The Relationship Between Leptin Concentration and Insulin Resistance in Chinese Type 2 Diabetic Patients

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Objectives. Leptin is an adipocyte-secreting hormone that regulates appetite and body weight. In non-diabetic subjects, its concentration correlates with insulin resistance. However, in type 2 diabetic patients, this relationship is inconsistent. Because of the differences in leptin concentration across ethnicities, compared with healthy subjects, in type 2 diabetic patients and the ethnic differences related to insulin resistance, the purpose of this study was to investigate the relationship between leptin concentration and insulin resistance in Chinese type 2 diabetic patients.

Methods. We recruited 172 type 2 diabetic patients (75 men and 97 women) into this study. Fasting plasma glucose, serum insulin, leptin concentration, and body mass index (BMI) were measured. Homeostasis model assessment (HOMA) was used to estimate insulin resistance.

Results. Simple linear regression analysis revealed that HOMA and BMI independently correlated with leptin concentration ($p < 0.001$) in both genders. Multiple linear regression analysis showed that in male subjects (n = 75) and female subjects (n = 97), HOMA and BMI were each significant predictors of leptin concentration, and that these factors accounted for 45.45% of the variance in leptin concentration ($R^2 = 0.4545$) in male subjects and 37.34% of the variance ($R^2 = 0.3734$) in female subjects. Even after further adjusting for insulin resistance and hypertension, and modifying the medication, HOMA and BMI were still shown to be independently correlated with leptin concentration in both genders.

Conclusions. Leptin concentration significantly correlated with insulin resistance in Chinese type 2 diabetic patients. This relationship was not gender specific. **(Mid Taiwan J Med 2003;8:141-7)**

Key words

leptin, homeostasis model assessment, type 2 DM

INTRODUCTION

Leptin, the product of the ob gene, is a 167-amino acid hormone secreted by adipocytes, which plays an important role in the regulation of body weight [1,2]. Its concentration positively correlates with percent body fat and body mass index (BMI) [3]. Percent body fat positively correlates with insulin resistance [4]. Therefore, it is predicted that leptin concentration should be positively correlated with insulin resistance. Many studies have found an independent positive

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correlation between leptin concentration and insulin resistance among non-diabetic subjects [4-8]. Sheu and coworkers [9] and Hattori and coworkers [10] reported that the correlation exists in non-diabetic men but not in non-diabetic women which indicates that gender affects this relationship.

Type 2 diabetes mellitus (DM) is an extreme manifestation of insulin resistance. Only a few reports have examined the relationship between leptin concentration and insulin resistance in type 2 diabetic patients and the results from these studies were inconsistent. Mohamed-Ali and coworkers found that leptin concentration was not significantly associated with insulin resistance in type 2 diabetic patients [11]. Other studies found that there is a correlation between leptin concentration and insulin resistance in type 2 diabetic patients [8] or only in type 2 diabetic men but not in type 2 diabetic women [10,12]. It has been demonstrated that leptin concentration in type 2 diabetic patients, compared with healthy subjects, is different among different ethnic groups. Abdelgadri and coworkers found lower leptin concentration in Sudanese type 2 diabetic patients than in healthy individuals [8]. Lower leptin concentrations were noted by Tatti and coworkers when data from both genders were combined, but such differences disappeared when the data from the population were analyzed according to gender [13]. Our data showed that, in Chinese female type 2 diabetic patients, leptin concentration was lower than in healthy subjects; however, this was not true in Chinese male type 2 diabetic patients [14]. In contrast, Fischer and coworkers demonstrated higher leptin concentrations in type 2 diabetic patients than in healthy subjects [12].

Insulin resistance also varies from ethnic group to ethnic group. People of African ancestry are more likely to be insulin resistant than white Americans [15]. Asian Indians have a higher rate of insulin resistance than Chinese or Malays [16]. Because of the differences in leptin concentration, compared with healthy subjects, among different ethnic type 2 diabetic patients and the ethnic differences of insulin resistance, the relationship between leptin concentration and insulin resistance in Chinese type 2 diabetic patients needs to be elucidated. However, there have been no reports concerning the relationship between leptin concentration and insulin resistance in Chinese type 2 diabetic patients. Therefore, the aim of this study was to investigate the relationship between leptin concentration and insulin resistance in Chinese type 2 diabetic patients.

MATERIALS AND METHODS

We recruited 172 type 2 diabetic patients (75 men and 97 women) into this study. Type 2 DM was diagnosed according to the 1985 World Health Organization criteria [17]. All type 2 diabetic patients were being treated with diet alone or diet plus oral hypoglycemic agents (diet alone 4.7%, sulfonylurea 85.5%, metformin 77.3%, α-glucosidase inhibitor 17.4%). Type 2 diabetic patients who were being treated with insulin or who had serum creatinine levels > 133 μmol/L (1.3 mg/dL) were excluded from the study. About half of the type 2 diabetic patients also had hypertension and were being treated concomitantly with antihypertensive agents (diuretics 2.3%, angiotensin converting enzyme inhibitors 27.3%, calcium channel blockers 18.6%, β-blockers 4%, α-blockers 17.4%, angiotensin II antagonists 5.8%). This study was approved by the Human Research Committee of the China Medical University Hospital.

