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Investigating for Insulin Resistance and Type 2 Diabetes Mellitus in Obese Children

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The incidence and prevalence of type 2 diabetes mellitus within the childhood period has increased in the worldwide, particularly among obese children. The aim of this study was to investigate impaired glucose tolerance and insulin resistance in obese children. Thirty-six children (18 girls and 18 boys) aged between 7.4 and 17 years with a body mass index (BMI) > 95th percentile and referred to our hospital between 1998 and 2003. Control group consisted of 30 children (13 girls and 17 boys) aged between 7.2 and 17.8 years with a body mass index between 5th and 95th percentile. Fasting and oral glucose tolerance test (OGTT) 120th min serum glucose and insulin levels were measured. The glucose results were characterized according to the World Health Organizations criteria. Insulin resistance (IR) was defined by homeostasis model assessment (HOMA) as IR_{HOMA}. Fasting glucose levels were in normal limits in all obese and control subjects. OGTT revealed that 9 of 36 obese children (25 %) had diagnosed impaired glucose tolerance and 2 children (6%) diabetes mellitus. Plasma glucose levels in OGTT were in normal limits in all control subjects. IR_{HOMA} revealed insulin resistance in 17 of 36 obese children (47%) and significantly correlated puberty (r=0.418, p=0.0217), BMI (r=0.507, p=0.002), age (r=0.513, p=0.001), and insulin level at 120th min of OGTT (r=0.821, p<0.001). Overall mean IR_{HOMA} in obese and control subjects were 4,1 ± 1.0 and 1,5 ± 0.9 , respectively. The difference of mean IR_{HOMA} levels between obese and control subjects was significantly different (p<0,001). IR_{HOMA} levels of 5 control subjects (16%) were above the level of cut-off point (2,5), however OGTT were normal in these subjects. In conclusion, the childhood obesity is one of the important risk factors for the early beginning of type 2 diabetes mellitus. An OGTT is more sensitive at identifying impaired glucose tolerance or diabetes mellitus than fasting glucose alone. Body-mass index (BMI) was strongest predictor of fasting and glucose stimulated insulin levels.

Keywords: Children, obesity, insulin resistance, Turkey

Introduction

Hypoglycemia defined as the occurence of a wide variety of sypmtoms in association with a plasma glucose concentration of 50 mg per dl or less (1). The causes of hypoglycemia can be drugs, endocrine disorders, malignancy, malnutrition and renal failure but the drugs which are used for diabetes mellitus (DM) is the most common cause of hypoglycemia (2).

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The incidence of hypoglycemia in hospitalized patients was reported 1.2% (3). As the morbidity and mortality associated with hypoglycemia isn't rare, early diagnosis and treatment may improve the diagnosis (2).

The childhood obesity is increasing rapidly world-wide. Half of the obese children have become obese adults with an especially high risk of metabolic syndrome which is characterized with insulin resistance, glucose intolerance, hypertension, lipid abnormalities, and atherosclerotic cardiovascular disease (1,2). The most important long-term health consequence of childhood obesity is an earlier onset of cardiovascular disease (3,4). The iden-tification insulin resistance and glucose intolarence

in obese children could lead to early intervention to prevent adult obesity and metabolic syndrome.

In this study we investigated an association between obesity and insulin resistance in obese children.

Material and Methods

The subjects were admitted for investigating of obesity to pediatric department between November 1998 and October 2003. Study group was involved 36 obese children [18 girls (9 prepubertal, 9 pubertal), 18 boys (6 prepubertal, 12 pubertal)] with body mass index (BMI) >95th centile, and aged between 7.4 years old and 17 years old. Control group was selected from healthy and non-obese children. Control group consisted of 30 children [(13 girls (6 pre-pubertal and 7 pubertal) and 17 boys (6 pre-pubertal, 12 pubertal)] aged between 7.2 and 17.8 years with a body mass index between 5th and 95th percentile. Family history was obtained regarding whether parents and/or siblings obese. A history of whether there were first- or second-degree relatives affected with type 2 diabetes mellitus was also recorded. Exclusion criteria were chronic illness, such as diabetes mellitus, Cushing syndrome, chronic renal failure, congenital or acquired heart disease, hematological disorders (especially thalassemia major), genetic disease (cystic fibrosis, Down syndrome, Turner Syndrome, and Prader_ Willi Syndrome), and the cases who were on chronic medical treatment (especially corticosteroids and growth hormone). Subjects were underwent thorough physical examination, including height (cm), weight (kg), blood pressure, acanthosis nigricans which is skin sign of insulin resistance, Tanner stage of puberty, and BMI. Height was measured by using a wall-mounted stadiometer, and weight was determined by using a balance scale. BMI was calculated a weight (in kilogram) divided by height (in meters) squared. Oral glucose tolerance test (OGTT) was conducted after 10- to 12-hour overnight fast with 1.75 g/kg body weight, maximum 75g glucose. Venous blood samples were taken fasting and OGTT 120th min for measurement of plasma glucose and insulin levels. The glucose results were characterized according to the World Health Organizations criteria as normal, impaired glucose tolerance, or diabetic (5). Insulin resistance (IR) was defined by homeostasis model assessment (HOMA) as IR_{HOMA} according to the formula (6);

