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INSULIN SENSITIVITY IN SKINNY, NORMAL WEIGHT, OVERWEIGHT AND OBESE CHILDREN

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Abstract

Burden of non-infection diseases of the world population is mainly represented by combination of problems which together are the components of metabolic syndrome. Insulin resistance is recognized as a key pathogenic element of those problems. It takes a long time to develop a full cluster of metabolic syndrome, which leads to some diagnostic difficulties.

The insulin sensitivity is the cornerstone of the burden of non-communicable diseases, which is not really well studied. In order to study early cardiovascular risk markers, insulin sensitivity parameters before and after the standard glucose load were analyzed in skinny (Body mass index Z-score < -1.0 SD, n=6), normal weight (BMI Z-score BMI±1.0 SD, n=12), overweight (BMI Z-score +1.1-2.0 SD) and obese (BMI Z-score +2.1-3.0 SD, n=18) children.

Anthropometric measurements were performed using standardized devices with further calculation of body mass index and assessment of abdominal adiposity by waist-to-height-ratio. The laboratory assessment of metabolic profile included fasting blood glucose and insulin followed by standard oral glucose tolerance test with 0, 15, 30, 60, 90, 120 time points. Insulin sensitivity has been studied by surrogate coefficients of fasting (central), tissue (peripheral) and whole body components. Fasting insulin sensitivity assessed by homeostasis model assessment of insulin resistance and quantitative insulin sensitivity check indices.

Peripheral insulin sensitivity was assessed by insulin sensitivity index ($ISI_{0.120}$) suggested by J. Cederholm in M. Gutt modification.

It was established that insulin sensitivity varies among adolescents with different trophological status. Whole body and fasting (central) insulin sensitivity decrease with growing visceral adiposity. Peripheral insulin sensitivity is decreased in skinny and severely obese children, but triggered by different causes. Impaired relations between hepatic glucose production and insulin secretion seem the target points for therapeutic metabolic correction in overweight and obese children. Lean mass gaining is necessary to predict potential health problems in lean subjects.

Keywords: *insulin sensitivity, children, skinny, overweight, obese.*

Introduction

According to the World Health Organization, 68% of the global mortality causes are non-communicable diseases. This group included cardiovascular disease associated with obesity, atherosclerosis and diabetes [*WHO, 2013*]. All those problems together were combined to the metabolic syndrome, which main conception is to stratify patients with high cardiovascular risk [*Alberti K et al., 2005*]. Insulin resistance was recognized as causal factor of the named complex disorders [*Reaven G, 1995*].

Homeostasis model assessment of insulin resistance index (HOMA-IR) reflects relations between fasting glucose and insulin and is usually used for the diagnosis of insulin resistance [*Matthews D et al., 1985*]. Euglycemic hyperinsulinemic clump is recommended as a golden standard to the detailed study of insulin sensitivity/resistance [*Schwartz B et al., 2008*].

We have shown previously that insulin sensitivity is decreasing with growing body mass index (BMI) as well as increasing area under the glycaemic curve [*Chaychenko T, 2011*]. It was also shown that insulin dynamics after standard glucose load

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is dependent on BMI: the peak of insulin response in normal weight and overweight occurs in the first 15 minutes after the load, in underweight is delayed (from 15 to 30 *min*). Insulin concentration starts to decrease at 60 *min* in normal weight and underweight. Whereas overweight and obese continues to increase insulin level or preserved plateau. Insulin concentration decreases at 120 *min* in all groups with a minimum in normal weight. The variability of insulin concentration in adolescents is inversely depended on BMI [*Chaychenko T et al., 2016*]. The above-mentioned is a marker of impaired insulin sensitivity, which can be recognized as a preclinical stage of type 2 diabetes and demands some pathogenic management.

By the conclusion of Insulin Resistance in Children Consensus Conference Group "Unfortunately we don't know how to assess insulin resistance in children, what are the risk factors and what is effective strategy of prophylaxis" [*Levy-Marchal C et al., 2010*]. Thus, insulin sensitivity is still corner stone of the burden of non-communicable diseases, which is not really well studied.

Present research aimed to study insulin sensitivity markers during standard glucose load in children.

Material and methods

Totally 64 overweight, underweight and normal weight children aged 13.56±2.47 years were examined with grouping by BMI Z-score: Group S (skinny, BMI<-1.0 SD, n=6), Group 0 (normal weight, BMI±1.0 SD, n=12), Group 1 (overweight, BMI+1.1-2.0 SD), n=14), Group 2 (obese, BMI+2.1–3.0 SD, n=18), Group 3 (obese, BMI>3.0 SD, n=14). There were no gender and age differences between groups (p>0.05).

