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Leptin levels in obese women with and without type 2 diabetes mellitus

Mehmet Akif Buyukbese[1,CA], Ali Cetinkaya[1], Ramazan Kocabas[2], Aytekin Guven[3] and Mehmet Tarakcioglu[2]

[1]Department of Internal Medicine and [3]Department of Cardiology, Kahramanmaras Sutcu Imam University, Faculty of Medicine, 46050 Kahramanmaras, Turkey; [2]Department of Biochemistry and Clinical Biochemistry, Gaziantep University, Faculty of Medicine, Gaziantep, Turkey

[CA]Corresponding Author
Tel: +90 532 545 66 70,
Fax: +90 344 221 23 71,
E-mail: akif_buyukbese@yahoo.com

***Introduction*: The role of leptin has been more clear in the endocrinology area after the discovery of its secretion from the adipose tissue. The aim of the study is to investigate the leptin levels in obese women in whom type 2 diabetes mellitus were present or absent.**

***Materials and methods*: Thirty-five obese women with type 2 diabetes mellitus (group 1) and 34 obese women without type 2 diabetes mellitus (group 2) were enrolled in the study. In both groups the body mass index (BMI), waist circumference, and waist-to-hip ratio were measured. Leptin, HbA1c, creatinine and the lipid profile were assessed.**

***Results*: Leptin was found to be statistically significantly lower in group 1 than in group 2 (40.22 ± 17.77 ng/ml versus 50.12 ± 15.51 ng/ml, respectively; $p = 0.019$). It was well correlated with BMI in group 1 ($r = 0.60$, $p = 0.0001$). In group 1 also, correlation of leptin was moderate with creatinine and high-density lipoprotein-cholesterol ($r = 0.36$, $p = 0.037$ versus $r = 0.37$, $p = 0.027$, respectively), whereas triglyceride had a negative correlation ($r = -0.34$, $p = 0.046$). In group 2, the only significant correlation with leptin was BMI ($r = 0.41$, $p = 0.02$). Leptin was also significantly lower in 17 subjects with poorly controlled diabetes mellitus than in 18 well-controlled diabetics (33.54 ± 15.82 ng/ml versus 44.61 ± 17.54 ng/ml, respectively; $p = 0.038$).**

***Conclusion*: Since leptin is lower in obese women with diabetes than without diabetes and additionally it is even lower in the poorly controlled diabetes subgroup, we think that further studies are required to make clear the issue for lower leptin levels, whether it is a reason or an outcome.**

Key words: Leptin, Type 2 diabetes mellitus, Obesity, Women

Introduction

Obesity that is associated with a chronic low-grade inflammation state is an increasing worldwide health problem.[1] In the pathogenesis, a genetic tendency, disturbances of thermogenesis in the central nervous system, and impairment of the signals from the adipose tissue on the way to the brain are believed to play a major role.[2,3] It is gaining more and more importance since the mechanism leading to type 2 diabetes mellitus—another epidemic metabolic issue—in both adolescents and adults is more comprehensible after recent studies.[4]

Leptin together with other molecules that are secreted from the adipose tissue does affect the insulin sensitivity, and it is accepted to play a role in the pathogenesis of obesity-related disorders[5,6] via stimulating vascular inflammation and oxidative stress that may contribute to pathogenesis of atherosclerosis and other cardiovascular complications of obesity.[7,8] It has also a link with nutritional status and energy balance—which are both important in the physiopathology of diabetes—and proinflammatory T-helper 1 immune responses.[9] Strong positive correlations found between interleukin-6, tumor necrosis factor alpha, leptin and serum C-reactive protein suggest that cytokines secreted by adipose tissue in obese subjects may play a role in increased inflammatory proteins secretion by the liver.[8,10] Its possible role in liver disease as a fat deposition, in inflammation and fibrosis,[11] in overexpression in intestinal inflammation,[12] by activating nuclear factor-kappaB,[13] and inappropriate increase independent of body mass index (BMI) in acute ulcerative colitis[14] have been studied by many investigators.

