Insulin sensitivity obtained from the oral glucose tolerance test and its relationship with birthweight

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BACKGROUND: Glucose intolerance and insulin sensitivity in preadolescent children might predict the risk of developing type 2 diabetes mellitus in adult life in small for gestational age (SGA) children. We aimed to investigate whether reduced birthweight is related to low insulin sensitivity in preadolescence.

SUBJECTS AND METHODS: Twenty-five SGA children and 29 appropriate for gestational age children (AGA) children born between 1993 and 1994 were evaluated for insulin sensitivity in preadolescence. At the beginning of the study, body mass index (BMI) was calculated and an oral glucose tolerance test (OGTT) was performed. Blood samples to measure glucose and insulin were taken every 30 minutes during OGTT. Homeostasis of model assessment-insulin resistance (HOMA-IR) and composite index (CI) values were measured to assess insulin sensitivity.

RESULTS: On the OGTT, 120-minute glucose and insulin levels were higher in SGA than AGA children ($P=0.02$ and $P=0.001$, respectively). Although there was no difference between HOMA-IR values, the mean CI value was lower in SGA than AGA children ($P=0.001$). There was an inverse correlation between birthweight and 120-minute glucose concentrations ($r=-0.30$, $P=0.02$). This correlation was stronger between birthweight and 120-minute insulin concentrations ($r=-0.50$, $P=0.001$). BMI was positively correlated with 120-minute insulin ($r=0.50$, $P=0.001$). There was no relationship between HOMA-IR values and birth size, but the CI index was positively correlated with birthweight ($r=0.40$, $P=0.002$).

CONCLUSIONS: Birthweight may be a predictive factor for insulin sensitivity and CI is more reliable than HOMA-IR to assess this sensitivity in preadolescence.

Reduced fetal growth is associated with an increased risk of developing adult diseases, such as type 2 diabetes mellitus, hyperlipidemia, hypertension and coronary heart disease.¹ Reduced growth in utero may affect beta-cell structure and function in young adults.²⁻⁵ It has been suggested that if we could describe glucose intolerance and insulin sensitivity in preadolescent children who were born SGA, we could determine the risk of developing type 2 diabetes mellitus in adult life.⁶ The aim of the present study was to investigate whether birthweight is related to insulin sensitivity in preadolescent Turkish children.

SUBJECTS AND METHODS

In this retrospective cohort study subjects were selected according to data registered at birth (gestational age, gender, birthweight and length). In 1993, 2716 babies were born in Ankara Training and Research Hospital.

Forty-six of all babies whose birthweight was below the tenth centile for gestational age with a cut-off value of 2500 g at term were defined as SGA. The ponderal index (PI) ($\text{weight/height}^3 \times 100$) was estimated according to birth records and <10th centile was defined as intrauterine growth retardation (IUGR).⁷ In preadolescence, approximately eight to nine years later, we recalled SGA children by mail. Twenty-five (54%) children participated in the study. The control group selected from the same birthdata included AGA children (birthweight >10th centile) because there are no standards of insulin sensitivity in the literature in children born AGA. Fifty-two AGA children were invited and 29 (55.7%) participated in the study. After full explanation of the study, all parents and children gave written informed consent.

At the time of the study all children were at a pre-pubertal stage according to the criteria of Tanner. They were in good health and had no family history of type

2 diabetes mellitus, hypertension, or coronary heart disease. Age, weight and height of the subjects were recorded. An electronic scale (Detecto scales inc. Brooklyn USA) was used to measure weight and height. BMI was calculated as weight (in kg) divided by the square of height (in m²). After a 10-hour fast, all children took an OGTT. They consumed 1.75 g/kg glucose orally, with a maximum of 75 g. Blood samples were taken to measure glucose and insulin concentrations at 0, 30, 60, 90, and 120 minutes during OGTT. All specimens were centrifuged at 1300g for 10 minutes.

