HOMEOSTASIS MODEL ASSESSMENT - INSULIN RESISTANCE AND SENSITIVITY (HOMA-IR AND IS) INDEX IN OVERWEIGHT CHILDREN BORN SMALL FOR GESTATIONAL AGE (SGA)

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ABSTRACT

Introduction: Children born small for gestational age (SGA) have increased prevalence of metabolic syndrome, diabetes mellitus type 2 (DM2), hypertension and cardiovascular and cerebrovascular events in adulthood.

Patients and Methods: In 100 children born SGA, and in second cohort having 32 obese children born in term with normal birth weight and height, anthropometric measurements and biochemical metabolic profiles were analysed. The Homeostasis Model Assessment - Insulin Resistance and Sensitivity (HOMA-IR and IS) were calculated.

Results: Four overweight/obese children (M:F=3:1) with normal height were found among 100 SGA children. The body mass index (BMI) in all 4 children was above the 98th percentile and the mean BMI z-score was (2.04±0.30 SDS). The HOMA-IR index in all four children was increased: 1.26-2.65 (>1). Two teenagers had significant hyperinsulinemia (198.00 uIU/ml and 275 uIU/ml) and were treated with metformin. Two girls needed only a diet and increased physical activity. The mean values of HOMA-IR (1.26-2.65; N< 1) and IS (58 ±17.12) in fo-ur SGA overweight/obese children who caught-up growth had indistinguishable values with the group of 32 (M: F=21:11) obese children (HOMA-IR 1.83±1.2 SDS; IS 82.99±64.53 SDS) born in term with normal birth weight and height.

Conclusions: SGA born children are usually thin; nevertheless we found overweight and obesity in 4% of the patients. Two of those children have metabolic syndrome. Excess weight, obesity and metabolic syndrome in SGA children result with increase of their inherent risk for DM2, cardiovascular and cerebrovascular diseases in adulthood.

Keywords: small for gestational age, overweight, obesity, cardiovascular and cerebrovascular diseases, type 2 diabetes mellitus

INTRODUCTION

Worldwide, there were 15.5% of children born on term with body weight (BW) less than 2500 grams (WHO and UNICEF) [1]. Developing countries had higher SGA incidence, 16.5% compared to the developed countries 5-7%. [1-4] In fact, worldwide there are more than 2 million children born with low birth weight (LBW) yearly. [1] About 10% of SGA children remain short after the age of 4 years. SGA children have a higher risk for obesity, hypertension and insulin resistance during childhood and adolescence and diabetes, osteoporosis and cardiovascular and

cerebrovascular diseases in adult age [5]. Obesity is an additional risk factor for all those SGA consequences. There are more than 2.1 billion adults and children on Earth who are overweight or obese. [6] An estimated worldwide prevalence of obesity in children and adolescents aged 2-19 years was 5%, or about 110 million. [7]

Body mass index (BMI) in adults less than 18.5 kg/m2 is considered underweight, BMI 18.5–24.9 kg/m2 is within normal weight range, overweight if BMI is 25–29.9 kg/m2, obese if BMI ≥30 kg/m2, and BMI above 40 kg/m2 is extremely obese (WHO classification). [8] For children, the BMI z-score for sex, age and ethnicity is more precise and a more often used tool than BMI. Children with body mass index (BMI) at or above the 95th percentile are considered to be "overweight" (2007 WHO Reference).

PATIENTS AND METHODS

100 children born SGA in term, irrespective whether they caught up appropriate height after the age of 4 years, were investigated. SGA was defined as BW and/or BL at least 2 standard deviations (SD) below the mean for gestational age (GA). [9] A second cohort was 32 obese children born in term with normal birth weight and lenght and height.

Birth length (BL), birth weight (BW), BL standard deviation score (SDS) and BW SDS, as well as chronological age, gender, height, weight, body mass index (BMI) and BMI z-score was assessed in all children. A Harpenden stadiometer, a wall mounted digital rod, was used for measurement of height. Weight was determined with a precision scale.