Approximately 80% of the subjects with type 2 diabetes mellitus are obese. As long as the obesity continues, the risk of development of type 2 diabetes

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mellitus increases at that rate.[15] It has been found that subjects who have obesity for over 10 years have a two times greater risk for diabetes than the subjects who have obesity for less than 5 years.[15] In gestational diabetes mellitus, major changes were in the expression profile of placental genes with a prominent increase in markers and mediators of inflammation.[16] Regarding this, upregulation of interleukins, leptin and tumor necrosis factor alpha receptors and their downstream molecular adaptors indicate an activation of pathway recruiting stress activated protein-kinases leading to reorganization of placenta.[16]

In an eastern Mediterranean area of Turkey where the prevalence of type 2 diabetes is quite high[17] we aimed to investigate leptin levels in obese female subjects with type 2 diabetes mellitus and in a small group with poor glycemic control.

Research design and methods

Subjects

In the study, subjects were collected consecutively from the Outpatient Department of Internal Medicine, Kahramanmaras Sutcu Imam University, Faculty of Medicine. All the participants were obese women with normal creatinine levels. Subjects with type 2 diabetes mellitus (group 1) numbered 35 and those without diabetes (group 2) numbered 34. All diabetic subjects met the American Diabetes Association criteria for type 2 diabetes mellitus.[18] Patients having HbA1c greater than 8.5% were accepted as poorly controlled diabetes. Seventeen subjects were poorly controlled diabetics.

The height (m), weight (kg) and BMI (kg/m^2) were recorded. All subjects had a BMI equal to or greater than 30 for participating in the study as the obese subject. The waist (waist circumference was measured with a soft tape on standing subjects, mid-way between the lowest rib and iliac crest), hip (hip circumference was measured over the widest part of the gluteal region) and therefore waist-to hip-ratio were all measured by the same investigator so as to minimalize interobserver variability during each measurement.

For group 2, in order to exclude new onset diabetes, subjects who were known not to have diabetes by taking history were asked to drink 75 g of glucose for the oral glucose tolerance test.

Local Research Ethics Commitee approval was taken for the study before it commenced. Patients were also asked to sign a consent form.

Physical examinations, BMI, waist and hip measurements and routine laboratory measurements except leptin were performed in Kahramanmaras Sutcu Imam University Faculty of Medicine.

Samples and measurements

Before collecting venous blood samples using standard venipuncture into plain tubes, subjects were asked to have a fasting period of 12 h. For the standardization blood was drawn in a sitting position from the antecubital vein. Leptin, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride and creatinine were kept in plain tubes, whereas for HbA1c special tubes containing K_3EDTA were provided so as not to give rise to coagulation. All measurements were performed daily except for leptin. Leptin levels were measured at the Laboratories of Department of Biochemistry, Gaziantep University, Faculty of Medicine.

Lipids and creatinine levels were measured by biochemical autoanalyzer via enzymatic-calorimetric method (Roche-Hitachi Modular Analytics, Tokyo, Japan). Low-density lipoprotein cholesterol was calculated via the Friedewald formula.[19] For HbA_1c an autoanalyzer (DCA 2000; Bayer, USA) was used via the method of inhibition of latex agglutination.

Sera that were separated immediately after centrifugation with $3000 \times g$ for 10 min were stored at $-20^{\circ}C$ until the assays for leptin were performed and the last subject fulfilling the inclusion criteria was admitted. Serum leptin levels were measured using the enzyme-linked immunosorbent assay kit (Diagnostic Systems Laboratories, Inc., Webster, TX, USA). Analytical sensitivity of the leptin assay was 0.05 ng/ml. The intra-assay coefficient of variation was 3.7% and the interassay coefficient of variation was 4.43%.

Statistical analysis

Results are presented as the mean $\pm$ standard deviation. Data collected were analyzed by SPSS for Windows package (version 9.05; SPSS, Chicago, IL, USA). Leptin levels of group 1 and group 2 were compared via an independent t-test. Correlation of leptin with the other parameters were evaluated via Pearson correlation analyses. For the comparison of the leptin levels between subgroups who had well and poorly controlled diabetes mellitus the Mann–Whitney U-test was used since the distributions of the data were not normal. For all statistical assessments a value of $p < 0.05$ was accepted to be statistically significant.

