at mean age 14.0 years old (range 3.5-17.11) mean BMI Z-score was 5.0 (range 2.1-9.6), BMI was 32.8 (range: 23.4-42.7). The mean value of fasting glucose level was 4.5 mmol/L (range: 2.4-6.6). Impaired fasting glucose (IFG) was detected in 1.6 % cases (n=9). The mean post-load glucose level was 5.9 mmol/L (range: 2.4-11.0). Impaired glucose tolerance (IGT) was detected in 8.2 % participants (n=47). Three suffered from both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) disorder. No case of diabetes mellitus (DM) was detected. 54 patients (29 girls and 25 boys at mean age 11.11 years old, range 3.7-16.1, 13 children with a positive family history for type 2 diabetes) underwent oral glucose tolerance test (OGTT) twice within 12-36 month (for details see Table 1.). Among those who underwent oral glucose tolerance test (OGTT) twice, 49 (91%) normal results of oral glucose tolerance test (OGTT) at the baseline and 46 (85%) at follow up were received. At the baseline, prediabetes was diagnosed in 9.3% subjects (n=5). The mean value of fasting glucose level was 4.7 mmol/L (range: 4.1-6.4). Impaired fasting glucose (IFG) was detected in two cases (40%). The mean post-load glucose level was 5.8 mmol/L (range: 3.5-9.6). Prediabetes was detected in four participants (2 girls) (80%) – one patient presented both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) disorder. In the repeated test, prediabetes was diagnosed in 14.8% subject (n=8). The mean value of fasting glucose level was 4.8 mmol/L (range: 3.5-5.8). Impaired fasting glucose (IFG) was detected in two cases (25%). The mean post-load glucose level was 6.1 mmol/L (range: 3.2-12.2). Impaired glucose tolerance (IGT) was detected in four participants (2 girls) (50%). Two cases (25%) of diabetes mellitus (DM) were diagnosed (17.6 years old boy with BMI Z-score 4.4 (BMI 33.4) who had plasma insulin level in 0' 28 mIU/L (168.0 pmol/L) and in 120' 207 mIU/L (1242.0 pmol/L) and positive autoantibodies to islet cell (ICA) and protein tyrosine phosphatase (IA2); 13.7 years old boy with BMI Z- score 3.4 (BMI 29.6) who had undergone the treatment against acute lymphocytic leukemia). After 12-36 months of follow up, in the previous presence of impaired glucose tolerance (IGT) (3 girls and 2 boys at mean age 12.9 years old (range 11.2-14.7) and mean BMI Z-score 3.7 (range 2.3-6.0), mean BMI 29.7 (range 25.4-36.0), one child with a positive family history for type 2 diabetes), 60% (n=3) reverted to normal glucose tolerance (NGT) (1 girl and 2 boys, mean age 13.0 years old (range 11.5-14.7), mean BMI Z-score 3.8 (range 2.3-6.0), mean BMI 30.5 (range 25.4-36.0), 20% persisted as impaired fasting glucose (IFG) (one girl with a positive family history for type 2 diabetes, age 11.2 years old, BMI Z-score 3.4, BMI 27.3) and 20% as impaired glucose tolerance (IGT) (one girl, age 14.3 years old, BMI Z-score 3.9, BMI 29.6) and no one progressed to diabetes mellitus (DM). In 11.1% of all subjects (n=6) occurred new, not diagnosed at baseline disorders (see Figure 1). One of them who developed impaired glucose tolerance (IGT) had a positive family history for type 2 diabetes. All the metabolic changes within those groups are presented as follows (see Table 2). There was no statistically significant correlation between the incidence of disorders of glucose metabolism in the first and second oral glucose tolerance test (OGTT) and age, BMI Z-Score, blood pressure, total cholesterol, LDL, HDL, triglycerides, uric acid, ALT and AST (alanine and aspartate aminotransferase) levels. However, in children progressing from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT), the increase of BMI Z-score (mean 3.1 vs 4.0), increase of the insulin levels both in 0' (mean 17.3 mIU/L (103.8 pmol/L) vs. 29.7 mIU/L (178.2 pmol/L)) and in 120' (mean 92.5 mIU/L (555.0 pmol/L) vs. 207.1 mIU/L (1242.6 pmol/L)) and decrease of insulin sensitivity measured by HOMA IR (3.8 vs. 6.8) were observed. In youth who had persistent prediabetes, the increase of BMI Z-score between the two oral glucose tolerance tests (OGTTs) were noticed but smaller than in previous group (mean 3.6 vs. 4.0), the insulin levels in 0' (mean 51 mIU/L (306.0 pmol/L) vs. 37 mIU/L (222.0 pmol/L)) and in 120' (mean 131.1 mIU/L (786.6 pmol/L) vs. 141 mIU/L (846.0 pmol/L)) were comparable. In those who reverted from impaired glucose tolerance (IGT) to normal glucose tolerance (NGT), the patients maintained comparable BMI Z-score (mean 2.7 vs. 2.8), there was the decrease of the insulin levels both in 0' (mean 21.2 mIU/L (127.2 pmol/L) vs. 17.3 mIU/L (103.8 pmol/L)) and in 120' (mean 213.4 mIU/L (1280.4 pmol/L) vs. 77.7 mIU/L (466.2 pmol/L)) and also the increase of insulin sensitivity between the assessments (HOMA IR mean 4.5 vs. 3.5). The insulin level at baseline in 120' in this group was particularly high. The alterations did not seem to be dependent on age or sexual development. In addition, the statistically significant results showed the correlation between the BMI Z-score changes between the first and the second assessment and changes of glucose level in 0' ($R=0.3$, $p<0.05$), insulin levels in 0' and 120' ($R=0.3$ and $R=0.4$, $p<0.05$), the insulin resistance index HOMA-IR ($R=0.3$, $p<0.05$) and LDL levels ($R=0.3$, $p<0.05$).

