# Lower Serum Leptin Concentrations in Female Subjects with Type 2 Diabetes Mellitus

Ching-Chu Chen, Tsai-Chung Li[1], Chwen-Tzuei Chang, Chih-Ming Chien,

Rong-Hshing Chen, Tzu-Yuan Wang

Division of Endocrinology and Metabolism, Department of Medicine, China Medical College Hospital;

[1]Institute of Chinese Medical Science, China Medical College, Taichung, Taiwan, R.O.C.

***Objectives.*** Leptin is an adipocyte-secreting hormone which regulates appetite and body weight. Its concentration differs among different diseases. The purpose of this study was to compare leptin concentrations between subjects with type 2 diabetes mellitus (DM) and healthy subjects.

***Methods.*** We recruited 172 subjects with type 2 DM (75 males and 97 females) and 158 healthy subjects (79 males and 79 females) for this study. Fasting plasma glucose, serum insulin and leptin concentrations, and body mass index (BMI) were measured.

***Results.*** The serum leptin concentration of subjects with type 2 DM was lower than in the control group (6.1 $\pm$5.2 *vs* 7.5 $\pm$ 5.8 ng/mL, $p = 0.020$; log leptin 1.5 $\pm$ 0.8 *vs* 1.7 $\pm$ 0.9, $p = 0.047$). In male subjects, the serum leptin concentration did not differ significantly between the two groups (3.9 $\pm$ 3.6 *vs* 3.8 $\pm$ 3.1 ng/mL, $p = 0.803$; log leptin 1.1 $\pm$ 0.7 *vs* 1.1 $\pm$ 0.7, $p = 0.906$). However, in female subjects, the serum leptin concentration was significantly lower than in the control group (7.8 $\pm$ 5.6 *vs* 11.3 $\pm$ 5.4 ng/mL, $p < 0.001$; log leptin 1.8 $\pm$ 0.7 *vs* 2.3 $\pm$ 0.5, $p < 0.001$). According to multiple linear regression analysis with log leptin as a dependent variable, the mean log leptin concentration of female subjects with type 2 DM was 0.455 ng/mL ($p < 0.001$) lower than the control group after adjusting for age and BMI.

***Conclusions.*** The leptin concentration of female subjects with type 2 DM is lower than in healthy subjects. **( Mid Taiwan J Med 2003;8:8-12)**

**Key words**

female, leptin, lower, male, type 2 DM

## INTRODUCTION

Leptin, the product of the ob gene, is a 167-amino acid peptide hormone secreted by adipocytes and plays an important role in the regulation of food intake and body weight [1,2]. Because obese humans have higher leptin concentrations, it has been suggested that they may be resistant to the 'lipostate' effect of leptin [3]. Previous studies found an independent positive correlation between leptin concentrations and insulin resistance in humans [4,5]. Type 2 diabetes mellitus (DM) is an extreme presentation of insulin resistance. Thus, the leptin concentration of subjects with type 2 DM may be different from healthy subjects. The aim of the present study was to investigate leptin concentrations between subjects with type 2 DM

Received : October 23, 2002. Revised : November 22, 2002.
Accepted : January 6, 2003.

Address reprint requests to : Ching-Chu Chen, Division of Endocrinology and Metabolism, Department of Medicine, China Medical College Hospital, 2 Yuh-Der Road, Taichung 404, Taiwan.