Results

Baseline characteristics and biochemical parameters of subjects in the diabetic and control groups are summarized in Table 1. The mean age of group 1 was 49.97 ± 6.45 years and that of group 2 was

Table 1. Baseline characteristics and biochemical parameters of subjects with diabetes and the control group

	Diabetic patients	Control group	*p*
Age (years)	49.97 ± 6.45	48.77 ± 4.08	Not significant
Weight (kg)	88.74 ± 8.72	89.43 ± 11.31	Not significant
Height (m)	155.25 ± 5.54	154.86 ± 5.7	Not significant
Body mass index (kg/m^2)	36.84 ± 3.60	37.58 ± 2.95	Not significant
Waist (cm)	107.08 ± 10.26	101.14 ± 10.65	Not significant
Hip (cm)	121.50 ± 12.11	115.85 ± 10.15	Not significant
Waist/hip (ratio)	0.88 ± 0.11	0.87 ± 0.08	Not significant
Leptin (ng/ml)	40.22 ± 17.77	50.12 ± 15.51	0.019
Creatinine (mg/dl)	0.78 ± 0.27	0.79 ± 0.09	Not significant
Total cholesterol (mg/dl)	208.17 ± 40.57	208.40 ± 48.65	Not significant
Low-density lipoprotein cholesterol (mg/dl)	125.55 ± 33.83	126.84 ± 43.88	Not significant
High-density lipoprotein cholesterol (mg/dl)	44.42 ± 10.21	50.86 ± 16.74	Not significant
Triglyceride (mg/dl)	208.68 ± 131.31	140.33 ± 74.21	Not significant
HbA1c (%)	8.08 ± 2.12	5.26 ± 0.48	0.001

48.77 ± 4.08 years ($p > 0.05$). The BMI for group 1 and group 2 was 36.84 ± 3.60 kg/m^2 and 37.58 ± 2.95 kg/m^2, respectively ($p > 0.05$).

When we compared group 1 and group 2 regarding weight, height, waist circumference, hip circumference, waist-to-hip ratio, creatinine and lipid profile, no difference was observed (Table 1).

However, the leptin level in group 1 (40.22 ± 17.77 ng/ml) was lower than in group 2 (50.12 ± 15.51 ng/ml) ($p = 0.019$) (Fig. 1). Of the thirty-five diabetic subjects the mean HbA1c was 8.08 ± 2.12%. The leptin level of 17 subjects who had poorly controlled diabetes was 33.54 ± 15.82 ng/ml, whereas 18 well-controlled diabetic subjects had a leptin level of 44.61 ± 17.54 ng/ml ($p = 0.038$) (Fig. 2).

Leptin was well correlated with BMI in group 1 ($r = 0.60$, $p = 0.0001$). In group 1, also, while the correlation of leptin was moderate with creatinine and HDL-cholesterol ($r = 0.36$, $p = 0.037$ versus $r = 0.37$, $p = 0.027$, respectively), triglyceride had a negative correlation ($r = -0.34$, $p = 0.046$). In group 2, the only correlation with leptin was BMI ($r = 0.41$, $p = 0.02$) (Table 2).

Discussion

After the discovery of leptin secretion from the adipose tissue, its role has been more clear in the endocrinology area. Even though leptin limits food ingestion and increases energy expenditure, it has been found high in obesity. This can be explained by the statement that "obesity may be the consequence of leptin resistance".[20] Decreased levels of leptin concentrations during food deprivation leading to impaired immune function gave rise to spending more time to understand role of this molecule in chronic inflammation and autoimmunity together with therapeutic implications of its modulators.[21]

Serum leptin levels are found higher in women than in men,[20,22–25] and this is probably owing to adipose tissue in women being higher than in the opposite sex, the existence of negative correlation between leptin and testosterone levels,[22,26] and the stimulation of mRNA production by 17β-estradiol, which is one of the female sexuality hormones.[27] All the subjects enrolled in our study were female obese subjects and we found no correlation between the

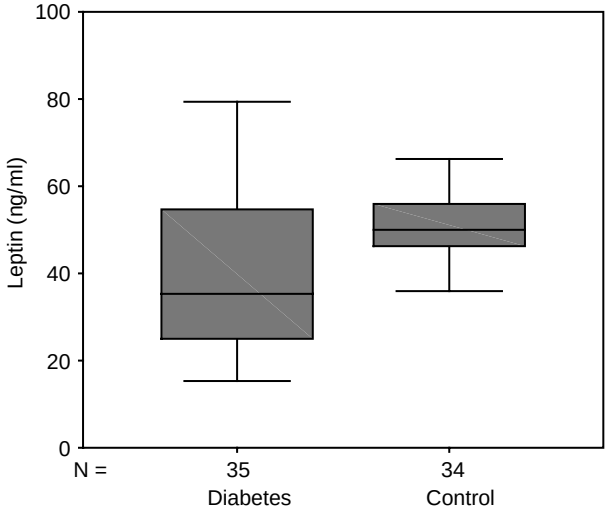

FIG. 1. Leptin levels in diabetes and control groups ($p = 0.019$).

