Association of parental history of type 2 diabetes mellitus with leptin levels in Jordanian male youths

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ABSTRACT

الأهداف: التحقق ما إذا كان هناك علاقة بين ارتفاع معدل مصل اللبتين (serum leptin) عند مجموعة من الذكور وبين وجود التاريخ المرضي للسكري من النمط الثاني عند الأبوين (T2DM) وكذلك علاقة هذا الارتفاع بمؤشر كتلة الجسم (BMI) لنفس الفرد.

الطريقة: تمت هذه الدراسة المقطعية في مختبرات قسم التقنيات الطبية، جامعة العلوم التطبيقية، عمّان، الأردن وذلك خلال الفترة من يناير إلى إبريل 2009م، وفيها تم تقسيم 116 طالبا من كلية التمريض تتراوح أعمارهم ما بين 24–18عاما إلى أربع مجموعات. تم هذا التقسيم بناءً على وجود تاريخ مرض (T2DM) عند الأبوين وكذلك مؤشر كتلة الجسم، وقبل الإفطار تم قياس سكر الدم، ومستويات الشحوم في الدم، و مستويات مصل اللبتين في الدم لدى الطلاب.

النتائج: تشير نتائج البحث إلى أن مستويات مصل اللبتين عند الذكور الذين يعانون من الوزن الزائد أو السمنة ممن لديهم تاريخ بمرض (T2DM) عند الأبوين كانت أعلى من قرناءهم الذين يعانون من السمنة أو الوزن الزائد ولكن لا وجود لتاريخ المرض عند الأبوين وتقدر القيمة الاحتمالية (p<0.001)، ولقد وصل عدد الذكور الذين لديهم تاريخ بمرض (T2DM) عند الأبوين 83 طالباً من أصل 116 (71.6%). وبالمقارنة مع المجموعات الأخرى فقد تم ملاحظة ارتفاعاً كبيراً في مستويات ثلاثي الجليسريد (TG) و معدل الكولسترول (TC) عند الطلاب الذين يعانون من السمنة أو الوزن الزائد وكان لديهم تاريخ بالمرض (p<0.001)، في حين لم يكن هناك فروق واضحة في مستويات البروتين الدهني عالي الكثافة (HDL) والبروتين الدهني منخفض الكثافة (LDL) وسكر الدم وذلك عند مجموع الطلاب الذين تضمنتهم الدراسة.

خاتمة: ارتفاع مستويات مصل اللبتين عند الذكور الأردنيين الذين يعانون من السمنة أو الوزن الزائد قد تكون أشد ارتباطا بوجود تاريخ مرض (T2DM) عند الأبوين من ارتباطها بمؤشر كتلة الجسم لنفس الفرد.

Objectives: To investigate the association between high level serum leptin in male youths in relation to parental history of type 2 diabetes mellitus (T2DM) and body mass index (BMI).

Methods: This cross-sectional study was carried out at the Department of Medical Technology, Applied Science University, Amman, Jordan during the period from January to April 2009. One hundred and sixteen Jordanian male nursing students aged 18-24 years were divided into 4 groups according to parental history of T2DM and BMI. Fasting blood samples were measured for blood glucose, lipid profile, and serum leptin.

Results: Serum leptin levels in overweight and obese male youth diabetic patients with parental history of T2DM were significantly higher than in those overweight and obese without parental history (p<0.001). Of the 116 subjects, 83 (71.6%) had a positive parental history of T2DM. Compared with other groups, significant (p<0.001) elevation was observed in the mean cholesterol and triglyceride levels of obese T2DM. No significant differences were detected in high-density lipoprotein, low-density lipoprotein, and blood glucose levels among all study groups.

Conclusions: High levels of leptin in overweight and obese Jordanian male youths were more likely associated with a positive parental family history of T2DM than BMI factor.