Oral glucose tolerance test (OGTT) was done in owerweight and obese children. The definiti-on for impaired fasting glycaemia (IFG) was fasting blood glucose >6.1 and <7.0 mmol/l, while the definition of impaired glucose tolerance (IGT) was fasting plasma glucose <7.0 mmol/l and the 2-hour sample 7.8-11.1 mmol/l (WHO 2007, ADA 2005). [10, 11]

IInsulin secretion and sensitivity was estimated by the Homeostasis Model Assessment (HOMA). HOMA2 model based on non-linear solutions is widely accepted. [12, 13] Values of HOMA-IR and IS are dependent on ethnicity, gender, age, metabolic state of the investigated patient and the clinical methods of calculation. Therefore, cut-off levels are difficult to compare among publications. [14, 15] A standard version of the HOMA Calculator is using a computerised HOMA2 model for estimation of insulin resistance (HOMA-IR) and insulin sensitivity (IS) from fasting plasma glucose and fasting plasma insulin concentrations.

Statistical analysis

The Kolmogorov-Smirnov test (KS test) is used to check whether the values have normal (Gaussian) distribution. A confidence interval (CI) is calculated for the mean of each of the quantities. For the comparison of 2 groups, Fisher's test is used to check the equivalence of variances. The result of this test is relevant for applying the test for equivalence of means. If the 2 samples have a size greater than 30, the z-test is used, otherwise the t-test. All tests are with 99% significance or $\alpha=0.01$.

RESULTS

Our cohort of 100 SGA children consists of 64 (64%) short children and 36 (36%) children who managed to catch up growth after 4y of age. In the 36/100 SGA born children four were overweight or obese. Those 32 SGA born non-obese children who caught-up growth (M:F=12:20) had BW (2490cm±2.19 SDS) and BL (50.97cm±1.58 SDS), their mean height was (118.51cm±0.10 SDS), weight (23.18kg±0.01 SDS) and BMI z-score (-0.24±1.61SDS) (Table 1).

The control group of 35 children (M:F=13:22) born appropriate for gestational age (AGA; BW (3572.22gr±0.21 SDS), BL (50.97cm±0.41 SDS) had appropriate for age and sex weight, height, BMI (height 140.70cm±0.92 SDS), weight (41.60kg±2.18 SDS) and BMI z-score (0.70±0.62 SDS) (Table 1).

In addition, a fourth group of children were obese. Those 32 children (M:F=21:11; mean age 11.7 year, within range 5.3-15.41y) were born in term AGA (birth weight 3399.76gr±0.01 SDS), birth length (51.32cm±0.66 SDS) (Table 1). Kolmogorov-Smirnov test (KS-test) showed normal distribution of values in all four groups.

Those four (4.0%) SGA children caught up growth by the fourth year, but their weight were

above normal sex and age-related standards. Mean BW was 2665gr±181.0 SDS and BW SDS was (-1.89±0.31 SDS), while BL was (46.75cm±0.95 SDS) and BL SDS (-1.78±0.48 SDS). Three girls and a boy were overweight with BMI above the 98th percentile, and mean BMI z-score (2.04±0.30 SDS) for age and sex. Two girls aged 6.6y and 8.15y had BMI-z score 2.25 and 1.73. Further, a boy aged 14,25y and girl 14,85y had BMI z-score 2.36 and 1.83 for age and sex. Therefore, the 3 girls were overweight and the boy was obese (2007 WHO Reference). It is noted that the BMI z-score values in obese children were similar to those seen in SGA overweight/obese children (2.39 versus 2.04) (table 1).

None of four children had impaired fasting glycaemia. Glycaemia at the 2h sample was within normal range: 4.42-5.86 mmol/l. Normal HOMA-IR value is 1, values above 1 are conside-red abnormal. HOMA-IR index in all 4 children was high: 1.26-2.65. Three girls had HOMA-IR values from 1.26 to 1.79, and the boy 2.65. The calculated value of IS in the four obese children was significantly decreased: 37.80-79.60%.

Strikingly, mean values of HOMA-IR (p-value 0.97) and insulin sensitivity (p-value 0.45) in four SGA overweight/obese children with normal height were similar with the estimated values of 2 parameters in a group of obese children (table 2 and Figures 1 and 2).

Two teenagers, a boy aged 14,25y and a girl 14,85y, had very high insulin concentration of 275.00 uIU/ml and 198 uIU/ml at 2h of OGTT and were treated with metformin. Those two children had acanthosis nigricans, striae and central fat distribution. The girls aged 6.6 and 8.15 year, had hyperinsulinemia of 77.50 and 70.20 uIU/ml and got a recommendation for a dietary regime and physical activity. HbA1c values in all four children were within normal range (N <5.7%).