IR_{HOMA} = [fasting glucose (mmol/L) x fasting insulin (mIU/L)] / 22.5

IR_{HOMA} >2.5 was interpreted as an impaired insulin sensitivity or insulin resistance.

Plasma glucose was determined by the glucose oxidase method using a commercial kit (Boehringer-Mannheim, Germany). Plasma insulin concentrations were determined with a radioimmunoassay kit (Equate RIA, Binax Corp, Portland, ME). The detection limit of insulin level was 2.0 mIU/L. The HbA_{1c} % was measured by the method of tur-bidimetric inhibition immunoassay (TINIA) using Tina-quant hemoglobin A_{1c} II kit (Roche Diagnostics GmbH, D-68298 Mannheim) in obese group.

This study was approved by the Committee on the use of Human Subjects in Research of the Faculty of Medicine, University of Abant İzzet Baysal, Düzce. Informed consent was obtained from the parents of children who were investigated from the aspects of glucose intolerance and insulin resistance. All results were explained to the parents by pediatric endocrinologist.

Statistical analysis

Student's t test was used for comparison of mean levels of variables among the subgroups (boy and girl, and pubertal and pre-pubertal). Bivariate correlations among parametric variables were computed using the Pearson's correlation test. The interrelationship between groups according to puberty and biochemical variables was analyzed using Spearman's correlation test. The descriptive statistical method was used where appropriate. Data are expressed as mean ± SD. A p value < .05 was considered to be statistically significant.

Results

Comparisons the mean levels of variables of pre-pubertal age and pubertal obese and control subjects are given in Table 1. According to puberty, the biochemical investigation results of obese children are given in Table 2.

According to the study protocol, BMI were > 95th percentile in all obese subjects and between 5th and 95th percentile in control subjects. Mean BMI were 16.3 ± 1.8 in pre-pubertal control subjects and 18.2 ± 2.7 in pubertal control subjects. There was no significant difference of mean BMI levels

Table 1. Comparisons the mean levels of variables of pre-pubertal age and pubertal obese and control subjects

		Obese group		Control group		P3
		Mean ± SD	P_1	Mean ± SD	P_2	
Age (y)	Pre-pubertal	9,2 ± 3.3		8,6 ± 1,3		NS
	Pubertal	12,2 ± 1,6	NS	11,5 ± 1,7	NS	NS
IR_{HOMA}	Pre-pubertal	3,4 ± 1,6		1,49 ± 0,9		<0,001
	Pubertal	4,5 ± 0,9	<0,05	1,51 ± 0,9	NS	<0,001
OGTT 0'	Pre-pubertal	4.4 ± 0,3		4,7 ± 0,4		NS
Glucose (mg/dl)	Pubertal	5.2 ± 0.8	<0,001	4,4 ± 0.6	NS	<0,05
OGTT 0'	Pre-pubertal	17,3 ± 7,9		7,4 ± 5,1		<0,001
Insulin (mIU/ml)	Pubertal	22,2 ± 4,3	0,004	7,7 ± 5,2	NS	<0,001
OGTT 120'	Pre-pubertal	7,1 ± 0,5		5,6 ± 1.1		<0,001
Glucose (mg/dl)	Pubertal	7,5 ± 1,2	<0,05	5,5 ± 1.0	NS	<0,001
OGTT 120'	Pre-pubertal	59,6 ± 35,4		22,1 ± 16,8		<0,001
Insulin (mIU/ml)	Pubertal	61,6 ± 44,1	NS	30,8 ± 21,8	NS	<0,001
BMI	Pre-pubertal	23,1 ± 4,2		16,3 ± 1,8	0,04	<0,001
	Pubertal	29,4 ± 3,8	<0.001	18,8 ± 2,8		<0,001

OGTT, oral glucose tolerance test; BMI, body mass index; NS, nonsignificant

Statistical significant at the P<0.05 levels

P1, comparison mean levels of variables of pre-pubertal and pubertal obese group

P2, comparison mean levels of variables of pre-pubertal and pubertal control group

P3, comparison mean levels of variables of pre-pubertal age and pubertal obese and control groups

Table 2. The clinical and biochemical characteristics of children with body mass index > 95% centile.