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Recent Jordanian studies have shown an increase in the prevalence of diabetes mellitus, impaired fasting glycemia, overweight, and obesity among Jordanians over 10 years by 31.5%.[1,2] Khader et al,[3] demonstrated that the prevalence of overweight among Jordanian children was high compared to the neighboring countries, but the prevalence of obesity was lower.[3] In contrast, Ibrahim et al[4] found that obesity was more frequent than overweight among Jordanian children aged 3-6 years. Although the paradoxical findings of the 2 reports, the results reflect increased prevalence of overweight and obesity among Jordanian children and emphasize the importance of common genetic variants effects on the risk for type 2 diabetes mellitus (T2DM).[5] The major risk factors associated with diabetes were age, family history, obesity, hypertension, and high triglycerides.[6] Genetics influence the development of T2DM, making family history of this condition a risk factor for patients. Subsequently, candidate gene studies suggest that, genetic influence on susceptibility to T2DM is increased with body mass index (BMI).[7] On the other hand, the levels of leptin, a hormone secreted by white adipose tissue, correlate strongly with BMI,[8] but there are large inter-individual variations and many other factors including body fatness appear to affect plasma leptin levels. As long as the obesity continues, the development risk of T2DM increase.[9,10] Furthermore, Koebnick[11] and Shahid[12] studies revealed that the increasing prevalence of obesity in childhood and adolescence accompanied by insulin resistance explain the increasing incidence of T2DM in particular families. Leptin has been implicated in the pathophysiology of obesity-related insulin resistance,[13,14] but the role of leptin in T2DM pathogenesis is still not completely clear and paradoxical. Several studies have confirmed that the elevated levels of both insulin and leptin are common features of obesity.[15-18] Furthermore, individuals with a family history of diabetes may have tendency to gain weight via central leptin resistance.[19,20] Dixon et al[21] found that approximately 80% of the subjects with T2DM are obese. Genetics tendency is believed to play a major role in the pathogenesis of obesity.[22,23] Therefore, family history is gaining more importance, since the mechanism leading to T2DM in youth is more comprehensible as indicated in the recent studies. On the other hand, many recent studies of T2DM have correlated leptin levels with obesity rather than family history of the disease.[24-27] Thus, the aim of the current study is to investigate whether parental history of T2DM or BMI of the subject is more closely associated with high levels of serum leptin in male youth.

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Methods. This was a cross sectional study carried out in the Applied Science University, Amman, Jordan during the period from January to April 2009. Information on parental history was obtained from subjects, either by self-reported or directly interviewed through a written anonymous questionnaire. This study was performed using a protocol for the protection of human subjects approved by the Applied Science University Ethical Committee, Amman, Jordan. Written informed consent and demographic characteristics and current medications were obtained from each subject. To avoid confounding factors known to affect leptin levels, subjects with chronic disease such as diagnosed cardiovascular diseases, cerebrovascular disease, dyslipidemia, stable hypertension treated by drugs, chronic hepatic, renal, or taking any kind of medications during the previous 2 months were excluded. One hundred and sixteen Jordanian male nursing students aged 18-24 years were divided according to the BMI, used as an index of general obesity and parental history of T2DM, into 4 groups.

Group 1 (control), subjects (n=18) with normal weight (BMI 18.5-24.9 kg/m^2) and without parental history of type 2 diabetes (-T2DM), (both parents never had diabetes). Group 2, subjects (n=15) were overweight and obese (BMI ≥25.0 kg/m^2) (-T2DM and without parental history of 2 diabetes). Group 3, subjects (n=44) with normal weight and positive parental history of T2DM (one parent had diabetes). Group 4 (n=39) overweight and obese subjects with parental history of 2 diabetes.

Fasting venous blood samples were obtained, centrifuged and stored at -20 °C until assayed. The following parameters were measured: blood glucose levels (using one touch test; Lifescan; Johnson & Johnson, Palmitas, CA, USA), serum leptin levels (by enzyme immunoassay; ELISA kit, DRG Diagnostics, Marburg, Germany), triglycerides, total cholesterol, and high density lipoprotein cholesterol (HDL) (by enzymatic colorimetric kits, Linear Chemicals, Barcelona, Spain). Low density lipoprotein cholesterol (LDL) was calculated from the Friedewald equation.[28]

Statistical analyses were performed using the STATISTICA 6.0 for Windows software (StatSoft, Tulsa, Oklahoma). Data were expressed as means±SD. The differences among subjects with or without parental history of type 2 diabetes were analyzed with a one-way ANOVA followed by LSD multiple comparison test. Differences were considered significant at $p<0.05$. Student's t test for independent samples was used to

Table 1 - Selected characteristics of 116 Jordanian male youth with normal or over-weight and with or without parental history of diabetes (mean±SD).