Anthropometric measurements were performed using standardized devices: Harpenden stadiometer (Great Britain), SECA weight scale (Germany). Body mass index was calculated as body weight (*kg*) divided by squared standing height (m^2), BMI z-scores were used to compare group means. Abdominal adiposity assessed by waist-to-height-ratio [*Barclay L, 2010*].

The laboratory assessment of metabolic profile included fasting glucose (*mmol/l*), insulin (μIU/ml) followed by standard oral glucose tolerance test [*Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003*] with determination of blood glucose and insulin levels in 0, 15, 30, 60, 90, 120 minutes after the glucose load.

Insulin sensitivity has been studied by surrogate coefficients of fasting (central, hepatic), tissue (peripheral, muscular) and whole body components.

Fasting insulin sensitivity assessed by HOMA-IR [*Matthews D et al., 1985*] and quantitative insulin sensitivity check index (QUICKI) [*Chen H et al., 2003*] indices. Peripheral insulin sensitivity was assessed by insulin sensitivity index ($ISI_{0.120}$) suggested by J. Cederholm in M. Gutt modification [*Gutt M et al., 2000*]. For the whole body insulin sensitivity Matsuda index was used [*Matsuda M, Defronzo R, 1999*].

The study was approved by Institutional Bioethics Committee and conforms to the principles outlined in the Declaration of Helsinki (Br Med J, 1964; p. 177) with subsequent additions.

Statistical analysis: The results were analyzed using StatSoft Statistica 10. Quantitative variables were described as means ± SD; qualitative variables were described as percentages. Differences between groups were established by ANOVA and Mann-Whitney U test. Reported p-values are two-tailed, and p-values <0.05 were considered as statistically significant.

Results and discussion

There were no gender and age differences between groups (p>0.05), while BMI was gradually growing together with abdominal adiposity and total % of the body fat (Table).

Hyperglycemic dysglycemia variants were diagnosed in 51.11% of examined children with BMI more than +1 SD. Diabetes mellitus (by WHO criteria) wasn't revealed at any subject. Impaired fasting glucose was detected in 15 patients with impaired glucose tolerance – in 4, and impaired fasting glucose + impaired glucose tolerance – in 4 subjects.

HOMA-IR index is the most popular between researchers and clinicians to study insulin resistance because of its simplicity and great correlation with direct insulin sensitivity measurements [*Bonora E et al., 2000*]. It reflects effectively pancreatic β-cellular function – balance between hepatic glucose production and insulin secretion due to physiological feed-back mechanism.

It is noteworthy that HOMA-IR was initially

TABLE

Basic parameters and insulin sensitivity indices in children with different body mass index

Parameters	Group S n=6		Group 0 n=12		Group 1 n=14		Group 2 n=18		Group 3 n=14		Significant differences between groups (p<0.05)
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Basic parameters											
Age	12.17	2.40	13.73	1.79	12.71	2.70	13.78	2.69	13.92	2.33	
% fat	19.64	4.25	27.04	5.80	37.97	4.49	41.75	2.89	43.93	2.41	S0, 01, S1, 12, 02, S2, 23, 13, 03, S3
Waist-to-height-ratio	0.34	0.17	0.35	0.18	0.53	0.05	0.56	0.03	0.68	0.15	01, S1, 12, 02, S2, 23, 13, 03, S3
Z-BMI	-1.61	0.28	-0.20	0.46	1.47	0.29	2.60	0.24	3.38	0.26	S0, 01, S1, 12, 02, S2, 23, 13, 03, S3
Z-height	-0.78	1.22	-0.29	1.19	0.95	2.00	0.64	0.91	0.54	0.93	
Gl.0	3.92	0.52	4.25	0.38	5.44	0.38	5.47	0.49	5.53	0.83	01, S1, 02, S2, 03, S3
Ins.0	8.91	5.43	10.17	5.23	25.84	13.16	30.71	14.87	42.23	12.90	S0, 01, S1, 02, S2, 23, 13, 03, S3
Insulin sensitivity											
HOMA-IR	1.74	1.09	2.3	1.5	5.62	2.75	6.85	3.97	9.27	3.97	S1, S2, S3, 01, 02, 03, 23
QUICKI	0.37	0.07	0.34	0.02	0.30	0.02	0.29	0.03	0.27	0.006	S0, 01, 23
Metabolic clearance rate	74.01	13.13	96.27	18.55	90.66	12.29	99.85	16.47	90.18	12.89	S0, S1, S2, S3
$ISI_{0.120}$	46.17	9.71	56.68	12.59	51.25	7.51	56.95	13.55	47.97	8.32	S0, 23
Matsuda index	7.56	4.31	4.65	1.16	2.66	0.95	2.98	2.07	1.74	0.35	S0, S1, S2, S3, 01, 02, 03, 23