Insulin sensitivity was evaluated by two methods. The first method was the HOMA-IR model, which provides a reasonable estimate of tissue sensitivity to insulin according to the formula [fasting plasma glucose (mmol/L) × fasting plasma insulin (μU/mL)]/22.5 and lower than the 2.5 value indicated greater insulin sensitivity (i.e., less insulin resistance).⁸ In the second method, to measure whole body insulin sensitivity, the composite index (CI), representing a composite of both hepatic and peripheral tissue sensitivity to insulin, was calculated according to the formula $10\,000 / [\text{fasting plasma glucose (mg/dL)} \times \text{fasting plasma insulin (μU/mL)}] \times [\text{mean glucose concentration (mg/dL)} \times \text{mean insulin concentration (μU/mL)}]^{1/2}$.⁸ There is no accepted, standard criterion for impaired insulin sensitivity based on the CI. Matsuda and DeFronzo derived a criterion by analysis of epidemiological data and the distribution of values for the CI in a population from San Antonio, Texas, USA. According to their research, higher CI values (>2.5) indicated greater insulin sensitivity (i.e., less insulin resistance).⁸ Impaired glucose tolerance was defined as 120 minute-glucose levels of 140 to 200 mg/dL. Blood glucose was measured by the glucose oxidase method using a Synchron LX-20 autoanalyser (Beckman Coulter, Inc., USA). Blood insulin was measured by the chemiluminescent method using Roche Modulare-170 hormone analyzer (Roche Diagnostics, Germany).

The statistical software used was Statistical Package for Social Sciences 10.0 for Windows (SPSS). Descriptive analysis was used to assess mean values. Mann Whitney U and Spearman's rank correlation tests were used for analysis. A *P* value of 0.05 or less was considered to be significant. The study protocol was approved by the ethics committee of Ankara Training and Research Hospital.

RESULTS

Of the 54 children studied all were born at term and divided into SGA or AGA according to their birthweights (Table 1). In 88% of SGA subjects the PI was

<10th centile and described as IUGR. Birthweight, birth length and ponderal index was lower in SGA than AGA (*P*<0.05). At the beginning of the study, the mean weight and BMI was significantly higher in the SGA group (*P*<0.05), although there was no difference in mean height.

Fasting glucose levels were lower than 120mg/dL in both groups (Table 2). OGTT revealed that 120-minute glucose and insulin levels were higher in SGA than AGA (*P*=0.02 and *P*=0.001, respectively). Second-hour glucose levels were between 140-200 mg/dL in 4 (16%) of the SGA subjects. Glucose levels were not higher than 200 mg/dL in all subjects at any point during OGTT. When calculated, the mean CI value was lower in SGA subjects than in AGA subjects, although there was no significant difference between the two groups in HOMA-IR values.

Birthweight and birth length were inversely related to 120-minute glucose (*r*=-0.30, *P*=0.02 and *r*=-0.32, *P*=0.008, respectively) and insulin concentrations (*r*=-0.50, *P*=0.001 and *r*=-0.50, *P*=0.001, respectively). PI was only correlated with 120-minute insulin concentrations (*r*=-0.50, *P*=0.001). In preadolescence weight was correlated with fasting glucose (*r*=-0.30 and *P*=0.005) and 120-minute insulin (*r*=0.40 and *P*=0.001). On the other hand, BMI was only correlated with 120-minute insulin (*r*=0.50, *P*=0.001). When assessed for the insulin sensitivity index, there was no relationship between HOMA-IR values and birth size, but the CI index was positively correlated with birthweight (*r*=0.40, *P*=0.002) (Table 3).

DISCUSSION

Infants with reduced birthweight have greater morbidity and mortality than appropriately grown, gestational age-matched infants in later life.⁹ SGA is defined as an infant whose birthweight is lower than the population norms. SGA and IUGR are not the same. IUGR is defined as failure of normal fetal growth caused by multiple adverse effects on the fetus due to a process that inhibits the normal growth potential of the fetus. Not all IUGR infants are small enough to fit the qualifications for SGA. The PI is used to determine those infants whose soft tissue mass is below normal for their stage of skeletal development.¹⁰ In our study population, according to birthweight and PI, 88% of the SGA infants were IUGR.

Lithell et al demonstrated that there was a weak inverse correlation between PI at birth and 60-minute insulin concentrations in the intravenous glucose tolerance test at age 50 years. They also showed that there was a stronger association between diabetes and PI.¹¹ In

Table 1. Characteristics of the children at birth and at the time of the study.

