SERUM LEPTIN AS A MARKER FOR INSULIN RESISTANCE IN NON-DIABETIC YOUNG ARAB FEMALES IN UNITED ARAB EMIRATES

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ABSTRACT

Change in lifestyle increased the prevalence of obesity, which is associated with high serum leptin (SL) concentration and insulin resistance (IR). IR may be present, many years before the appearance of diabetes mellitus. The aim is to investigate the relationship between SL and IR in non-diabetic young female. Eighty students (aged 18-30 years) were recruited in this cross-sectional study. Fasting SL, serum insulin, blood glucose, HDL, LDL, total cholesterol, and triglycerides were measured in addition to anthropometric measurements and blood pressure. IR, Body Mass Index (BMI), Waist-hip ratio (WHR) and Waist-height ratio (WHtR) were calculated. The mean BMI was 26.7±6.0 kg/m2, mean fasting SL was 30.1 ± 15.4 mg/ml and serum HDL-cholesterol was 59.2 ± 12.2 mg/dl. BMI correlated directly with fasting SL (P<0.01), fasting insulin (P<0.01) and IR (P<0.01). IR was best predicted by Fasting SL (value± SE: 0.343±0.007, P<0.01) with which it had a strong positive correlation (P<0.01). There was a positive correlation between fasting SL and WHtR (P<0.01) but not with WHR. In addition IR correlated positively with systolic and diastolic blood pressure (r = 0.292, P<0.01 and r = 0.298, P< 0.01 respectively). There is a significant association between fasting SL and IR in non-diabetic young females that depends on body fatness and its parameters. Early preventive measures and treatment of those with IR could prevent progression to DM.

INTRODUCTION

Although many research works have been performed worldwide, there is very little information on obesity and metabolic dysfunction among young females in the United Arab Emirates (UAE). Because of changes of lifestyle in recent years, the prevalence of obesity has increased rapidly in the UAE[1] and other countries.[2] Obesity represents a significant predictor of high rate of cardiovascular disease, diabetes mellitus (DM), osteoarthritis and cancer, which in the future will demand public health action.[1] Leptin, the obese (ob) gene product, is a lipostatic hormone which is produced and secreted primarily by the adipose tissue[3,4] and to a lesser extent from non-adipocyte tissues.[5] It is believed that leptin contributes to body weight regulation through modulating feeding behavior and energy expenditure.[6,7] Impairment of leptin production or leptin receptor function causes excessive food intake, decreased energy expenditure and severe obesity[8,9] and dyslipidemia.[10] High serum leptin (SL) concentration in obesity causes oxidative stress in endothelial cells and has a vascular calcifying effect, which promotes atherogenesis.[11-14] Leptin has been associated with insulin resistance (IR) in adults; some studies report this association to be dependent on body fatness[15] and others as independent of body fatness.[16] Since IR is characterized by diminished response to the biological actions of insulin; it involves not only the carbohydrate metabolism, but also the lipid metabolism. [17] IR may be present with or without any clinical manifestation, often, many years before the appearance of frank DM, which would occur when the pancreas failed to secrete enough insulin to compensate such resistance and keep the person euglycemic.[18] Because both leptin and IR are strongly related to adiposity and other cardiovascular risk factors, studying this relationship may help clarify some aspects in the development of IR. It is important to note that obesity, IR, hypertension and dyslipidemia are important components of the metabolic syndrome.[19-21] In addition, metabolic syndrome has also been suggested to include markers of fibrinolysis, endothelial dysfunction and other substances synthesized and secreted by adipose tissue like leptin. [22] Since there are little or no documented evidences about the relationship of SL and the development of IR in our population, we aimed to investigate this relationship in non-diabetic young Arab females in UAE completing and bridging what have been done worldwide for the last few years.

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SUBJECTS AND METHODS

This cross-sectional descriptive study was carried out in the female clinic of the University of Sharjah, UAE. The following parameters were measured: weight, height, waist, blood pressure, blood glucose, insulin, lipid profile and leptin. This work was approved by the Ethical Committee at the College of Health Sciences, University of Sharjah.

1. Subjects

Because sex differences have been reported in SL, we chose to study females only.[17] Eighty young Arab female students aged between 18-30 years (mean ± SD: 21± 2.4) were included in this study. Subjects with DM or other chronic illnesses and those on medications were excluded. All subjects read the information sheet and signed the consent form before participation.

2. Biochemical methods

Blood samples were obtained in the morning by venous puncture after overnight fasting. SL concentrations were measured by ELISA. Insulin was assessed by electrochemiluminescence analyzer. Glucose was measured by enzymatic reference method with hexokinase. Total cholesterol and triglycerides were tested by enzymatic colorimetric method. LDL-cholesterol and HDL–cholesterol were measured by homogenous enzymatic colorimetric method. All samples were processed and examined according to principles of good laboratory practice by Al-Tiqani medical analysis laboratory which is certified by international external quality control program (RIQAS).