Characteristics	N-T2DH	O-T2DH	N+T2DH	O+T2DH
Number of patients	18	15	44	39
Age (years)	22.30±1.8	21.53 ±1.12	21.82±1.94	22.19±1.83
Body mass index (kg/m^2)	23.05±1.58	26.94±2.07	22.34±1.94	29.92±3.76
Height (m)	173.8 ±7.40	176.93±6.08	175.09±4.8	175.92±6.86
Weight (kg)	69.90±7.80	85.46±7.80	68.4± 6.6	92.97±12.34
Blood glucose (mg/dl)	85.06±12.11	85.20±12.4	86.3±11.08	87.6 ±10.91
Cholesterol (mg/dl)	183.50±31.7	167.46±20.68	165.6± 33.98	187.17±32.08*
LDL cholesterol level (mg/dl)	106.20±31.48	93.13±19.18	97.43± 34.91	112.25±32.04
HDL cholesterol level (mg/dl)	52.66±8.10	51.73±9.13	48.81±8.40	49.54±8.56
Triglyceride level (mg/dl)	128.60±48.20	128.6±48.20	112.4±45.8	157.82±68.73*

*Significant difference (p<0.01) in O+T2DH group compared with other groups. N-T2DH - Normal weight subjects without parental history of type 2 diabetes. O-T2DH - Overweight and obese subjects without parental history of 2 diabetes. N+T2DH - Normal weight subjects with parental history of type 2 diabetes. O+T2DH - overweight and obese subjects with parental history of type 2 diabetes.

Table 2 - Probability values and Pearson correlations (r) between serum leptin levels with anthropometric variables and blood parameters in four study groups.

Variable	N-T2DH (n=18)		O-T2DH (n=15)		N+T2DH (n=44)		O+T2DH (n=39)	
	r	*P*-value	r	*P*-value	r	*P*-value	r	*P*-value
Age (years)	0.453	0.059	-0.605*	0.017	-0.305	0.101	0.192	0.301
Body mass index (kg/m^2)	0.261	0.295	0.309	0.262	-0.45	0.781	0.581†	0.000
Height (m)	-0.307	-0.216	-0.179	0.524	0.154	0.336	0.017	0.920
Weight (kg)	-0.102	0.687	0.179	0.523	0.034	0.834	0.596†	0.000
Cholesterol (mg/dl)	0.400	0.100	-0.285	0.303	0.194	0.223	0.119	0.472
LDL cholesterol level (mg/dl)	0.391	0.108	-0.221	0.429	0.144	0.369	0.804†	0.000
HDL cholesterol level (mg/dl)	-0.094	0.711	-0.227	-0.415	0.121	0.453	-0.060	0.725
Triglyceride level (mg/dl)	0.149	0.556	-0.143	0.610	-0.204	0.184	0.250	0.124

†Correlation is significant at the 0.01 level (2 tailed), *Correlation is significant at the 0.05 level (2 tailed)

evaluate the differences between negative T2DH and positive T2DH individuals.

Results. ***General characteristics of study subjects.*** Baseline clinical and laboratory features of the 116 subjects included in the study are shown in **Table 1.** The mean age of all 116 subjects was 21.98 ± 1.78 years and ranged from 18-24 years. Eighty-three subjects (71.6%) had a parental history of T2DM and 47% of these were overweight or obese (39 subjects). No significant differences were noted in the serum high density lipoproteins (HDL)-cholesterol (p=0.346) and low density lipoproteins (LDL) cholesterol (p=0.106) levels among all study groups, whereas triglyceride (p<0.001) and total cholesterol (p≤0.011) were significantly elevated in normal weight subjects with and without parental history of T2DM compared with other groups (**Table 2**). No difference in serum mean levels of glucose was also observed between 4 groups in this study.

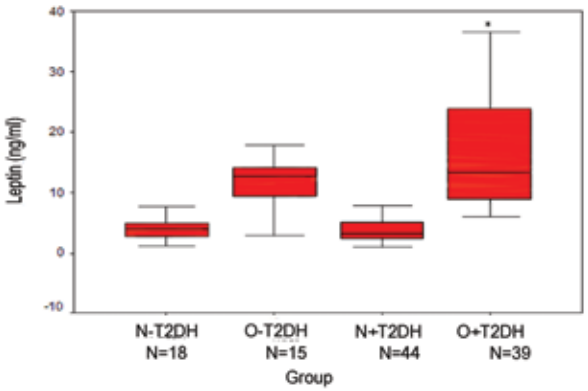

Figure 1 - Serum leptin levels in 116 Jordanian male youth with normal or overweight and with or without parental history of diabetes. *Significant correlation (p<0.001) between the serum leptin levels and parental history of type 2 diabetes in O+T2DH when compared to other three groups. N-T2DH - normal weight subjects without parental history of type 2 diabetes. O-T2DH - overweight and obese subjects without parental history of 2 diabetes, N+T2DH - normal weight subjects with parental history of type 2 diabetes, O+T2DH - overweight and obese subjects with parental history of 2 diabetes.