		SGA (n=25) mean±SD	AGA (n=29) mean±SD	P value
At birth	Gender (Girl/boy)	13/12	14/15	0.7
	Birthweight (g)	2284±133	3451±367	0.001
	Birth length (cm)	47.8±1.5	50.5±1.2	0.001
	Ponderal index (weight/length ³ × 100)	2.09±0.2	2.67±0.2	0.001
At the time of the study	Age (year)	8.6±0.6	8.4±0.5	0.05
	Body weight (kg)	30.1±5.1	25.7±3.9	0.001
	Body height (cm)	128±8.17	128±6.7	0.9
	Body mass index (kg/m ²)	18.4±2.9	15.6±1.70	0.001

SGA=small for gestational age

AGA= appropriate for gestational age

P value for Mann Whitney U test

Table 2. Glucose-insulin concentrations, HOMA-IR, and composite index values obtained from OGTT in SGA and AGA subjects.

		SGA (n=25) mean ± SD	AGA (n=29) mean ± SD	P value
Glucose (mg/dl)	0-min	86.6±6.3	84.8±7.2	0.30
	120-min	113.5±34.7	96.1±17.4	0.02
Insulin (mU/L)	0-min	8.0±3.3	8.3±3.4	0.80
	120-min	38.6±12.4	14.8±16.3	0.001
HOMA-IR		1.7±0.7	1.8±0.7	0.90
Composite index		8.5±3.01	13.9±7.09	0.006

HOMA-IR =Homeostasis of model assessment-insulin resistance

SGA=small for gestational age

AGA= appropriate for gestational age

P value for Mann Whitney U test

our study PI was inversely correlated with 120-minute insulin concentrations, although there were no subjects with diabetes.

Poor nutrition in utero may lead to permanent changes in the insulin-glucose metabolism, even if the effect on fetal growth is small. It has been proposed that this association results from fetal programming in response to the intrauterine environment (the thrifty phenotype hypothesis).¹² It has been suggested that insulin resistance is associated with reduced fetal growth, genetic factors and an unfavorable fetal environment. Jaquet et al studied 171 SGA and 233 AGA subjects

and performed the OGTT. The SGA group showed higher serum insulin concentrations than the AGA group at fasting and after stimulation, but no difference in serum glucose concentrations was observed.¹³ In this study, 120-minute glucose levels were between 140-200mg/dL in 16% of the SGA subjects in preadolescence and were defined as impaired glucose tolerance. There was a significant difference between the SGA and AGA groups in 120-minute glucose and insulin levels.

Reduced birthweight is associated with several chronic diseases in adults, including hypertension, cardiovascular disease, glucose intolerance or diabetes mel-

Table 3. Correlations of size at birth and at the time of the study to glucose-insulin concentrations, HOMA-IR and composite index (CI) values obtained from the OGTT.

		Glucose 0 min (mg/dl)	Glucose 120 min (mg/dl)	Insulin 0 min (mU/L)	Insulin 120 min (mU/L)	HOMA-IR	CI
At Birth	Weight	$r=0.01$	$r=-0.32$	$r=0.05$	$r=0.51$	$r=0.06$	$r=0.40$
		$p=0.90$	$p=0.02$	$p=0.68$	$p=0.001$	$p=0.61$	$p=0.002$
	Length	$r=-0.21$	$r=-0.32$	$r=0.10$	$r=-0.51$	$r=0.12$	$r=0.30$
		$p=0.10$	$p=0.008$	$p=0.20$	$p=0.001$	$p=0.46$	$p=0.01$
	Ponderal index	$r=0.10$	$r=-0.11$	$r=-0.02$	$r=-0.50$	$r=0.01$	$r=0.30$
		$p=0.40$	$p=0.15$	$p=0.80$	$p=0.001$	$p=0.90$	$p=0.006$
At the time of the study	Weight	$r=-0.30$	$r=0.15$	$r=-0.05$	$r=0.40$	$r=-0.10$	$r=-0.20$
		$p=0.005$	$p=0.25$	$p=0.70$	$p=0.001$	$p=0.40$	$p=0.10$
	Height	$r=-0.2$	$r=0.19$	$r=0.20$	$r=0.09$	$r=0.10$	$r=-0.10$
		$p=0.10$	$p=0.15$	$p=0.10$	$p=0.40$	$p=0.16$	$p=0.20$
	Body mass index	$r=-0.20$	$r=0.04$	$r=-0.10$	$r=0.50$	$r=-0.10$	$r=-0.20$
		$p=0.10$	$p=0.70$	$p=0.40$	$p=0.001$	$p=0.20$	$p=0.10$