	Girls		Boys	
	Tanner stage I (N=9)	≥ Tanner stage II (N=9)	Tanner stage I (N=6)	≥ Tanner stage II (N=12)
Age (y)	8.4 ± 0.5	15.2 ± 0.7	8.7 ± 0.3	16.4 ± 0.6
Fasting glucose (mmol/L)	4.4 ± 0.1	5.6 ± 0.7	4.7 ± 0.2	5.4 ± 0.4
Fasting insulin (mIU/L)	18,4 ± 2,1	31,6 ± 4,4	19,3 ± 2,0	24,6 ±3,2
OGTT glucose 120th min (mmol/L)	6.9 ± 0.3	7.6 ± 0.4	6.7 ± 0.2	7.2 ± 0.4
OGTT insulin 120th min (mIU/L)	67,6 ± 6,2	89,4 ± 8,5	64,4 ± 5,7	74,6 ± 7,1
IR_{HOMA}	4.4 ± 0.4	5.4 ± 0.3	4.3 ± 0.3	4.7 ± 0.2
HbA_{1C} %	4.9 ± 0.2	5.4 ± 0.5	4.7 ± 0.3	5.2 ± 0.4

N, the number of cases; OGTT, oral glucose tolerance test; IR_{HOMA} , insulin resistance homeostasis model assessment; HbA_{1C}, glucolyse hemoglobin (normal, between 4.8% and 6.0%)

between pre-pubertal and pubertal control subjects. Mean BMI were 23.1 ± 4.2 in pre-pubertal obese subjects and 29.4 ± 3.8 in pubertal obese subjects. There was a significant difference the mean levels of BMI between pre-pubertal and pubertal subjects (p<0.001). As expected, BMI values were significantly different between pre-pubertal obese and control subjects (p<0.001), and also between pubertal obese and control subjects (p<0.0001). BMI showed important positive correlation with fasting and OGTT 120th min insulin levels (r=0.37, p=0.026) and IR_{HOMA} (r=0.507, p=0.002). Obesity in one or both parents correlated with BMI of the subjects (r=0.346, p=0.018).

Fasting glucose were below than 6.1 mmol/L in all obese and control subjects. However, OGTT revealed that 9 of 36 (25%) obese children had impaired glucose tolerance and 2 (6%) diabetes mellitus. There was no impaired OGTT or type 2 diabetes mellitus between control subjects. The characteristics of the subjects with impaired OGTT and type 2 diabetes in obese subjects were given in Table 3. Family history of obesity and type 2 diabetes in one or both parents were positive in 17 and 9 obese children, respectively. Diabetic two children have a positive family history for type 2 diabetes and obesity. There was no hypertension on physical examination, but acanthosis nigricans was found in 14 (39%) of 36 obese subjects.

Table 3. The characteristics of the subjects with impaired OGTT and type 2 diabetes

	Impaired OGTT (N=9)	Type 2 DM (N=2)
Age (y)	15.7 ± 1.4	16.2 ± 1.2
Fasting glucose (mmol/L)	5.8 ± 0.9	5.9 ± 0.3
Fasting insulin (mIU/L)	34,6 ± 3,2	37,8 ± 2,4
OGTT 120. min. glucose (mmol/L)	9.4 ± 1.6	13.6 ± 1.8
OGTT 120. min. insulin (mIU/L)	94,9 ± 7,3	109,7 ± 6,4
IR_{HOMA}	6.3 ± 0.4	6.9 ± 0.9
HbA_{1C} %	5.9 ± 0.4	6.8 ± 0.8

N, the number of cases
OGTT, oral glucose tolerance test
IR_{HOMA} , insulin resistance homeostasis model assessment
HbA_{1C}, glucolyse hemoglobin (normal, between 4.8% and 6.0%)

Fasting insulin and IR_{HOMA} was significantly higher in pubertal obese girls than in pubertal obese boys (31 ± 4 mIU/L vs. 24 ± 3 mIU/L, p=0.019 and 5.4 ± 0.3 vs. 4.8 ± 0.2, p=0.023, respectively). There was no significant difference of mean levels of fasting or OGTT 120th glucose levels between gender, pre-pubertal and pubertal control subjects. However, BMI was significantly different (p=0.04) between pre-pubertal and pubertal control subjects (16,3 ± 1,8 and 18,8 ± 2,8, respectively) (Table 1). Mean fasting insulin and IR_{HOMA} were higher in pre-pubertal girls than pre-pubertal boys in obese subjects, but the difference was not significant.