**Table 1. Clinical and metabolic characteristics of the study subjects**

| | Total | | | Male | | | Female | | |
|---|---|---|---|---|---|---|---|---|---|
| Variables | DM | Control | *p* | DM | Control | *p* | DM | Control | *p* |
| N | 172 | 158 | - | 75 | 79 | - | 97 | 79 | - |
| Age (yr) | 56.6 ± 10.9 | 44.8 ± 11.8 | <0.001 | 54.6 ± 11.1 | 48.0 ± 9.9 | <0.001 | 58.1 ± 10.5 | 41.6 ± 12.7 | <0.001 |
| BMI (kg/m$^2$) | 26.0 ± 4.5 | 25.8 ± 4.8 | 0.600 | 25.7 ± 4.0 | 24.7 ± 5.5 | 0.200 | 26.3 ± 4.8 | 26.8 ± 3.9 | 0.380 |
| FPG (mg/dL) | 147.3 ± 31.9 | 94.8 ± 7.5 | <0.001 | 144.0 ± 30.6 | 95.4 ± 7.2 | <0.001 | 149.4 ± 32.4 | 9.5 ± 7.2 | <0.001 |
| FSI (μ/mL) | 10.9 ± 9.5 | 9.1 ± 7.1 | 0.050 | 10.5 ± 7.8 | 7.4 ± 4.4 | 0.003 | 11.2 ± 10.7 | 10.7 ± 8.7 | 0.752 |
| Leptin (ng/mL) | 6.1 ± 5.2 | 7.5 ± 5.8 | 0.020 | 3.9 ± 3.6 | 3.8 ± 3.1 | 0.803 | 7.8 ± 5.6 | 11.3 ± 5.4 | <0.001 |
| Log leptin | 1.5 ± 0.8 | 1.7 ± 0.9 | 0.047 | 1.1 ± 0.7 | 1.1 ± 0.7 | 0.906 | 1.8 ± 0.7 | 2.3 ± 0.5 | <0.001 |
| Log leptin$_{adj}$ | 1.6 ± 0.1 | 1.6 ± 0.1 | 0.924 | 1.1 ± 0.1 | 1.1 ± 0.1 | 0.476 | 1.9 ± 0.1 | 2.2 ± 0.1 | 0.008 |

Values are arithmetic means ± standard deviation except log leptin$_{adj}$ (mean ± standard error); DM = diabetes mellitus; BMI = body mass index; FPG = fasting plasma glucose; FSI = fasting serum insulin; Log leptin$_{adj}$ = log leptin adjusting for age.

and healthy subjects.

## MATERIALS AND METHODS

We recruited 172 subjects with type 2 DM (75 males and 97 females) and 158 healthy subjects (79 males and 79 females) for this study. Healthy subjects were defined as individuals with normal blood pressure, normal renal and liver function, fasting plasma glucose < 110 mg/dL, normal hemoglobin (male > 13 g/dL, female > 12 g/dL), normal urine routine, no medication history, and no other major diseases. They were recruited from those individuals visiting the hospital for an annual physical check-up. Type 2 DM was diagnosed according to 1985 World Health Organization criteria [6]. All subjects with type 2 DM were being treated with diet alone or diet plus oral hypoglycemic agents (diet alone 4.7%, sulfonylurea 85.5%, metformin 77.3%, $\alpha$-glucosidase inhibitor 17.4%). Subjects with type 2 DM being treated with insulin or who had serum creatinin levels > 1.5 mg/dL were excluded.

Subjects came to the out-patient clinic after overnight fasting. They were weighed in light clothing and their heights were recorded. Body mass index (BMI) was calculated in kg/m$^2$. Blood was drawn for assay of fasting plasma glucose, serum insulin and leptin concentrations. Plasma glucose concentration was assayed using the glucose oxidase method (Astra-8, Beckman, CA, USA). Serum insulin concentration was determined using 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 concentration was 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%.

*Statistical analysis* All data are presented as means ± standard deviation except log leptin$_{adj}$ (mean ± standard error). Student's *t* test was used to compare differences between subjects with type 2 DM and healthy subjects. Analysis of Covariance was used to adjust log leptin for age. Serum leptin concentration was log transformed to improve normality. Multiple linear regression analysis identified the independent effects of other metabolic variables on log leptin concentration. A *p* value of less than 0.05 was considered statistically significant.

## RESULTS

The mean HbA$_{1c}$ of male and female type 2 diabetic subjects was 6.8 ± 1.2% and 6.9 ± 1.2%, respectively ($p$ = 0.910). The serum leptin concentration of subjects with type 2 DM was lower than in the control group (6.1 ± 5.2 *vs* 7.5 ± 5.8 ng/mL, $p$ = 0.020; log leptin 1.5 ± 0.8 *vs* 1.7 ± 0.9, $p$ = 0.047) (Table 1). However, there was no significant difference between the two groups after adjusting for age (log leptin 1.6 ± 0.1 *vs* 1.6 ± 0.1, $p$ = 0.924) (Table 1). Also, there was no significant difference in serum leptin concentrations between the male subjects with type 2 DM and the control group (3.9 ± 3.6 *vs*

**Table 2. Multiple linear regression analysis with log leptin (ng/mL) as a dependent variable**

| | Male (n = 154) | | | Female (n = 176) | | |
|---|---|---|---|---|---|---|
| Variables | $\beta$ | SE | $p$ | $\beta$ | SE | $p$ |
| Intercep | −0.455 | 0.390 | 0.244 | 0.297 | 0.372 | 0.426 |
| Age (yr) | 0.001 | 0.004 | 0.711 | 0.001 | 0.004 | 0.711 |
| BMI (kg/m$^2$) | 0.067 | 0.010 | <0.001 | 0.073 | 0.010 | <0.001 |
| DM | −0.036 | 0.102 | 0.726 | −0.455 | 0.101 | <0.001 |
| | F = 15.76 | total $R^2$ = 23.96% | | F = 31.87 | total $R^2$ = 35.86% | |

SE = standard error; BMI = body mass index; DM = diabetes mellitus.