suggested for the adult population, but pediatric references were also elaborated later on. Thus, generally recommended cut-off 2.5 units is also could be used for the pre-pubertal children with 61% sensitivity and 74% specify [*Madeira I et al., 2008*]. At the same time there are some evidences of physiologic decrease of insulin sensitivity in puberty [*Kurtoğlu S et al., 2010*]. There are ethnic [*Fasting Indicators of Insulin Sensitivity, 2011*] and gender [*Aldhoon-Hainerová I et al., 2014*] influences at the HOMA-IR in adolescents. So absence of gender and age differences makes valid the results of our study.

Our data demonstrate gradual increasing of insulin resistance by HOMA-IR while growing BMI and it correspondents to the data of other researchers, which have shown link with visceral adiposity as well [*Zhang M et al., 2015*]. In our study the lowest results were registered in skinny patients, which is statistically significant vs. normal weight children ($p=0.02$).

QUICKI ≤ 0.33 is usually determined as an insulin resistance [*Chen H et al., 2003*]. By our data normal insulin sensitivity by QUICKI index can be registered just in skinny and normal weight children.

Peripheral insulin sensitivity, which reflects muscular glucose uptake, can be described by $ISI_{0.120}$ by J. Cederholm and J Wibell. It could be assessed as decreased when the result is below 45*mgl*^{2}/*mmol/mIU/min* [*Cederholm J, Wibell L, 1990*].

We found the lowest results in skinny and obese +>3SD children. At the same time the glucose metabolic clearance rate is decreased in skinny subjects, but doesn't show differences between normal weight, overweight and obese.

Glucose metabolic clearance rate is a valid parameter for the peripheral insulin sensitivity assessment [*Richter E et al., 1988*]. In studies peripheral insulin sensitivity was impaired in overweight due to excessive fat depots in skeletal muscles [*Masharani U et el., 2011*], and also in type 2 diabetes in skinny subjects [*Blesson C et al., 2010*]. European Group for the Study of Insulin Resistance has shown that insulin sensitivity is dependent on lean body mass [*European Group for the Study of Insulin Resistance, 2000*]. Logically, skinny subjects can also be insulin resistant because of lean (muscular) mass deficiency. It can explain our data about deceased insulin sensitivity in our skinny cohort, where glucose MCR after the standard glucose load was decreased. Thus, analysis of peripheral insulin sensitivity components has shown that parameter is decreased in skinny due to decreased muscular glucose uptake, but in obese due to chronic hyperinsulinemia.

Whole body insulin sensitivity can be calculated by Matsuda index which reflects relations between fasting and post-load glucose and insulin rates. Matsuda ≤ 4.3 is correspondent to insulin resistance [*Matsuda M, Defronzo R, 1999*]. Our data suggest normal results in skinny and normal weight children and decreased IS in overweight and obese. There is a tendency to statistical decreasing from group to group while growing BMI. It corresponds to studies where M. Matsuda results correlated to body composition assessed with using DEXA scan. Trunk fat standard deviation score correlated with M. Matsuda and J. Cederholm indices but not fasting parameters [*Kurtoğlu S et al., 2010*].

Conclusively, normal relations between fasting hepatic glucose production and insulin secretion might be registered in skinny and normal weight children, which can be confirmed by any fasting indices.

Peripheral insulin sensitivity is decreased in skinny and obese (BMI+>3SD) subjects. But this parameter is impaired in body mass deficiency due to glucose metabolic clearance rate, which could be caused by lean mass deficiency). The constant hyperinsulinemia could be suspected as a causative agent in obese subjects. Whole body insulin sensitivity significantly decreases with growing BMI mainly due to the impaired relationship between fasting hepatic glucose production and pancreatic β-cell activity.

Conclusion

Insulin sensitivity varies among adolescents with different body mass index.

Whole body and fasting (central) insulin sensitivity decrease with growing visceral adiposity. Peripheral insulin sensitivity is decreased in skinny and severely obese children, but triggered by different causes.

Impaired relations between fasting hepatic glucose production and insulin secretion seems the target points for therapeutic metabolic correction in overweight and obese children. Lean mass gaining is necessary to predict potential health problems in lean subjects.

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