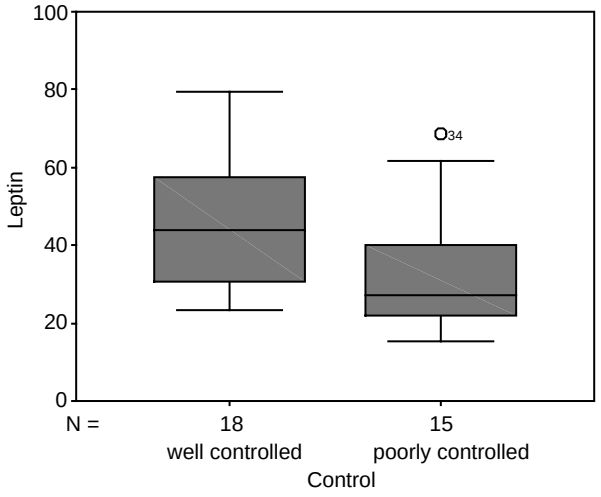

FIG. 2. Leptin levels in subjects who have well and poorly controlled diabetes mellitus ($p = 0.038$).

Table 2. Correlations of leptin levels with biochemical parameters in diabetes and control groups

Leptin correlation	Diabetic patients		Control group	
	r	*p*	*r*	*p*
Age (years)	0.24	Not significant	0.18	Not significant
Weight (kg)	0.29	Not significant	0.27	Not significant
Height (m)	−0.11	Not significant	−0.99	Not significant
Body mass index (kg/m^2)	0.6	0.0001	0.41	0.02
Waist (cm)	0.51	Not significant	0.33	Not significant
Hip (cm)	0.03	Not significant	0.13	Not significant
Waist/hip (ratio)	0.41	Not significant	0.24	Not significant
Creatinine (mg/dl)	0.36	0.037	0.26	Not significant
Total cholesterol (mg/dl)	0.05	Not significant	0.1	Not significant
Low-density lipoprotein cholesterol (mg/dl)	0.06	Not significant	0.04	Not significant
High-density lipoprotein cholesterol (mg/dl)	0.37	0.027	0.28	Not significant
Triglyceride (mg/dl)	−0.34	0.046	0.52	Not significant
HbA1c (%)	−0.28	Not significant	−0.05	Not significant

age and serum leptin levels. Many investigators demonstrated that leptin had a major correlation with BMI.[20,22–24,28–33] In our study, also, leptin had a correlation with BMI both for subjects with diabetes and subjects who did not have diabetes. The BMI seems to be applied easily at outpatient departments; however, obesity itself cannot be defined simply by this method only. Therefore, waist and hip circumferences and the waist-to-hip ratio have all been performed. As a result, we found no relationship with leptin and waist or waist-to-hip ratio measurements in diabetic and non-diabetic groups.

Leptin correlated positively with HDL-cholesterol and negatively with triglycerides in the diabetic group, as in the study where serum leptin concentrations were investigated in a group of patients with moderate and severe obesity.[24] The same correlations were found to be independent of age and gender in a Caucasion population.[30]

Creatinine was found to have a correlation with leptin in our diabetic group. This was matching with the findings of another investigation, but none of the participants had diabetes in that study.[34] Leptin is known to accumulate in a uremic state; however, leptin levels and renal creatinine clearence showed no significant correlation in peritoneal dialysis patients.[35]

Leptin has the ability of regulation of insulin secretion from the pancreatic islet cells.[36,37] After leptin was given to mice who had leptin deficiency, it has been demonstrated that there had been a decrease in hyperglycemia and hyperinsulinemia, inhibition in hepatic gluconeogenesis and insulin secretion via direct effects on beta cells.[29,38,39]