Patients reported to the out-patient clinic following an overnight fast. They were weighed in light clothing and their heights were recorded. BMI was calculated in kg/m^2. Blood was drawn for assays of fasting plasma glucose, serum insulin, and leptin concentration. The glycated hemoglobin A_1c (HbA_1c) level for the three months preceding the study was recorded. Insulin resistance from fasting serum insulin and plasma glucose concentration was estimated by HOMA [18].

Plasma glucose concentrations were assayed by the glucose oxidase method (Astra-8,

Table 1. Clinical and metabolic characteristics of the study patients

	Men (N = 75)	Women (N = 97)	*p*
Age (yr)	54.6 ± 11.1	58.1 ± 10.5	0.032
BMI (kg/m^2)	25.7 ± 4.0	26.3 ± 4.8	0.401
FPG (mmol/L)	8.0 ± 1.7	8.3 ± 1.8	0.370
FSI (pmol/L)	75.3 ± 56.0	80.4 ± 76.8	0.633
HOMA	3.8 ± 2.9	4.2 ± 4.1	0.454
Leptin (ng/mL)	3.9 ± 3.6	7.8 ± 5.6	< 0.001
HbA_{1c} (%)	6.8 ± 1.2	6.9 ± 1.2	0.913

Values are mean ± standard deviation. BMI = body mass index; FPG = fasting plasma glucose; FSI = fasting serum insulin; HOMA = homeostasis model assessment.

Table 2. Simple linear regression analysis with leptin as a dependent variable

	Men (N = 75)				Women (N = 97)			
Variables	EC (β)	SE	*p*	R^2	EC (β)	SE	*p*	R^2
HOMA	0.701	0.119	< 0.001	0.323	0.605	0.126	< 0.001	0.196
FPG	0.027	0.013	0.047	0.053	−0.013	0.018	0.472	0.006
BMI	0.537	0.081	< 0.001	0.374	0.659	0.098	< 0.001	0.321
Age	− 0.030	0.037	0.432	0.009	−0.092	0.054	0.094	0.029
HbA_{1c}	0.270	0.312	0.390	0.010	−0.068	0.495	0.891	< 0.001

EC = estimated coefficient; SE = standard error; HOMA = homeostasis model assessment; FPG = fasting plasma glucose; BMI = body mass index.

Beckman, CA, USA). HbA_{1c} levels were measured by ion-exchange HPLC (HLC-723 GHbV, Tosoh, Tokyo, Japan). Serum insulin concentrations were determined by a commercial radioimmunoassay (RIA) kit (Diagnostic Products Corp., Los Angels, CA, USA). The inter-assay coefficient of variation (CV) of insulin was 8.7% and the intra-assay CV was 3.5%. Serum leptin concentrations were measured with a commercial RIA kit (Linco Research, St. Louis, MO, USA). The inter-assay CV of leptin was 6.5% and the intra-assay CV was 3.6%.

All data are presented as mean ± standard deviation (SD). Differences between genders were compared by Student's *t* test. The correlation between leptin concentrations and other metabolic variables were assessed by simple linear regression analysis. The independent effect of other metabolic variables on leptin concentrations was identified by multiple linear regression analysis. A *p* value of less than 0.05 was considered statistically significant. Data were analyzed by SAS 6.12 (SAS Institute Inc., NC).

RESULTS

Table 1 shows the clinical and metabolic characteristics of the patients. Female patients had significantly higher leptin concentrations than male patients ($p < 0.001$). Simple linear regression analysis revealed that there was a positive correlation between leptin concentration and HOMA and BMI in both genders ($p < 0.001$) (Table 2). Fasting plasma glucose levels correlated with leptin concentration only in male patients; however, age and HbA_{1c} did not correlate with leptin concentration (Table 2). Multiple linear regression analysis revealed that both HOMA and BMI were independent significant predictors of leptin concentration in both genders. These two predictors explained 45.45% of the variance in male patients (R^2 = 0.4545) and 37.34% of the variance in female patients (R^2 = 0.3734) (Table 3). Since some medications, such as metformin, diuretics, α-blockers, and β-blockers, may affect insulin resistance, the effect of these medications was accounted for in the model. HOMA and BMI

Table 3. Multiple linear regression analysis with leptin as a dependent variable

	Men (N = 75)			Women (N = 97)		
Variables	EC (β)	SE	*p*	EC (β)	SE	*p*
HOMA	0.401	0.131	0.003	0.357	0.127	0.006
BMI	0.399	0.096	<0.001	0.551	0.107	<0.001
Age	0.028	0.029	0.341	0.031	0.047	0.513
HOMA	0.368	0.125	0.005	−0.359	0.127	0.006
BMI	0.479	0.096	<0.001	0.534	0.109	<0.001
Age	0.052	0.029	0.078	0.027	0.048	0.579
Medication	−2.538	0.894	0.006	1.127	1.112	0.314
HOMA	0.369	0.127	0.005	0.387	0.129	0.003
BMI	0.480	0.097	<0.001	0.490	0.113	<0.001
Age	0.053	0.030	0.081	0.0126	0.049	0.800
Medication	−2.526	0.918	0.008	0.681	1.158	0.558
HTN	−0.046	0.643	0.943	1.368	1.031	0.188

