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The role of leptin, soluble leptin receptor, adiponectin and visfatin in insulin sensitivity in preterm born children in prepubertal ages

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ABSTRACT

Background: There are still controversies whether insulin resistance (IR) develops in preterm born children during early childhood.
Objective: To investigate the role of leptin, soluble leptin receptor (sOB-R), adiponectin, visfatin and insulin sensitivity in the pathogenesis of possible IR in preterm born children during early childhood.
Patients and metods: Twenty-nine preterm small for gestational age (SGA) born children (Group 1) and 25 preterm appropriate for gestational age (AGA) born children (Group 2), matched for gestational age and sex were included in the study. Mean chronological age at investigation was 3.3 ± 0.7 years and not different between the groups. Blood samples for fasting blood glucose, insulin, proinsulin, adiponectin, leptin, sOB-R and visfatin were obtained.
Results: Mean height and weight standard deviation scores (SDS) at investigation were significantly lower in Group 1 than in Group 2, but there was no significant difference in body mass index (BMI) SDS between the groups. Catch-up growth (CUG) was higher in Group 1 than in Group 2. There was no difference regarding homeostasis model assessment for IR (HOMA-IR), leptin, sOB-R, adiponectin, proinsulin and visfatin values between the groups. In the whole group, log visfatin showed a negative correlation with Δweight SDS. There was a positive correlation between HOMA-IR and BMI SDS. Adiponectin levels showed a positive correlation with log visfatin levels in all groups.
Conclusion: Preterm born children whether AGA or SGA do not show IR in early childhood if BMI is normal. Significant differences between the preterm SGA and preterm AGA groups regarding the adipocytokine levels were not detected.

1. Introduction

Insulin resistance (IR) is the underlying metabolic abnormality in the pathogenesis of the most important adult onset morbidities including metabolic syndrome, type 2 diabetes and cardiovascular disease. The growing prevalence of obesity and metabolic syndrome worldwide even among adolescents have made it urgent for researchers to provide an explanation for possible causal and underlying mechanisms to determine the best ways to intervene [1]. The criteria for metabolic syndrome are central obesity (increased waist circumference), dyslipidemia [high triglyceride, low high density lipoprotein (HDL)-cholesterol], impaired glucose tolerance or IR and hypertension. IR has been also recognized as a proinflammatory and prothrombotic state [2]. Chronic inflammation in obesity and altered levels of adipocytokines like adiponectin, leptin, resistin, and ghrelin have been shown to play part in the development of IR [3,4]. Adipocytokines are secreted by adipocytes and the mononuclear cells in adipose tissue. Leptin has specific receptors on target tissues, also circulating soluble leptin receptor (sOB-R) is suggested to regulate leptin signaling. Leptin/sOB-R system plays a key role in energy homeostasis [5]. Leptin levels may be high during the catch up growth (CUG) of term small for gestational age (SGA) children at early ages but they have been found usually low during childhood in thin SGAs compared to normal appropriate for gestational age (AGA) children [6]. Adiponectin plays an important role in carbohydrate metabolism, favoring peripheral insulin-induced glucose uptake. Low adiponectin [7],

Abbreviations: IR, insulin resistance; HDL, high density lipoprotein; sOB-R, soluble leptin receptor; CUG, catch up growth; SGA, small for gestational age; AGA, appropriate for gestational age; BMI, body mass index; SDS, standard deviation scores; IRMA, immunoradiometric assay; ELISA, Enzyme-Linked Immunosorbent Assay; HOMA-IR, homeostasis model assessment for IR..

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Table 1
Anthropomertric parameters and clinical findings of the groups. Values are given as mean ± SD.

	Group 1 Preterm SGA *n* = 29	Group 2 Preterm AGA *n* = 25	*p*
At birth			
Gestational age (week)	33.7 ± 0.823 (27.4–36.7)	33.2 ± 2.1 (28.6–36.4)	0.397
Birth weight (g)	1327 ± 334.2	1993.2 ± 606.3	**0.000**
Birth weight SDS	−2.5 ± 0.5	0.07 ± 0.5	**0.000**
Birth length (cm)	38.6 ± 3.3	42.8 ± 3.4	**0.000**
Birth length SDS	−2.5 ± 1.0	−0.3 ± 0.8	**0.000**
Birth head circumference SDS	−1.9 ± 1.0	−0.1 ± 0.7	**0.000**
Catch-up growth *n*(%)	26 (83.9)	9 (39.1)	**0.001**
At investigation			
Chronological age (year)	3.3 ± 0.8 (2.4–4.8)	3.3 ± 0.1 (2.5–4.6)	0.768
Gender			
Female	17	9	0.097
Male	12	16	
Weight SDS	−1.0 ± 1.2	−0.06 ± 0.9	**0.003**
ΔWeight SDS	1.5 ± 1.2	−0.2 ± 1.3	**0.000**
Height SDS	−0.9 ± 0.9	0.01 ± 0.9	**0.001**
ΔHeight SDS	1.5 ± 1.2	0.2 ± 1.1	**0.000**
BMI SDS	−0.4 ± 0.98	−0.2 ± 0.9	0.412
Waist circumference SDS	−0.27 ± 0.97	−0.35 ± 1.4	0.613
Waist/Hip circumference ratio (cm/cm)	0.94 ± 0.2	0.91 ± 0.04	**0.017**
BMI SDS			
<1 SDS	29 (96.7%)	22 (81.5%)	0.152
⩾1 SDS	1 (3.3%)	5 (18.5%)	