Discussion

As reported in the literature, the prevalence of impaired fasting glucose (IFG) in children and adolescents with obesity ranges from 3.7% to 6.5%, whereas the prevalence of impaired glucose tolerance (IGT) ranges from 2.1% to 31%[10], [11], [12]. According to the different studies, depending on the ethnicity, BMI Z-score at baseline, the increase in the oral disposition index or the amount of gained weight during the follow up, the reversibility of prediabetes in pediatric patients with obesity varies from 45% to 65% (lifestyle modification alone) or even to 84.2% (lifestyle modification and metformin)[12], [13], [14]. In adults, those kind of interventions let achieve the reversal rate of 24%. Better results may also be attained but through second-line treatments e.g. glucagon-like peptide-1 analogues or bariatric surgery. These differences are explained by age-related changes leading to diminished insulin secretion[15], [16]. Obese youth present higher insulin levels during oral glucose tolerance tests (OGTTs) and rates of progression from impaired glucose tolerance (IGT) to type 2 diabetes (DM2) are lower in pediatric population than in adults. On the other hand, mean transition time from prediabetes to type 2 diabetes (DM2) in children with obesity is more rapid due to faster deterioration of the beta cells. Additionally, different from the adults, because of reduction in insulin sensitivity particularly expressed at mid-puberty, some obese youth may improve their results in oral glucose tolerance test (OGTT) upon repeated testing at the later pubertal stage[6]. Glucose levels depend on many hormonal, neural and metabolic factors. This interplay is governed by insulin and glucagon secreted from beta and alpha cells respectively. The reduced insulin sensitivity in children with obesity is mostly associated with increased visceral, intra-hepatic and intramyocellular lipid deposition. To compensate for insulin resistance, both