3.8 ± 3.1 ng/mL, $p$ = 0.803; log leptin 1.1 ± 0.7 *vs* 1.1 ± 0.7, $p$ = 0.906) (Table 1), but female subjects with type 2 DM had significantly lower leptin concentrations than those in the control group (7.8 ± 5.6 *vs* 11.3 ± 5.4 ng/mL, $p < 0.001$; log leptin 1.8 ± 0.7 *vs* 2.3 ± 0.5, $p < 0.001$) (Table 1). Even after adjusting for age, the difference between female subjects with type 2 DM and the control group was still significant (log leptin 1.9 ± 0.1 *vs* 2.2 ± 0.1, $p$ = 0.008) (Table 1). According to multiple regression analysis with log leptin as a dependent variable, BMI and DM independently correlated with leptin concentration, which accounted for 35.86% of the variance ($R^2$ = 35.86%) in female subjects; however, only BMI was a significant predictor, explaining 23.96% of the variance ($R^2$ = 23.96%) in male subjects (Table 2). The mean log leptin concentration in female subjects with type 2 DM was 0.455 ($p < 0.001$) lower than in the control group after adjusting for age and BMI (Table 2).

## DISCUSSION

In this study, leptin concentration correlated with BMI in both genders, a result consistent with previous studies [4,5,7]. However, age did not correlate with leptin concentration in multiple linear regression analysis when BMI and DM were taken into account. Considine et al [7] also found that age had no independent effect on serum leptin concentration after adjusting for body fat. Yet, there was one study [8] which found an inverse relationship between age and plasma leptin concentration. Determination of the relationship between leptin concentration and age therefore needs to be further investigated.

Previous studies found that leptin concentration changes in some diseases but not all. For example, Sheu et al found that leptin concentration was higher in hypertensive men but not in hypertensive women [9]. Chen et al found that leptin concentration did not differ in type 2 diabetic patients with secondary failure of oral hypoglycemic agents [10]. Song et al noted that leptin concentrations were not different in different thyroid function groups [11], and Haffner et al reported that leptin concentrations were not different in diabetic and non-diabetic subjects [12]. In contrast, other studies have revealed that patients with gestational diabetes mellitus have relative hypoleptinemia [13]. Panarotto et al found that leptin concentration was 44% lower in women with DM or impaired glucose tolerance but no such difference was found in men [14]. In our study, there was no significant difference in serum leptin concentrations between the male subjects with type 2 DM and the control group. In female subjects with type 2 DM, the leptin concentration according to Student's $t$ test and multiple linear regression analysis was lower than in the control group. Panarotto et al suggested that hyperglycemia interferes with the stimulatory effect of plasma insulin on the synthesis of leptin by adipose tissue [14]. Because the age of our female subjects with type 2 DM was significantly older than the control group, an estrogen effect may be one of the possible factors of lower leptin concentration in female subjects with type 2 DM. However, Haffner et al found that leptin concentrations were not significantly different among premenopausal women, postmenopausal women on hormone replacement therapy and postmenopausal women [15]. Other hormone

effects on leptin concentration in female subjects need further elucidation in the future.

In conclusion, the leptin concentration of female subjects with type 2 DM was lower than in the healthy subjects. Furthermore, there was no significant difference between the male subjects with type 2 DM and the healthy subjects.