Some investigators have found that in more obese patients with type 2 diabetes mellitus, the leptin levels were less in patients with not well controlled diabetes than in well-controlled diabetic subjects.[40] This was related to the insulin deficiency. In our study also, leptin levels were significantly lower in patients who have HbA1c above 8.5%. It has been found that untreated diabetes gave rise to a reduction in leptin levels owing to an ineffective release of insulin by the monodrug therapy.[41] An absence of leptin receptor expression in human diabetic foot ulcer, which is the consequence of poor glycemic control for many years, was well documented while investigating the role of leptin for the inflammatory response in diabetes-impaired skin repair.[42] This may show that leptin itself might function as a regulatory link between endocrine and immune system in the context of skin repair.[42] However, contrarily to these findings, no significant relation between leptin levels and the degree of the severity of diabetes was observed in another study.[23]

Abdominal fat tissue that can be detected by densitometry, hydrometry, dual-energy X-ray absorbtiometry, a chemical multicompartment model, bioelectrical impedance, computerized tomography and magnetic resonance imaging is also well correlated with leptin levels.[31] Leptin's relationship with total body fat and insulin resistance was independent of age and gender.[24,25,43] In our study we did not investigate the abdominal fat tissue percentage in the participants with the aforementioned instruments and imaging techniques.

We speculate that as a consequence of insulin deficiency and the different distribution of fat tissue throughout the body, we have found low leptin levels in diabetic subjects and even lower levels in subjects who have poorly controlled diabetes. Further large-scale studies—which should investigate the physiopathologic mechanisms—are required to make clear the issue for lower leptin levels, whether it is a reason or an outcome.