Table 2 summarizes the correlations between serum leptin levels with blood parameters and anthropometric variables. Among all 4 study groups and of all blood parameters and anthropometric variables, only 3 items in group overweight and obese subjects with parental history of T2DM revealed significant with $p<0.001$; BMI (r= 0.581; $p<0.001$), weight (r=0.596; $p<0.001$), and LDL cholesterol (r= 0.804; $p<0.001$).

Association between serum leptin levels and parental history of diabetes. As shown in **Figure 1**, subjects in overweight and obese subjects with parental history of T2DM group have significant ($p<0.001$) higher leptin levels when compared to those in the other 3 groups: normal weight subjects without parental history of T2DM, normal weight subjects with parental history of T2DM, and overweight and obese subjects without parental history of T2DM (17.31±5.67 versus 3.99±1.8, 11.43±4.23 and 3.72±2.03 ng/ml).

Discussion. In this cross sectional study on Jordanian male youth, we found that high leptin levels in overweight and obese subjects were more associated with a positive parental history of T2DM than BMI in overweight and obese subjects. The most consistent association found among the different study groups was observed between leptin levels and parental history of diabetes in overweight and obese groups. Interestingly, the variability of serum leptin levels was higher among overweight and obese subjects with positive parental history of diabetes mellitus. Such variability was not noted among overweight and obese subjects without parental history of diabetes mellitus. Although there was no significant difference in LDL-cholesterol levels among 4 study groups, yet there is a positive correlation between LDL-cholesterol levels and serum leptin levels in overweight and obese subjects with parental history of T2DM group (**Table 2**). The age of an individual, when the disease is diagnosed, is an important factor in determining further family history risk assessment.[29] Notably, many reports have correlated high leptin levels in diabetic relatives with ages[30-32] and BMI,[33] but the extent to which changes may contribute these modulations still unclear.[321,34] However, our results may reflect obesity gene activity during the period of youth in overweight and obese subjects who had a positive parental history of T2DM. Further study required to clarify this issue. Our data are in agreement with previous studies.[11,35,36] In a case-control study including 190 Italian newborns with and without family history of diabetes, Buongiorno et al[36] found that newborns with grandparents affected by diabetes mellitus have increased plasma levels of leptin. Koebnick et al[11] noted that family history of T2DM was associated with higher leptin levels in overweight Latino children. Similarly, Shahid et al[12] indicated that T2DM associated risk factors are more vigorously expressed in male offspring with a history of diabetes in both parents. On the other hand, Brito al[27] reported that, increased concentrations of serum leptin in the relatives appear to be associated with the insulin resistance, but not with a family history of T2DM. Obesity and family history of T2DM confer approximately equal and synergistic risks for the prevalence of T2DM in National Health and Nutritional Examination Survey studies.[36] In the present study, increased BMI paralleled by an increase in serum leptin and associated with positive parental history of T2DM, therefore, our data emphasize presence of candidate genes as a part of genetic influence of a family history on susceptible individuals to T2DM. Although obesity and T2DM have been described as synergistic civilization syndromes to emphasize the important association between environmental and genetic factors in their pathophysiology,[37,38] there is no such study in the literature that can quantify the degree of genetic influence for the family history of T2DM. Schwarts and Chadha[39] reported that the genetics may influence the development of T2DM. Thus, making family history of this condition a risk factor for patients. Recently, Poulsen et al[40] in adult twins found that a 50% of T2DM concordance rate in monozygotic twins and a 37% concordance rate in dizygotic twins. Therefore, the major limitations of current study were the lack of DNA related study test and some contributing obesity factors such as waist circumflex, physical inactivity, dietary, smoking, and drinking.

In conclusion, this study has demonstrated that high levels of leptin in overweight and obese Jordanian male youth were more associated with a positive parental family history of T2DM than BMI factor. Further studies detecting inter-individual DNA variations is required to clarify this dogma.

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