EC = estimated coefficient; SE = standard error; HOMA = homeostasis model assessment; BMI = body mass index; HTN = hypertension.

were still shown to be independently correlated with leptin concentration (Table 3). It has been shown that leptin concentrations of hypertensive patients are different from healthy subjects [19-23]; therefore, we further adjusted for hypertension in our model. Again, HOMA and BMI still correlated with leptin concentration (Table 3).

DISCUSSION

Previous studies [24,25] have demonstrated that subcutaneous fat correlates more closely with leptin concentration than visceral fat does. In addition, upper body fat is more closely associated with insulin resistance than lower body fat is [26]. Wang and coworkers reported that Asians (Chinese, Japanese, Koreans, Filipinos) have more subcutaneous fat, in particular more upper-body subcutaneous fat, than Caucasians [27]. In this study, we found that leptin concentration positively correlated with insulin resistance in Chinese type 2 diabetic patients. This result is consistent with Sudanese [8] and Caucasian [12] type 2 diabetic patients. Mohamed-Ali and coworkers [11] did not find this relationship in their study; however, they had a relatively small patient population (22 males and 10 females). The HbA_1c levels in their study (median HbA_1c 9.9% in men, 12.0% in women) were higher than in our study (mean HbA_1c 6.9 ± 1.2%). However, the different condition of blood sugar control can not explain these contrasting results since leptin concentration was not shown to be associated with HbA_1c levels (Table 2). Hyperglycemia has (referred to as "glucose toxicity") been shown to have a deleterious effect on insulin action [28]; the relationship between leptin concentration and altered insulin resistance in poorly controlled type 2 diabetic patients needs further elucidation. The fact that the relationship between leptin concentration and insulin resistance is independent of BMI suggests an important role of insulin in the regulation of leptin concentration in type 2 diabetic patients.

We found that leptin concentrations are significantly higher in women than in men, a result consistent with previous reports [4,8-13]. Haffner and coworkers showed that women have higher levels of overall adiposity and greater subcutaneous adiposity than men [29]. As previously mentioned, subcutaneous fat produces more leptin than visceral fat [24,25]. The difference in fat distribution between men and women may contribute to the difference in leptin concentration [30,31].

In this study, simple linear regression

analysis revealed an inverse correlation between age and leptin concentration; however, this correlation was not evident when multiple linear regression analysis, incorporating the effects of HOMA and BMI, was used. Considine and coworkers [3] also found no independent effect of age on serum leptin concentration after adjusting for body fat in healthy subjects; however, another study [32] revealed an inverse relationship between age and leptin concentration in healthy subjects. The reason behind the discrepancy between these studies is unknown at present.

In conclusion, leptin concentration was significantly correlated with insulin resistance in both male and female Chinese type 2 diabetic patients. The relationship between leptin concentration and insulin resistance in poorly controlled type 2 diabetic patients and the relationship between age and leptin concentration need further investigation.

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中國人第2型糖尿病病人瘦素濃度與胰島素抗性的相關性

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目的 瘦素是脂肪細胞所分泌的荷爾蒙，能夠調節食慾和體重。在非糖尿病病人，瘦素濃度和胰島素抗性是呈相關性的；然而，此種相關性在第2型糖尿病病人仍未確立。由於瘦素濃度和胰島素抗性，會因種族或有無第2型糖尿病而有所差異，本研究旨在探討中國人第2型糖尿病病人，其瘦素濃度和胰島素抗性的相關性。

方法 一百七十二位第2型糖尿病病人(男性75位，女性97位)納入本研究。測量其空腹血糖、血清胰島素、瘦素濃度、身體質量指數及胰島素抗性(Homeostasis Model Assessment，HOMA)。

結果 在簡單線性迴歸分析中，不論男性或女性病人，身體質量指數和胰島素抗性均與瘦素濃度呈顯著的相關($p < 0.001$)。複迴歸線性分析顯示，在男性病人，身體質量指數及胰島素抗性是瘦素濃度的預測因子，可解釋45.45%的變異性；在女性病人，此二項預測因子，可解釋37.34%的變異性。進一步校正會改變胰島素抗性的藥物和高血壓後，此種相關性在兩性間仍然呈顯著而獨立的相關。

結論 在中國人第2型糖尿病病人，瘦素濃度和胰島素抗性呈顯著的相關性。此相關性無性別上的差異。（中台灣醫誌 **2003;8:141-7**）

關鍵詞

瘦素，胰島素抗性，第2型糖尿病

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