3. Indexes

Body Mass Index (BMI) = body mass (kg)/height $(m)^2$

Waist Hip Ratio (WHR) = waist circumference (cm)/hip circumference (cm)

Waist Height Ratio (WHtR) = waist circumference (cm)/height (cm)

The homeostatic index of insulin resistance (HOMA IR) was calculated according to the homeostasis model of assessment [23] as follows: HOMA-IR= fasting insulin (µU/ml) X fasting glucose (mg/dl)/405.

4. Statistical

Statistical analysis were performed using Statistical Package of Social Sciences (SPSS-version 15). Mean and standard deviation was calculated for all parameters. Pearson's correlation coefficient(r) was used for correlation analysis.

Finally, because variables are inter-related, a stepwise regression analysis was performed to find the most important explanatory variables for insulin resistance. A p value < 0.05 was considered significant.

RESULTS

The detailed characteristics of our study population are shown in (Table-1).The mean age of the studied population was 21± 2.4 years and the mean BMI was 26.7±6.0 kg/m^2. The mean fasting SL level was high together with relatively low serum HDL cholesterol levels as compared to normative values. (Table-1)

Table 1. ***Characteristics of subjects under study***

Parameter (N = 80)	Mean ± S.D	Normal
Age (yrs)	21.0 ± 2.4	-
Body Mass Index (kg/m^2)	26.7 ± 6.0	18-25
Waist / Hip Ratio	0.7 ± 0.1	< 0.8
Waist / Height Ratio	0.5 ± 0.1	< 0.5
Systolic Blood Pressure (mmHg)	112.7 ± 9.8	120
Diastolic Blood Pressure (mmHg)	70.8 ± 10.3	80
Fasting Blood Glucose (mg/dl)	79.9 ± 5.8	60-110
Total Cholesterol (mg/dl)	153.4 ± 23.6	< 200
Triglyceride (mg/dl)	69.2 ± 26.75	<150
HDL-Cholesterol (mg/dl)	59.2 ± 12.2	> 65
LDL-Cholesterol (mg/dl)	80.0 ± 21.6	< 100
HDL-Cholesterol / Total Cholesterol Ratio	0.4 ± 0.1	> 0.3
Fasting Insulin (U/ml)	8.8 ± 5.5	2.6-24.9
Fasting Serum Leptin (ng/ml)	30.1 ± 15.4	18.7-25.9
HOMA Insulin Resistance	1.8 ± 1.2	1.7-2.5*

* *Tripathy D et al and Bonora E. et al*[24, 25].

BMI showed a significant positive correlation with WHR (r=0.42, P<0.01), Fasting Insulin (r=0.377, P<0.01), fasting SL (r=0.951, P<0.01) and IR (r=0.372, P<0.01) and inverse correlation with HDL (r=-0.281, P=0.01) and HDL /Cholesterol ratio (r=-0.336, P< 0.01) as shown by (Table-2).

Table 2. ***Correlation Coefficients between BMI and different variables.***

	r =	P
Waist Hip Ratio	0.42	<0.01
Systolic blood pressure	0.281	0.012
Diastolic blood pressure	0.22	0.05
Fasting blood glucose	0.119	0.293
Total cholesterol	0.116	0.30
High density lipoprotein (HDL)	-0.281	0.011
Low density lipoprotein (LDL)	0.166	0.141
HDL/Cholesterol Ratio	-0.336	<0.01
Fasting Insulin	0.377	<0.01
Fasting Leptin	0.951	<0.01
Insulin resistance	0.372	<0.01

Body Mass Index (n=80)

Fasting SL level showed significant direct correlations with WHtR (r = 0.513, P<0.01), fasting blood glucose (0.235, P = 0.036), total cholesterol (r = 0.275, P = 0.014), fasting insulin (r = 0.417, P<0.01) and IR (r = 0.428, P<0.01) while it showed an inverse correlation with HDL / Cholesterol Ratio (r = -0.248, P = 0.027) as demonstrated in (Table-3).