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References

1. Vidal H. Obesity and inflammation: the adipocytokines. *Ann Endocrinol* 2003; **64**: S40–S44.

2. Considine RV, Sinha MK, Heiman ML, *et al*. Serum immunorecative-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996; **334**: 292–295.
3. Frederich RC, Hamann A, Anderson S, Lollmann B, Lowell BB, Flier JS. Leptin levels reflect body lipid content in mice: evidence for diet-induced resistance to leptin action. *Nat Med* 1995; **1**: 1311–1314.
4. Chen KW, Boyko EJ, Bergstrom RW, *et al*. Earlier appearance of impaired insulin secretion than of visceral adiposity in the pathogenesis of NIDDM. 5-year follow-up of initially nondiabetic Japanese-American men. *Diabetes Care* 1995; **18**: 747–753.
5. Mohamed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. *Int J Obes Relat Metab Disord* 1998; **22**: 1145–1158.
6. Prins JB. Adipose tissue as an endocrine organ. *Best Pract Res Clin Endocrinol Metab* 2002; **16**: 639–651.
7. Correia ML, Haynes WG. Leptin, obesity and cardiovascular disease. *Curr Opin Nephrol Hypertens* 2004; **13**: 215–223.
8. Shamsuzzaman AS, Winnicki M, Wolk R, *et al*. Independent association between plasma leptin and C-reactive protein in healthy humans. *Circulation* 2004; **109**: 2181–2185.
9. La Cava A, Matarese G, Ebling FM, Hahn BH. Leptin-based immune intervention: current status and future directions. *Curr Opin Investig Drugs* 2003; **4**: 1327–1332.
10. Stejskal D, Adamovska S, Bartek J, Jurakova R, Proskova J. Resistin — concentrations in persons with type 2 diabetes mellitus and in individuals with acute inflammatory disease (abstract). *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2003; **147**: 63–69.
11. Siddiqui AR, Abbas ZA. Leptin and liver disease: facts and presumptions. *J Coll Physicians Surg Pak* 2004; **14**: 122–124.
12. Barbier M, Vidal H, Desreumaux P, *et al*. Overexpression of leptin mRNA in mesenteric adipose tissue in inflammatory bowel diseases. *Gastroenterol Clin Biol* 2003; **27**: 987–991.
13. Sitaraman S, Liu X, Charrier L, *et al*. Colonic leptin: source of a novel proinflammatory cytokine involved in IBD. *FASEB J* 2004; **18**: 696–698.
14. Tuzun A, Uygun A, Yesilova Z, *et al*. Leptin levels in the acute stage of ulcerative colitis. *J Gastroenterol Hepatol* 2004; **19**: 429–432.
15. Everhart JE, Pettitt DJ, Bennett PH, Knowler WC. Duration of obesity increases the incidence of NIDDM. *Diabetes* 1992; **41**: 235–240.
16. Radaelli T, Varastehpour A, Catalano P, Hauguel-de Mouzon S. Gestational diabetes induces placental genes for chronic stress and inflammatory pathways. *Diabetes* 2003; **52**: 2951–2958.
17. Satman I, Yilmaz T, Sengul A, *et al*. Population based study of diabetes and risk characteristics in Turkey: results of the Turkish diabetes epidemiology study (TURDEP). *Diabetes Care* 2002; **25**: 1551–1556.
18. Report of the Expert Committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2003; **26**: 5–20.
19. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18**: 499–502.
20. Wei M, Stern HM, Haffner SM. Serum leptin levels in Mexican American and non-Hispanic whites: association with body mass index and cigarette smoking. *Ann Epidemiol* 1997; **7**: 79–80.
21. La Cava A, Alviggi C, Matarese G. Unraveling the multiple roles of leptin in inflammation and autoimmunity. *J Mol Med* 2004; **82**: 4–11.
22. Vettor R, De Pergola G, *et al*. Gender differences in serum leptin in obese people: relationship with testosterone, body fat distribution and insulin sensitivity. *Eur J Clin Invest* 1997; **27**: 1016–1024.
23. Tasaka Y, Yanagisawa K, Iwamoto Y. Human plasma leptin in obese subjects and diabetics. *Endocr J* 1997; **44**: 671–676.
24. Liuzzi A, Savia G, Tagliaferri M, *et al*. Serum leptin concentrations in moderate and severe obesity: relationship with clinical, anthropometric and metabolic factors. *Int J Obes Relat Metab Disord* 1999; **23**: 1066–1073.
25. 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**: 1092–1096.
26. Jockenhovel F, Blum WF, Vogel E, *et al*. Testosteron substitution normalizes elevated serum leptin levels in hypogonadal men. *J Clin Endocrinol Metab* 1997; **82**: 2510–2513.
27. Sweeney G. Leptin signalling. *Cell Signal* 2002; **14**: 655–663.
28. Gomez-Ambrosi J, Salvador J, Paramo JA, *et al*. Involvement of leptin in the association between percentage of body fat and cardiovascular risk factors. *Clin Biochem* 2002; **35**: 315–320.
29. Kieffer TJ, Heller RS, Leech CA, Holz G, Hebener JF. Leptin suppression of insulin secretion by the activation of ATP-sensitive K^+ channels in pancreatic beta cells. *Diabetes* 1997; **46**: 1087–1093.
30. Bertin E, Rich N, Schneider N, *et al*. Insulin and body fat distribution have no direct effect on plasma leptin levels in obese Caucasian women with and without type 2 diabetes mellitus. *Diabetes Metab* 1998; **24**: 229–234.
31. Johannsson G, Karlsson C, Lonn L, *et al*. Serum leptin concentration and insulin sensitivity in men with abdominal obesity. *Obes Res* 1998; **6**: 416–421.
32. Haluzik M, Matoulek M, Svacina S, Hilgertova J, Haas T. The influence of short-term fasting on serum leptin levels, and selected hormonal and metabolic parameters in morbidly obese and lean females. *Endocr Res* 2001; **27**: 251–260.
33. Hodge AM, Boyko EJ, de Courten M, *et al*. Leptin and other components of the metabolic syndrome in Mauritius — a factor analysis. *Int J Obes Relat Metab Disord* 2001; **25**: 126–131.
34. J Bedir A, Topbas M, Tanyeri F, Alvur M, Arik N. Leptin might be a regulator of serum uric acid concentrations in humans. *Jpn Heart J* 2003; **44**: 527–536.
35. Aguilera A, Bajo MA, Rebollo F, *et al*. Leptin as a marker of nutrition and cardiovascular risk in peritoneal dialysis patients. *Adv Perit Dial* 2002; **18**: 212–217.
36. Ceddia RB, William WN Jr, Carpinelli AR, Curi R. Modulation of insulin secretion by leptin. *Gen Pharmacol* 1999; **32**: 233–237.
37. Muoio DM, Lynis Dohm G. Peripheric metabolic actions of leptin. *Best Pract Res Clin Endocrinol Metab* 2002; **16**: 653–666.
38. Pelleymounter MA, Cullen MJ, Baker MB, *et al*. Effects of the obese gene product on body weight regulation in ob/ob mice. *Science* 1995; **269**: 540–543.
39. Rossetti L, Massilon D, Barzilai N, *et al*. Short time effect of leptin on hepatic gluconeogenesis and invivo insulin action. *J Biol Chem* 1997; **272**: 27758–27763.
40. Clement K, Lahlou N, Ruiz J, *et al*. Association of poorly controlled diabetes with low serum leptin in morbid obesity. *Int J Obes Relat Disord* 1997; **21**: 556–561.
41. Sivitz WI, Wayson SM, Bayless ML, *et al*. Leptin and body fat in type 2 diabetes and monodrug therapy. *J Clin Endocrinol Metab* 2003; **88**: 1543–1553.
42. Goren I, Kampfer H, Podda M, Pfeilschifter J, Frank S. Leptin and wound inflammation in diabetic ob/ob mice: differential regulation of neutrophil and macrophage influx and a potential role for scab as a sink for inflammatory cells and mediators. *Diabetes* 2003; **52**: 2821–2832.
43. de Courten M, Zimmet P, Hodge A, *et al*. Hyperleptinaemia: the missing link in the metabolic syndrome? *Diabet Med* 1997; **14**: 200–208.

