Could Interleukin (IL)-6 Values be Used in the Identification of Glucose Intolerance in Obese Pediatric Population

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Abstract

Background: Adipose tissue is the source of a wide variety of molecules involved in the regulation of energy output and carbohydrate metabolism. Among these, cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, appear to play a role in modulating insulin sensitivity in peripheral tissues and have been associated with the development of insulin resistance in adults.

Aim of study: The aim of the study was to ascertain the relationship among the degree of adiposity, circulating fasting insulin levels, with plasma IL-6 in an obese child and adolescent population with or without glucose intolerance.

Subjects and Materials: Eighty obese children and adolescents were studied. Plasma interleukin (IL)-6 were measured for those obese with normal oral glucose tolerance Test (OGTT), and obese with glucose intolerance. These patients were compared with eighty healthy children matched for age and sex.

Results: Plasma fasting insulin concentration and HOMA (Homeostatic model assessment) were significantly higher in glucose intolerance obese patients [(28.2±14.9µIU/ml),(5.7±4.8)] compared with their results in normotolerance obese patients [(20.9±8.3µIU/ml),(4.5±2.7)] and control subjects[(14.8±6.3µIU/ml),(3.2±1.9)] ($p<0.005$,0.001) respectively, Plasma levels of (IL-6) in glucose intolerance obese patients were significantly higher (2.9±1.3 ng/ml) compared with normotolerance obese patients (2.0±1.1 ng/ml) and control subjects (1.5±0.9 ng/ml)($p<0.005$).

Interleukin (IL-6) was positively correlated with BMI, (r=0.37; $p<0.001$), waist and hip circumferences(r=0.35; r=0.33) respectively, ($p<0.001$), insulin levels (r=0.30; $p<0.001$), TG and VLDL-C (r=0.27; $p<0.001$)

Conclusion: Plasma IL-6 appears to be involved in glucose metabolism, insulin resistance, and dyslipidemia in obese children and adolescents with glucose intolerance.

Key words: Obese, interleukin-6.

Introduction:

Obese children and adults, after a period of time with obesity, may develop type 2 diabetes.[1,2]Glucose intolerance, an intermediate stage in the progression toward type 2 diabetes, may become apparent in the obesity.[3,4,5]

Insulin resistance in obese children frequently precedes the development of type 2 diabetes, metabolic syndrome, or both [6,7,8,9,10],and pre-diabetes has been reported in obese adolescents.[11,12,13]The mechanisms implicated in insulin resistance in obese subjects remain to be fully established. Adipose tissue is the source of a wide variety of molecules involved in the regulation of energy output and carbohydrate metabolism.[14,15] Among these ,proinflammatory cytokines such as tumor necrosis factor(TNF)-α and interleukin (IL)-6[16],in particular ,appear to play a role in modulating insulin sensitivity in peripheral tissues and have been associated with the development of insulin resistance in adults.[17]In addition to that, glucose induces oxidative stress ,it is also increases the transcription of nuclear factor –kB-dependent proinflammatory genes(TNF-α, and IL-6)[18,19].

Early detection of subjects with obesity – associated metabolic disorders, especially those at risk for glucose intolerance, is considered to be a priority in the public health system, given the significant medical and social repercussions of type 2 diabetes.[20,21,22]

To date, no sensitive accessible parameter has been defined that permits adequate identification of patients with glucose intolerance, although the oral glucose tolerance test (OGTT) is currently used for this purpose.[23]

Aim of study:

The aims of the study were to ascertain the relationship among the degree of adiposity, circulating fasting insulin levels, and plasma IL-6 in an obese child and adolescent population and to compare cytokine concentration among obese children and adolescents with or without glucose intolerance to determine whether these parameters could reliably identify obese children with glucose intolerance.

Subjects and Methods:

Subjects:

A total of eighty (80) obese children and adolescents [(44) boys and (36) girl], aged (12.5±2.1yrs)with a range of (8-16yrs) have participated in this study. They attended the pediatric department, of National Diabetes Center (NDC), AL-Mustansiriya University- Baghdad, from April 2011 to September 2011.All had no chronic diseases and were not taking long –term medication.

The obese subjects were compared with 80 apparently healthy children after taking their medical history as a control group matched for age and sex.

Methods:

Ten (10) ml of venous blood were collected from 10-12 hrs fasting obese and control groups. The blood sample was allowed to clot in plain tube at room temperature and serum was aspirated after centrifugation at (3000 rpm) for thirty minutes,

divided in plastic tubes and stored at (-20 C^0) until the time of estimation of:

1- Fasting plasma glucose (FPG): which was measured directly after separation using PAP Enzymatic method ,Bicon kit Germany
2- Plasma fasting insulin: using ELISA kit ,DRG Instruments, Germany.
3- Plasma Interleukin(IL-6) : using ELISA kit ,US Biological Company, USA.
4- Serum total cholesterol (TC), and triglycerides (TG) using CHO-POD Enzymatic Colorimetric kit, SPINRECT, Spain.
5- Serum HDL-C using manual HDL-cholesterol precipitation method, RANDOX, United Kingdom.

Body mass index (BMI) was calculated as the weight in Kilogram (kg) per height in meter squared (m^2) (National Institute of Health 1998) [24]

BMI (kg/m^2) = weight (kg) /Height (m^2)

Homeostatic model assessment (HOMA) was determined using the equation of Wallace et al, 2004 [25]

HOMA = FPI $\times$ FPG/ 22.5

Where FPI is fasting plasma insulin concentration (μIU/ml) and FPG is fasting plasma glucose (mmol/l)

Results:

Sex (male/female)(M/F), age, puberty stage, BMI, waist, hip circumferences, and waist to hip ratio for obese with normal OGTT, obese with glucose intolerance and control subjects, are listed in table (3.1).