Table 3. ***Correlation Coefficients between Fasting Leptin and different variables***

	r =	P
Waist Hip Ratio	0.21	0.062
Waist Height Ratio	0.513	<0.01
Systolic blood pressure	0.101	0.371
Diastolic blood pressure	0.132	0.243
Fasting blood glucose	0.235	0.036
Total cholesterol	0.275	0.014
High density lipoprotein (HDL)	-0.055	0.627
Low density lipoprotein (LDL)	0.190	0.091
HDL/Cholesterol Ratio	-0.248	0.027
Fasting Insulin	0.417	<0.01
Insulin Resistance	0.428	<0.01

IR was within the normal range (Table-1) and showed a significant positive correlation with WHR (r=0.38, P<0.01), WHtR (r=0.338, P<0.01), systolic blood pressure (r=0.292, P<0.01) and diastolic blood pressure (r = 0.298, P< 0.01). (Table-4)

Table 4. ***Coefficients of simple correlation (r) between Insulin Resistance and different variables.***

	r =	P
Waist Hip Ratio	0.380	<0.01
Waist Height Ratio	0.338	<0.01
Systolic blood pressure	0.292	<0.01
Diastolic blood pressure	0.298	<0.01
Total cholesterol	0.028	0.805
High density lipoprotein (HDL)	-0.198	0.078
Low density lipoprotein (LDL)	0.126	0.266
HDL/Cholesterol Ratio	-0.184	0.103

In order to isolate the most important predictor for IR, a stepwise multiple regression analysis was performed. The variables entered in the model were the following: BMI, WHR, systolic blood pressure, diastolic blood pressure and fasting SL. The WHR, diastolic blood pressure and fasting SL emerged as significant predictors for IR (P=0.007, P=0.036 and P=0.001 respectively). The adjusted R^2 for the IR model was 0.285 (Table-5).

Table 5. ***Multiple regression analysis of insulin resistance* with other variables*****

Independent variables	β coefficient	P-value	SE	P
BMI	NS	NS	NS	NS
WHR	0.273	5.738	2.067	0.007
Systolic blood pressure	NS	NS	NS	NS
Diastolic blood pressure	0.207	0.024	0.011	0.036
Fasting leptin	0.343	0.026	0.007	0.001

***Dependent variable**

****Independent variables (BMI, WHR, Systolic blood pressure, Diastolic blood pressure and fasting leptin)**

DISCUSSION

We examined for the first time the relationship between fasting SL and IR in young Arab females living in the U.A.E. It has been reported that being overweight increases the risk of experiencing at least one component of the metabolic syndrome by approximately threefolds [26] The participants in our study were found to be overweight, as defined by BMI. This together with a borderline WHtR,[27] significant positive correlation of BMI with the blood pressure and a relatively low mean HDL-cholesterol level increase the chances of development of metabolic impairments and cardiovascular dysfunction in this population which is consistent with another study in the region.[28] It has been reported that obesity along with continuous weight gain especially in youth is associated with the development of altered glucose metabolism and other elements of metabolic syndrome. [29] The BMI in our subjects was positively correlated with fasting insulin and IR. This, along with very strong positive correlation of BMI with fasting serum leptin indicates that the subjects may have elements of glucose metabolism impairment, putting this group at high risk for the development of type 2 diabetes mellitus in the future. The fasting SL level in our sample was high and it showed a significant positive correlation with BMI, WHtR, total cholesterol, fasting blood glucose, fasting insulin and IR (Table-2&3). The correlation of fasting SL with WHtR and not with WHR could suggest the enormous impact of abdominal obesity on hyperleptinemia rather than the accumulation of fat around the hip and thighs. The positive correlation of fasting SL with fasting insulin was stronger than that with fasting blood glucose. This could probably indicate early stage of development of IR in our study population where hyperinsulinemia precedes the development of hyperglycemia.[30,31] Positive associations of leptin and hyperinsulinemia have been reported independent of adiposity, [32] suggesting that there may be an increased resistance to the effects of leptin in insulin-resistant states. Because of such strong correlations, it is reasonable to suggest that leptin may play a role in the development of insulin resistance. It has been speculated that weight management could potentially modify the relation between leptin and IR and modify the development of metabolic syndrome and cardiovascular risks.[33] It is interesting to note that IR shows a significant positive correlation with systolic and diastolic blood pressure. This indicates the subjects with hyperinsulinemia could develop hypertension in the future. [31] Multivariate analysis demonstrated that WHR, diastolic blood pressure and fasting SL are important variables to predict IR. Among these variables, fasting serum leptin showed the strongest correlation further reinforcing the important relationship between fasting serum leptin levels and the development of IR.

In conclusion, Our studied subjects were overweight with hyperleptinemia and had significant association between fasting SL and IR. This together with significant correlations of IR with the blood pressure makes them at high risk of development of DM and cardiovascular disorders in the future. Therefore, preventive measures could be adopted early, such as giving the people adequate dietetic orientation and a advising them for an early consultation with a nutritionist, developing special programs of physical activity and treating those who have IR with medications, which may be a therapeutic option in the near future**.** Additional studies are necessary, including larger samples with a control group of non-obese subjects incorporating a longitudinal follow-up in order to confirm the prevalence of IR in the youth.

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