## REFERENCES


1. Zhang Y, Proenca R, Maffei M, et al. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994;372:425-32.
2. Caro JF, Sinha MK, Kolaczynski JW, et al. Leptin: the tale of an obesity gene. *Diabetes* 1996;45:1455-62.
3. Lonnqvist F, Arner P, Nordfors L, et al. Overexpression of the obese (ob) gene in adipose tissue of human obese subjects. *Nat Med* 1995;1:950-3.
4. Donahue RP, Prineas RJ, Donahue RD, et al. Is fasting leptin associated with insulin resistance among nondiabetic individuals? The Miami Community Health Study. *Diabetes Care* 1999;22:1092-6.
5. Haffner SM, Mykkanen L, Rainwater DL, et al. Is leptin concentration associated with the insulin resistance syndrome in nondiabetic men? *Obes Res* 1999;7:164-9.
6. WHO Study Group. Diabetes Mellitus. Technical Report Series no. 727. Geneva: World Health Organization, 1985.
7. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal weight and obese humans. *New Engl J Med* 1996; 334:292-5.
8. Ostlund RE Jr, Yang JW, Klein S, et al. Relation between plasma leptin concentration and body fat, gender, diet, age, and metabolic covariates. *J Clin Endocrinol Metab* 1996;81:3909-13.
9. Sheu WH, Lee WJ, Chen YT. High plasma leptin concentrations in hypertensive men but not in hypertensive women. *J Hypertens* 1999;17:1289-95.
10. Chen MD, Song YM, Tsou CT, et al. Plasma concentrations of leptin and selected minerals do not differ in type 2 diabetic patients with or without sulfonylurea inefficacy. *Diabetes Nutr Metab* 2000;13:284-6.
11. Song YM, Sheu WH, Lee WJ, et al. Plasma leptin concentrations are related to body fat mass and gender but not to thyroid dysfunction. *Kaohsiung J Med Sci* 1999;15:119-26.
12. Haffner SM, Stern MP, Miettinen H, et al. Leptin concentrations in diabetic and nondiabetic Mexican-Americans. *Diabetes* 1996;45:822-4.
13. Festa A, Shnawa N, Krugluger W, et al. Relative hypoleptinemia in women with mild gestational diabetes mellitus. *Diabet Med* 1999;16:656-62.
14. Panarotto D, Ardilouze JL, Tessier D, et al. The degree of hyperinsulinemia and impaired glucose tolerance predicts plasma leptin concentrations in women only: a new exploratory paradigm. *Metabolism* 2000;49: 1055-62.
15. Haffner SM, Mykkanen L, Stern MP. Leptin concentrations in women in the San Antonio Heart Study: effect of menopausal status and postmenopausal hormone replacement therapy. *Am J Epidemiol* 1997;146:581-5.

# 女性第2型糖尿病病人血清瘦素濃度較低

陳清助 李采娟[1] 張淳堆 簡誌銘 陳榮興 王子源

中國醫藥學院附設醫院 內科部 新陳代謝科

中國醫藥學院 中醫研究所[1]

**目的** 瘦素是脂肪細胞分泌的賀爾蒙，可調節食慾及體重，其濃度隨疾病種類不同而有所不同。本研究在比較第2型糖尿病病人瘦素濃度與健康人，是否有所差異。

**方法** 一百七十二位第2型糖尿病病人(男75位，女97位)及158位健康人(男79位，女79位)納入本研究。測定其空腹血漿血糖、血清胰島素、血清瘦素濃度及身體質量指數。

**結果** 第2型糖尿病病人血清瘦素濃度較對照組低(6.1 ± 5.2 *vs* 7.5 ± 5.8 ng/mL, $p$ = 0.020; log leptin 1.5 ± 0.8 *vs* 1.7 ± 0.9, $p$ = 0.047)。男性第2型糖尿病病人，血清瘦素濃度與對照組比較並無統計學上的差異(3.9 ± 3.6 *vs* 3.8 ± 3.1 ng/mL, $p$ = 0.803; log leptin 1.1 ± 0.7 *vs* 1.1 ± 0.7, $p$ = 0.906)；女性第2型糖尿病病人，血清瘦素濃度與對照組比較爲低且達統計學上的差異(7.8 ± 5.6 *vs* 11.3 ± 5.4 ng/mL, $p$ < 0.001; log leptin 1.8 ± 0.7 *vs* 2.3 ± 0.5, $p$ < 0.001)。以log leptin當作獨立變項進行複迴歸分析，結果顯示調整年齡及身體質量指數後，女性第2型糖尿病病人平均log leptin濃度較對照組低0.455 ng/mL ($p$ < 0.001)。

**結論** 女性第2型糖尿病病人血清瘦素濃度較健康人低。（中台灣醫誌 **2003;8:8-12**）

**關鍵詞**

女性，瘦素，較低，男性，第2型糖尿病

聯絡作者：陳清助

地　　址：404台中市北區育德路2號

中國醫藥學院附設醫院 內科部 新陳代謝科

收文日期：2002年10月23日　　修改日期：2002年11月22日

接受日期：2003年1月6日