Significance was granted for $p \leqslant 0.05$.

high leptin and low sOB-R levels [3,5,7] have been associated with IR and metabolic syndrome. Visfatin was defined recently as an adipocytokine and is found to be elevated in obesity, metabolic syndrome and type 2 diabetes. Visfatin is a cytokine predominantly produced in adipose tissue and it is found to be a regulatory factor in proinflammation and immunomodulation and, associated with IR. It has insulin-mimetic effects and lowers plasma glucose levels [8,9]. It has been reported that an increased visfatin concentration may be related to body mass index (BMI) and IR in obese children [10].

Studies have shown that adverse intrauterine environment and early postnatal period increase the risk for obesity, metabolic syndrome and type 2 diabetes [11]. Low birth weight is associated with impaired glucose tolerance, IR and cardiovascular disease in young adults [11,12]. Rapid growth/CUG is also found to be related to IR [12,13]. Advances in neonatal care have significantly increased the survival rate for extremely premature babies. A few studies have suggested that prematurity itself is a risk factor for IR. In our previous study, we have shown that preterm born children did not have IR during early childhood [14].

The aim of the present study was to investigate the role of different adipocytokines in insulin sensitivity in the pathogenesis of possible IR in preterm born children during early childhood.

2. Materials and methods

2.1. Subjects

Fifty-four (26 females, 28 males) preterm born children (gestational age <37 weeks) who were born in Istanbul Faculty of Medicine Hospital and followed by Neonatology Unit were included in the study. These children were completely different from the ones in our previous study [14]. Group 1 consisted of 29 children with birth weight less than 10th percentile (preterm SGA group; between 27.4 and 36.7 weeks) and group 2 consisted of 25 children with birth weight between 10th and 90th percentile (preterm AGA group; between 28.5 and 36.4 weeks) [15]. The chronological age of subjects at the time of investigation was between 2 and 5 years. Groups were matched for age and sex (Table 1).

Past medical history including details of the perinatal period and family history was obtained from hospital records and the parents. None of the children had severe systemic disease, neurological impairment or malformations.

Following physical examination, anthropometric measures including height, weight, waist and hip circumferences were taken by the same person in the Pediatric Endocrinology Unit using standard methods. Harpenden equipment was used for height measurement. BMI was calculated as weight (kg)/[height (m)]^2. Waist/hip ratio was calculated. All children were evaluated for puberty according to Tanner classification and all were prepubertal (testicular volume <4 ml in boys, breast stage 1 in girls and no pubic or axillary hair in both sexes) [16]. For the percentiles of birth weight and birth length national standards for preterm babies were used [15]. Height, weight, BMI and waist circumference were expressed as standard deviation scores (SDS) calculated according to national standards [17–20]. Subjects with BMI SDS between −1 and +1 were accepted as normal, those with BMI SDS between +1 and +2 were classified as overweight, those with > +2 were obese. Group 1 (SGA) and group 2 (AGA) were divided into 2 subgroups with regard to CUG. When the difference (Δ) between birth length SDS and current height SDS (Δ height SDS) was over 0.67, the subject was accepted to have a CUG in height. Similarly when the difference (Δ) between birth weight SDS and current weight SDS (Δ weight SDS) was greater than 0.67, the subject was regarded as having a CUG in weight [21], in other words, those who had moved one centile band up were regarded as having shown a CUG in height or weight. Those who moved one centile band down were regarded as having a catch-down growth. Both the preterm SGA and preterm AGA groups were divided into 2 subgroups with respect to the presence or absence of CUG.

2.2. Blood samples

After an overnight fast of 10–12 h, venous blood samples were obtained for glucose, insulin, proinsulin, sOB-R, leptin, adiponectin and visfatin levels. Glucose levels were studied immediately. Sera were stored at −80 °C in the Pediatric Endocrinology Laboratory