Impaired fasting glycaemia has not been detected in a group of obese children as well as in overweight/obese SGA born children. In 31 obese children the value of glycaemia at 2h was within the normal reference range, with the exception of an 8-year-old girl with a value 8.1 mmol/l. In addition the obese children had normal HbA1c, values.

Table 1. *Birth weight (BW), BW standard deviation score (SDS), birth length (BL) and BL SDS, height (H) and height SDS (H SDS), weight (W) and weight SDS (W SDS), BMI and BMI z-score in 4 groups of children: SGA overweight/obese children with normal height, 32 SGA children with normal height, but not obese, 35 children born appropriate for gestational age (AGA) and 32 obese children*

GROUPS PARAMETERS		SGA overweight /obese children		SGA children with normal weight and height		AGA		Obese children	
		mean	p-value	mean	p-value	mean	p-value	mean	p-value
BW	gr	2665 ±181.0	0.68	2490 ±321.87	0.98	3572.22 ±451.30	0.91	3399.76 ±475.22	0.91
BW SDS	-	-1.89±0.31	0.89	-2.19 ±0.57	0.49	0.21±0.96	0.98	-0.06±0.78	0.88
BL	cm	46.75±0.95	0.94	46.62 ±2.23	0.90	50.97±1.23	0.56	51.32±1.99	0.57
BL SDS	-	-1.78±0.48	0.58	-1.58 ±1.17	0.97	0.41±2.15	0.85	0.7±0.99	0.99
H	cm	150.42±14.97	0.93	118.41 ±16.65	0.70	140.70±21.75	0.83	149.94±16.78	0.50
H SDS	-	1.04±1.51	0.86	0.10 ±1.14	0.67	0.86±1.10	0.78	1.52±1.61	0.95
W	kg	63.2±23.97	0.98	23.18 ±9.61	0.44	41.60±18.13	0.73	69.4±20.51	0.94
W SDS	-	2.64±0.47	0.88	-0.01 ±1.54	0.73	2.01±2.30	0.88	7.64±4.14	0.32
BMI	kg/m²	27.09±5.63	0.79	16.06 ±2.26	0.95	20.19±4.52	0.38	30.22±4.56	0.09
BMI z-score	-	2.04±0.30	0.79	-0.24 ±1.61	0.54	0.70±1.01	0.59	2.39±0.62	0.50
Patients	M	n= 1		n= 12		n= 13		n= 21	
	F	n= 3		n= 20		n= 22		n= 11	

Table 2. *HOMA-IR and Insulin sensitivity estimated values in 2 groups of children: group of 4 SGA overweight/obese children and group of 32 obese children*