HOMA-IR=Homeostasis of model assessment-insulin resistance
P and *r* values for Spearman rank correlation between variables

litus, and obesity. This association is the result of the adaptational changes of the fetal endocrine-metabolic mechanisms in the impaired intrauterine milieu assuring survival in the short term. The persistence of these changes after birth can be detrimental in adult life.

Veening et al studied 29 SGA and 24 AGA children at the prepubertal stage and found no differences in glucose tolerance and beta cell function between the two groups. However, they demonstrated that the hyperinsulinemic clamp reduced insulin sensitivity in SGA children, which may contribute to the enhanced risk of developing type 2 diabetes mellitus in adult life, especially in SGA children with catch-up growth and a high BMI.¹⁴ In another study, 28 SGA and 22 AGA prepubertal children were studied to assess the effect of body size during childhood on beta cell capacity and insulin sensitivity. It had been demonstrated that there was decreased insulin sensitivity rather than decreased beta cell capacity in SGA children. Investigators concluded that interventions to improve fetal growth and prevent overweight after the second year of life appeared to be important factors in the prevention of type 2 diabetes mellitus.¹⁵ In the present study, we studied 25 SGA and 29 AGA subjects. In preadolescence, BMI was higher in SGA subjects and among them 24% were between the 75th and 95th percentiles (overweight) and 12% were >95th percentile (obese). When analyzed, BMI

was positively correlated to 120-minute insulin levels in OGTT.

In a different study, 236 SGA and 281 AGA were studied at 20 years. Adult height, concentrations of glucose, insulin, and proinsulin during OGTT, lipid and fibrinogen concentrations and blood pressure were measured. Researchers reported that SGA had long-term consequences, such as raised insulin and proinsulin concentrations, which could be markers of early changes in insulin sensitivity.¹⁶ Jaquet et al studied 12 insulin-resistant subjects at 25 years to test whether in utero undernutrition would affect beta-cell function in young adults. Their data did not argue in favor of an impairment of beta cell function at 25 years of age as a consequence of in utero undernutrition, but rather suggested that insulin resistance might be the primary defect responsible for the development of metabolic disorders associated with IUGR in adulthood.¹⁷

Our study showed that birthweight was inversely correlated with 120-minute insulin levels and there was a significant difference between SGA and AGA subjects. Fifty-two per cent of the SGA subjects had a value of insulin >38 mU/L at the end of the OGTT at age of 8-9 years. In different studies the relation between birthweight and cumulative incidence of adult hypertension, incidence of non-insulin-dependent diabetes mellitus and the prevalence of obesity were studied and the data

suggested that early life exposures such as birthweight were a marker associated with several chronic diseases in adulthood.¹⁸⁻¹⁹ In our study birthweight was inversely related to glucose and insulin concentrations in OGTT in preadolescence. SGA subjects tended to be overweight in this period and BMI was positively correlated with insulin levels.

Several methods have been proposed to evaluate insulin sensitivity from the data obtained from the OGTT. Turner and colleagues proposed the HOMA as an index of insulin sensitivity and it has been shown to provide a reasonable estimate of tissue sensitivity to insulin.²⁰ Matsuda and DeFronzo proposed a simple index of whole-body insulin sen-

sitivity derived from the OGTT.⁸ This index represented a composite of both hepatic and peripheral tissue sensitivity to insulin. In this study we used both the HOMA-IR index and CI obtained from OGTT to evaluate the relationship between birthweight and insulin sensitivity. We found that the mean CI value was lower in SGA than AGA subjects and there were no correlation between birthweight and HOMA-IR.

This is the first study done on preadolescent SGA children from Turkey. We concluded that birthweight may be a sensitive predictive factor for insulin sensitivity in preadolescence and that CI is more reliable than HOMA-IR to assess this sensitivity.

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