enhanced insulin secretion and reduced insulin clearance by the liver are activated. This continuous stress on the beta cells leads to firstly, their deterioration, and secondly, increasing glucose levels needed to stimulate them to secrete adequate amounts of insulin. It explains why children with obesity, and with impaired glucose tolerance (IGT) are comparable insulin resistant while those with normal glucose tolerance (NGT) may range from highly sensitive to markedly resistant. It has been shown that the ability of the child with obesity to described compensation is limited by genetic and epigenetic factors in which ethnic background is main clinical modifier. Genetic factors may affect both individual insulin sensitivity and beta cell response[6],[12]. The results of the present study revealed the common prevalence of prediabetes amounting to 9.2% (including 1.6% of impaired fasting glucose (IFG) and 8.2% of impaired glucose tolerance (IGT)) and uncommon prevalence of type 2 diabetes (DM2) (no one at the first and two cases at the second assessment). Those two patients had additional risk factors for diabetes mellitus (DM) development, presenting positive autoantibodies to islet cell (ICA) and protein tyrosine phosphatase (IA2) and undergoing the treatment against acute lymphocytic leukemia. Furthermore, high reversibility of prediabetes has been shown, with 60% of the patients reverting from impaired glucose tolerance (IGT) to normal glucose tolerance (NGT). No one progressed from impaired glucose tolerance (IGT) to type 2 diabetes (DM2). Although, the study did not prove the statistically significant factors determining the reversibility of prediabetes or progression to diabetes, the results suggested that firstly, the glucose metabolism disorders are dependent on the balance between insulin secretion and insulin sensitivity and secondly, not only weight loss but also maintenance of BMI Z-score increases a chance of regression from impaired glucose tolerance (IGT) to normal glucose tolerance (NGT) in pediatric population. The statistically significant correlation was showed between the BMI Z-score changes between two assessments and changes of LDL levels. To compare, in Galderisi's prospective study (39% Non-Hispanic White, 31% Non-Hispanic Black and 30% Hispanic) after median follow-up of 2.9 years, 65% of youth with impaired glucose tolerance (IGT) at baseline reverted to normal glucose tolerance (NGT), 27% adolescents had persistent impaired glucose tolerance (IGT) whereas 8% progressed to type 2 diabetes (DM2). Participants who reverted from impaired glucose tolerance (IGT) to normal glucose tolerance (NGT) showed a four-fold increase in the oral disposition index. Among youth with persistent impaired glucose tolerance (IGT) and those who progressed to type 2 diabetes (DM2) insulin secretion declined. Non-Hispanic White ethnic background conferred an odds of reverting from impaired glucose tolerance (IGT) to normal glucose tolerance (NGT) five times greater than Non-Hispanic Black[12]. In Weiss's initial cohort (47% Caucasians, 32% African Americans and 21% Hispanics), all with impaired glucose tolerance (IGT) at baseline, 45% reverted to normal glucose tolerance (NGT), 30% remained impaired glucose tolerance (IGT) and 24.2% developed type 2 diabetes (DM2). Those who presented improvements in glucose tolerance had lower BMI Z-scores at baseline and gained much less weight on follow-up than those who developed type 2 diabetes (DM2). In youth who progressed to type 2 diabetes (DM2), seven of eight subjects were African-American with a significantly higher BMI and BMI Z-score and they continued to gain excessive weight during the follow-up period[13]. In Numbenjapon's prospective study (100% Thai, all with impaired glucose tolerance (IGT) at the baseline), apart from lifestyle modification, part of the patients received at least 6 months of treatment with metformin. In this group 84.2% reversed to normal glucose tolerance (NGT). It seems that the patients in the reversed impaired glucose tolerance (IGT) group had also the LDL levels less than the patients in the remained impaired glucose tolerance (IGT) group both pre- and post-intervention periods[14]. Conversely, in the adult population (55% Caucasian, 20% African-American, 16% Hispanic, 5% American Indian and 4% Asian-American, all had impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) at baseline) in the Diabetes Prevention Program only 24% reverted to normal glucose tolerance (NGT) over 3 years of follow up. Predictors for regression to normal glucose tolerance (NGT) were lower baseline fasting and 2-h glucose, younger age and a greater insulin secretion to the oral glucose load. Intensive lifestyle modification and greater weight loss had significant and independent effects on regression[15],[17].

Study Limitations

A limitation of our study is that the classification of glucose tolerance relied on a single oral glucose tolerance test (OGTT). Previous studies showed poor reproducibility of the oral glucose tolerance test (OGTT) in obese youth, in particular for the 2-h plasma glucose[18]. Another potential limitation is limited number of patients resulting in lack of some statistically significant correlations.