GROUPS		SGA overweight /obese children			Obese children		
PARAMETERS		mean	p-value	CI 99%	mean	p-value	CI 99%
HOMA-IR	-	1.85 ±0.58	0.79	0.15 ÷ 3.54	1.83 ±1.2	0.52	1.29 ÷ 2.36
Insulin Sensitivity	%	58 ±17.12	0.94	7.99 ÷ 108.00	82.99 ±64.33	0.08	54.48 ÷ 111.50
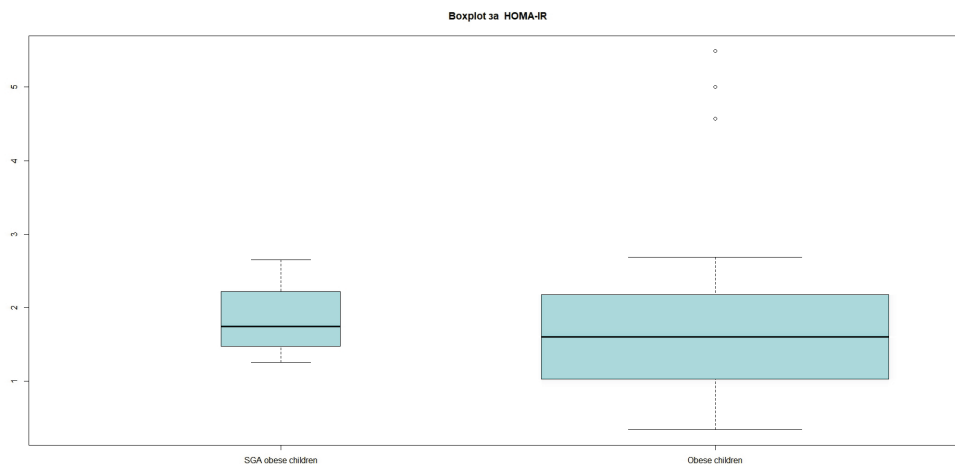
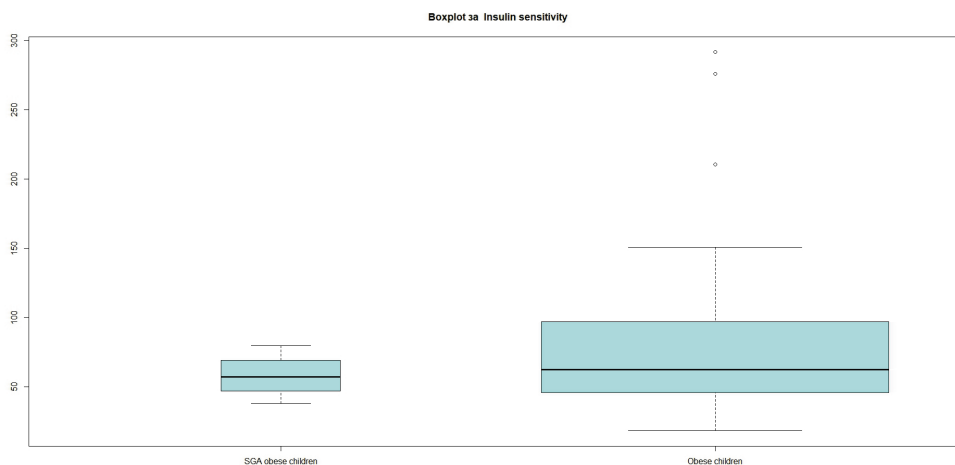**Figure 1.** *Boxplot for HOMA-IR*

Figure 2. *Boxplot for Insulin Sensitivity*

DISCUSSION

SGA born children are usually thin regardless of their height or sex. Increased BMI is rare and predominantly found in girls. [16, 17]. Longitudinal analysys in Italian children observed a tendency of weight gain in childhood in SGA born children compared to their AGA peers. After 2 years of age SGA children are found to be overweight/obese 5-6 times more than their AGA peers (5.2% at 2 years versus 29.12% at 10 y). [18] Again, this is more frequent in girls.

In 18 SGA born girls in term, who caught-up growth and 13 AGA girls aged between 2 and 8 year with normal height, there were no diferences in auxology parameters at the age of 2y.

[19] However, increased body and visceral adiposity and metabolic disturbancies have been detected at the age of 8y only in SGA born girls.

In 111 SGA children (with and without catch-up growth) and 52 AGA born children the highest BMI SDS values with increased body and visceral fat were found in group of 40 SGA born children (M:F=17:23) who caught up growth and weight by the age of two year. [20]

A study performed in young adults aged around 20y born IUGR have shown higher mean BMI and triglyceride values with decreased insulin sensitivity as early signs of impaired glucose metabolism. [21]

We also observed higher frequency of overweight/obese children among girls (3:1). They were all children who cought-up growth measured at the age of referral. The height, weight and BMI z-scores values in all 4 overweight/obese SGA children were comparable with BMI z-scores values of the group of 32 obese children.

A three-fold increased metabolic disturbances in AGA obese children, twice-fold in SGA children compared to the AGA non obese children were reported. [22]

Deng et al. [2012; 20] found significantly higher values of HOMA-IR in SGA born children which caught up growth by 2 years of age, compared to AGA children. The insulin resistance increased with height and BMI catch-up growth in SGA born children. Values of HOMA-IR index in SGA born children without catch up growth have been comparable to HOMA-IR values in AGA born children.

Others have shown similar glucose homeosthasis in SGA children before and after cessation of treatment with growth hormone (GH) [23, 24]. The insulin resistance was found in 8% of short SGA born children before the GH treatment and in 10% of patients 6 months after discontinuation of GH treatment. [23] SGA born young adults have had similar fat mass distribution 5 years after discontinuation of GH treatment, insulin sensitivity and pancreatic β-cell function with the group of untreated short SGA adults. [24]

In this study of two groups of children with excessive weight gain (the 4 overweight/obese SGA born children with catch up growth and group of 32 obese children) the results of HOMA-IR in both groups were abnormal with decreased insulin sensitivity.