From a total of eighty (80) obese children and adolescents, sixty-two (62) [thirty-four (34) boys and twenty-eight (28)girls] had a normal response to the OGTT, and eighteen (18), [ten (10) boys and eight (8) girls], had a response consistent with glucose intolerance. None had type 2 diabetes criteria, table (3.1).

Table (3.2) shows fasting plasma glucose (FPG), fasting plasma insulin (FPI), Homeostatic model assessment (HOMA), plasma interleukin- 6 (PIL-6), total cholesterol (TC), triglycerides(TG),high density lipoprotein(HDL-C), low density lipoprotein (LDL-C) and very low density lipoprotein(VLDL-C) for obese with normal OGTT, obese with glucose intolerance and control subjects.

Plasma fasting insulin concentration and HOME were significantly higher in glucose intolerance obese patients compared with their results in normotolerent obese patients and control subjects (p<0.005, 0.001) respectively, table (3.2).

Circulating plasma levels of IL-6 in glucose intolerant obese patients were significantly higher compared with normotolerent obese patients and control subjects (p<0.005) table (3.2)

Interleukin (IL-6) was positively correlated with BMI (r=0.37; p<0.001),and with waist and hip circumferences (r=0.35 and r= o.33) respectively, (p<0.001), insulin level (r=0.30; p<0.001), TG and VLDL-C(r=0.27; p<0.001)

Discussion:

Plasma IL-6 levels increase in parallel with obesity and glucose intolerance[11].In the present study, our data confirm the above fact and agree with others[3,12,6,11],since the circulating plasma levels of IL-6 and BMI in glucose intolerant obese patients were significantly higher (2.9±1.3 ng/ml)(32.0±3.1) compared with normotolerent obese patients (2.0±1.1 ng/ml) (31.2±2.9)and control subjects (1.5±0.9ng/ml)(25.2±2.0) (p<0.005)(p< 0.001) respectively table (3.1,3.2).

Table 3.1: Sex (M/F), age, puberty stage, BMI, waist, hip circumferences, and waist to hip ratio for obese with normal OGTT, obese with glucose intolerance and control subjects

Subject	Obese with normal OGTT	Obese with glucose intolerance	Control	P Value
Number(n)	62	18	80	
Sex (M/F)	34/28	10/8	44/36	N.S
Age (yrs) (Mean ± SD)	12.4± 2.0	12.5±1.9	12.9±2.2	N.S
Prepubertal	24	3	27	N.S
Puberty	25	10	35	N.S
Young adult	13	5	18	N.S
BMI (Kg/m^2) (Mean ± SD)	31.2 ± 2.9	32.0±3.1	25.2±2.0	< 0.001
Waist(cm) (Mean ± SD)	79.1 ± 10.3	92.0±11.9	77.9±9.4	< 0.001
Hip (cm) (Mean ± SD)	104.5±12.3	114.1±10.5	98.2±8.5	< 0.001
Waist/Hip ratio	0.81	0.85	0.75	0.04

N.S: Non –Significant ,   SD: Standard Deviation

Table 3.2 PFG, PFI, HOMA, PIL-6, TC, TG, HDL-C, LDL-C and VLDL-C for obese with normal OGTT, obese with glucose intolerance and control subjects.

Subject	Obese with normal OGTT	Obese with glucose intolerance	Control	P Value
FPG(mmol/l) (Mean ± SD)	4.6 ± 1.2	4.3 ± 1.1	4.9 ± 0.9	N.S
FPI(µIU/ml) (Mean ± SD)	20.6 ± 8.3	28.2 ± 14.9	14.8 ± 6.3	< 0.005
HOMA (Mean ± SD)	4.5 ± 2.7	5.7 ± 4.8	3.2 ± 1.9	< 0.001
PIL-6(ng/ml) (Mean ± SD)	2.0 ± 1.1	2.9 ± 1.3	1.5 ± 0.9	< 0.005
TC (mg/dl) (Mean ± SD)	97.5 ± 50.3	149.2 ± 110.9	75.2 ± 29.7	< 0.005
TG(mg/dl) (Mean ± SD)	152.3 ± 30.1	143.8 ± 25.2	150.2 ± 20.2	N.S
HDL-C (mg/dl) (Mean ± SD)	45.9 ± 9.8	43.2 ± 11.1	48.2 ± 10.3	< 0.02
LDL-C (mg/dl) (Mean ± SD)	90.2 ± 23.9	84.7 ± 22.7	89.6 ± 23.1	N.S
VLDL-C (mg/dl) (Mean ± SD)	19.2 ± 10.1	29.8 ± 21.9	15.1 ± 5.9	< 0.005

N.S: Non –Significant,   SD: Standard Deviation

In addition to that, this study show that Interleukin (IL)-6 was positively correlated with BMI (r=0.37; p<0.001), waist and hip circumferences (r=0.35; o.33) respectively, (p<0.001), insulin levels (r=0.30; p<0.001), TG and VLDL-C(r=0.27; p<0.001) in a similar way to that observed in adult subjects in other studies [17, 20, 21, 22].

Although a pathophysiological role cannot be deduced with this study design, the association between circulating IL-6 and several anthropometric and metabolic markers linked to insulin resistance (BMI, waist to hip and triglycerides) points to participation of this cytokine in childhood insulin resistance, as has been in adults. Although the present data suggest that plasma IL-6 could be used in the identification of glucose intolerance in the obese pediatric population, wider studies should determine whether IL-6may be an early biomarker and lipid alteration associated with obesity in children and adolescents.

Conclusion:

Plasma IL-6 appears to be involved in glucose metabolism, insulin resistance, and dyslipidemia in obese children and adolescents with glucose intolerance.

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