Conclusions

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are common consequences of obesity in pediatric population, while the progression to type 2 diabetes (DM2) is a rare condition. Glucose metabolism disorders have reversible character in pediatric population. Every change of BMI Z-score has a significant impact on changes of carbohydrate metabolism parameters and LDL cholesterol. The results need to be confirmed by further, prospective studies on this matter.

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Table 1. Clinical and metabolic characteristics of the study groups of those who underwent oral glucose tolerance test (OGTT) twice

	Clinical and metabolic characteristics of the study group	
Parameter (units) mean and range or standard deviation or % and number of patients	**At the first assessment (n=54)**	**At the second assessment (n=54)**
Age (years)	11.1 (3.7-16.1)	13.11 (6.6-17.11)
Sex - Female	 54% (n=29)	 54% (n=29)
Tanner Stage - Prebubertal	 35% (n=19)	 14% (n=8)
BMI Z-score	4.1 (2.1-10.0)	4.4 (0.5-8.1)
Hipertension - Isolated systolic hipertension - Hipertension 1 grade - Hipertension 2 grade	 14% (n=8) 16% (n=9) 0%	 5% (n=3) 12.5% (n=7) 2.5% (n=1)
Glucose in 0' (mmol/L)	4.7 (0.4)	4.8 (0.4)
Glucose in 120' (mmol/L)	5.8 (1.4)	6.1 (1.8)
Insulin in 0' (mIU/L) **Insulin in 0' (pmol/L)**	24.0 (12.0) 134.5 (71.8)	20.1 (12.0) 127.2 (72.0)
Insulin in 120' (mIU/L) **Insulin in 120' (pmol/L)**	111.2 (73.4) 645.7 (440.6)	107.2 (78.4) 609.2 (473.7)
Total cholesterol (mmol/L)	4.2 (0.8)	4.3 (0.9)
LDL cholesterol (mmol/L)	2.6 (0.7)	2.7 (0.7)
HDL cholesterol (mmol/L)	1.1 (0.3)	1.1 (0.2)
Triglycerides (mmol/L)	1.6 (1.0)	1.6 (0.8)
Urine acid (µmol/L)	329.4 (69.4)	357.6 (72.6)
ALT (U/l)	34.9 (16.1)	32.6 (19.2)
AST (U/l)	29.0 (9.8)	28.6 (10.9)

Table 2. Detailed analyse of the groups with different glucose metabolic alterations

Parameter (units)	**NGT -> IGR**	**IGR -> IGR**	**IGR -> NGT**
Δ BMI Z-score	0.9	0.4	0.1
Δ Glucose in 0' (mmol/L)	0.2	-0.5	-0.1
Δ Glucose in 120' (mmol/L)	3.5	0	-2.8
Δ Insulin in 0' (mIU/L) **Δ Insulin in 0' (pmol/L)**	12.4 74.4	-20.4 -81.6	-3.9 -23.4
Δ Insulin in 120' (mIU/L) **Δ Insulin in 120' (pmol/L)**	114.6 687.6	9.9 59.4	-135.6 -813.6
Δ HOMA IR	3.0	-6.6	-0.9
Δ Total cholesterol (mmol/L)	0.2	-0.9	-0.1
Δ LDL cholesterol (mmol/L)	0.4	-0.4	0.1
Δ HDL cholesterol (mmol/L)	-0.1	-0.1	-0.1
Δ Triglycerides (mmol/L)	-0.3	-0.4	0.6
Δ Urine acid (µmol/L)	31.7	10.0	118.0
Δ ALT (U/l)	5.9	-34.7	2.0
Δ AST (U/l)	13.0	-20.0	-8.6

Table's Legend: NGT – normal glucose tolerance; IGR – impaired glucose regulation