The difficulties in diagnosing metabolic syndrome (MetS) are widely discussed. [25] Strikingly, only 2% of patients [26] met the criteria although overall prevalence of MetS in children and adolescents ranged between 6% and 39%. [26] The metabolic syndrome diag-nostic criteria (at least 3) [25] we found that 2/4 overweight/obese SGA born children children fulfilled at least 3 criteria. In fact, all 4 children have BMI greater than the 98th percentile with abdominal fat tissue distribution, 2 of them have BMI z-score > 2 SDS (+2.25 and +2.36 SDS), but the other 2 children have BMI z-score between 1.5-2.0 SDS (1.73 and 1.83 SDS), HOMA-IR in all 4 children is also abnormal, 1 child had HOMA-IR 1.25 and 3 children between 1.7-2.65, and 2 children have insulin >104 uIU/ml (198.00 and 275.00).

CONCLUSIONS

Contrary to the perception of lean SGA children, some SGA children are overweight or obese. They often have metabolic syndrome, increased insulin resistance and decreased insulin sensitivity. Therefore, their inherent risk of late severe complications is significantly increased. A follow-up and counceling would help decrease the chances of severe late complications.

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Резиме

МОДЕЛ ЗА ПРОЦЕНКА НА ХОМЕОСТАЗАТА – ИНДЕКС НА ИНСУЛИНСКА РЕЗИСТЕНЦИЈА И СЕНЗИТИВНОСТ (ХОМА-ИР И ИС) КАЈ ДЕЦАТА СО ПРЕКУМЕРНА ТЕЖИНА, РОДЕНИ МАЛИ ЗА ВОЗРАСТА

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Вовед: Децата родени мали за гестациската возраст (СГА) имаат зголемена преваленца за метаболен синдром, дијабетес мелитус тип 2 (ДМ2), хипертензија, кардиоваскуларни и церебро-васкуларни проблеми во адултна возраст.

Пациенти и методи: Во група од 100 деца родени мали за возраста и во друга група од 32 обезни деца, родени во термин, со нормална породилна тежина и висина, беа направени антропо-метриски мерења и биохемиски анализи за проценка на метаболичката состојба. Моделот за проценка на хомеостазата беше употребен за проценка на инсулинска резистенција и инсулинска сензитивност.

Резултати: Во групата од 100 СГА родени деца најдовме четири со прекумерна тежина/обез-ни деца (М : Ж = 3 : 1), а со нормална висина. Индексот на телесната маса (БМИ) кај сите четири деца беше над 98-иот перцентил, а БМИ з-скорот (+2,04 ± 0,30 СДС). Вредноста на моделот за проценка на хомеостазата – индекс на инсулинска резистенција (ХОМА-ИР) кај сите четири деца беше покачен, 1,26–2,65 (>1). Двајца тинејџери имаа значителна хиперинсулинемија (198 uIU/ml и 275 uIU/ml) и беа лекувани со Метформин. Другите две девојчиња беа само на диетален режим и зголемена физичка активност. Проценетите вредности на индексот ХОМА-ИР (1,26-2,65; N< 1) и инсулинската осетливост (ИС) (58 ±17,12) кај четирите обезни СГА родени деца со нормална висина не се разликуваа од истите параметри кај групата од 32 обезни (М : Ж = 21 : 11) деца (ХОМА-ИР 1,83 ± 1,2 СДС и ИС 82,99 ± 64,53 СДС), родени во термин со нормална родилна тежина и должина и актуелна висина.

Заклучоци: СГА родените деца обично се тенки. Сепак, ние кај 4% од пациентите најдовме прекумерна телесна тежина, па дури и обезност. Две од овие деца имаат метаболен синдром. Прекумерната тежина, дебелината и метаболниот синдром кај СГА родените деца го зголемуваат ризикот за дијабетес тип 2, својствен за нив, како и за кардиоваскуларни и цереброваскуларни болести и дијабетес тип 2 во зрелоста.

Клучни зборови: мали за гестациската возраст, прекумерна телесна тежина, дебелина, кар-диоваскуларни болести, шеќерна болест тип 2