The overall mean fasting insulin levels was significantly higher in pubertal obese children than pre-pubertal obese children (23 ± 4 mIU/L vs. 18 ± 2 mIU/L, p=0.013). Fasting insulin levels showed insignificant difference between pre-pubertal and pubertal control subjects. Fasting insulin showed important correlation with puberty (r=0.545, p<0.001) and BMI (r=0.548, p=0.001) in obese group.

IR_{HOMA} were above cut-off level in 17 (47%) of 36 obese subjects. IR_{HOMA} was significantly correlated with puberty (r=0.418, p=0.0217), BMI (r=0.507, p=0.002), and insulin level at 120th min of OGTT (r=0.821, p<0.001).

Discussion

Child obesity has been one of the important health problems in developed countries and increasing problem in developing countries. Multifactor influence stimulating excess weight gain in children. One of the important environmental factors affect weight gain in childhood period is life style. Many countries have been developing their health policy to prevent childhood obesity and its consequences, such as early beginning of cardiovascular disease, metabolic X syndrome, and non-insulin dependent diabetes mellitus. The identification of obese children could lead to early intervention to prevent adult obesity and diabetes mellitus. Pediatricians should provide more guidance to parents regarding weight management in their children, particularly if parents are obese or diabetic.

An elevated fasting insulin level and BMI in childhood period predict of insulin resistance. Puberty is another synergistic factor for insulin resistance. In this study, fasting insulin and IR_{HOMA} showed significantly correlation in pre-pubertal or pubertal obese subjects. These findings revealed that pre-pubertal obesity is important triggering factor for insulin resistance. Puberty is one of other triggering factors for insulin resistance in adolescence period. Increased insulin resistance during puberty has been found to be mediated by hormonal changes (7-10). The sex steroids from adrenal cortex and gonads, growth hormone and related peptides increase during puberty. Sex steroids, growth hormone, and glucoocrticoids are well known factors for insulin resistance (11). Insulin stimulated glucose metabolism correlates inversely with sex steroids, GH and related peptid levels (12,13). In the presence of normal function of pancreatic ß-cells, puberty-related insulin resistance is compensated for by increased insulin secretion, leading

to peripheral hyperinsulinemia. In this study, the children who are diagnosed type two diabetes mellitus or impaired glucose tolerance had Tanner II or more pubertal stage. However, there was no subject with impaired glucose tolerance in control subjects. All these results indicate that puberty and increased body mass index show a synergistic interaction for insulin resistance in children.

We have demonstrated a significant correlation between the presence of obesity in one or both parents and higher percent BMI in their children. Environmental influences stimulating excess weight gain include decreased physical activity among children (14), owing to sedentary activities such as television viewing and playing computer game (15). Diminished physical activity can induce insulin resistance and exercise can improve insulin sensitivity (16).

Prevalence of obesity among healthy children is reported approximately 14% when both parents are lean, increasing to 40% when one parent is obese, and 80% when both parents are obese (17,18). Family history of type 2 diabetes mellitus increases the risk for future development of diabetes mellitus in obese children (8,19). In our study, two children who were diagnosed type 2 diabetes mellitus have a positive family history for type 2 diabetes and obesity.

Normal glucose tolerance is maintained in the insulin-resistant individuals by augmentation of pancreatic insulin secretion, which results in hyperinsulinemia (20). Although fasting glucose levels were in normal limits in all obese subjects, IR_{HOMA} calculation revealed insulin resistance in 47% subjects. BMI showed significant correlation with fasting insulin levels (r=0.548, p=0.001) and OGTT 120 min insulin levels (r=0.371, p, 0.026). OGTT revealed the diagnosis of impaired glucose and diabetes mellitus in 9 (25%) and 2 (6%) children, respectively. Obese children with elevated fasting serum insulin concentration are at greater risk for developing type 2 diabetes mellitus (21).

In conclusions; OGTT is more sensitive than fasting glucose at identifying insulin resistance in obese children. Increased BMI and insulin resistance in pubertal children predict impaired glucose tolerance and/or type 2 diabetes mellitus in near future. A national comprehensive preventive policy for childhood obesity should be introduced before puberty, especially in primary school-children.

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