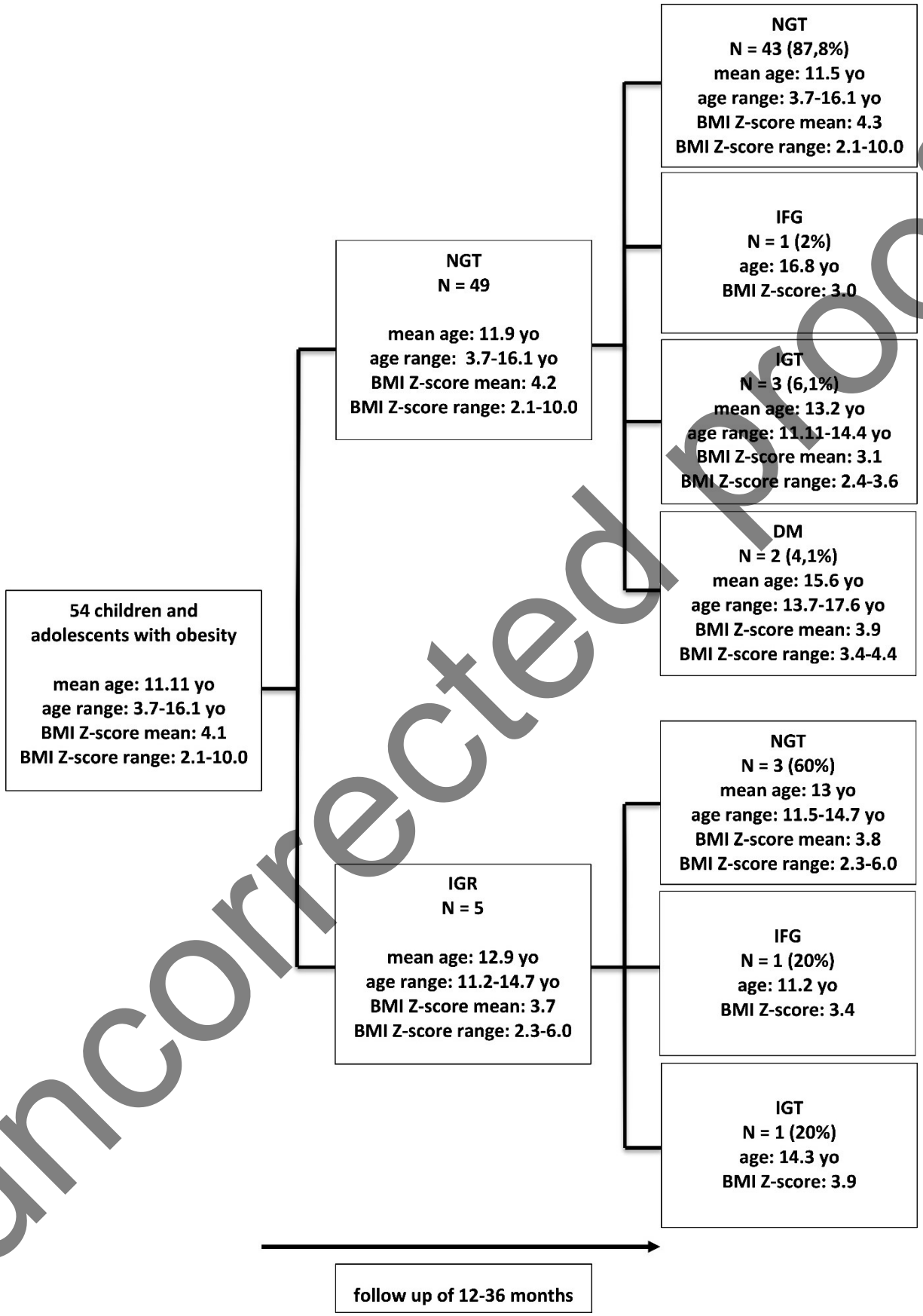

Figure 1. Trajectories of changes in carbohydrate metabolism disorders in the study group.
Figure's Legend: NGT – normal glucose tolerance; IGR – impaired glucose regulation; IFG - impaired fasting glucose; IGT- impaired glucose tolerance; DM - diabetes mellitus; yo – years old;