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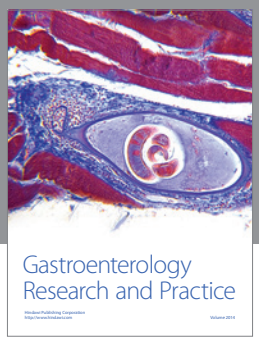

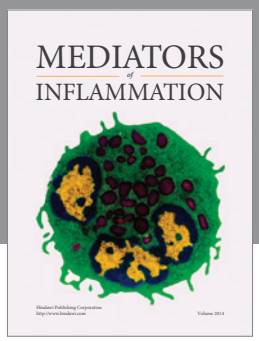

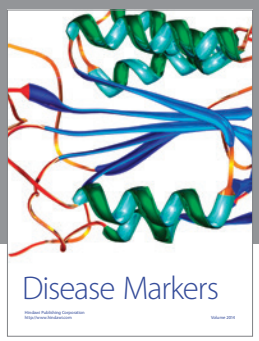

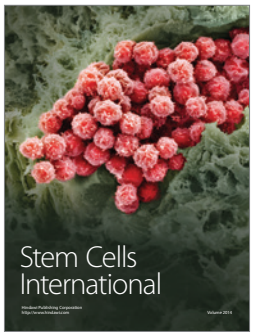

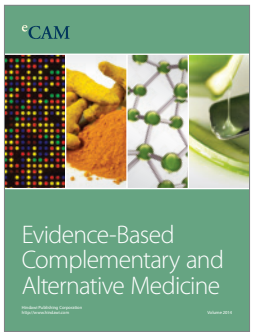

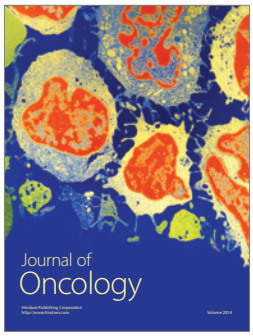

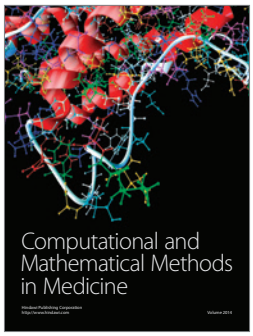

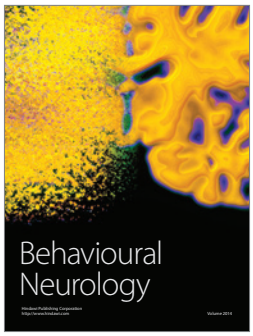

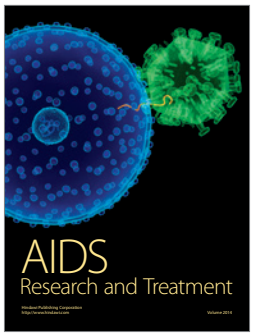

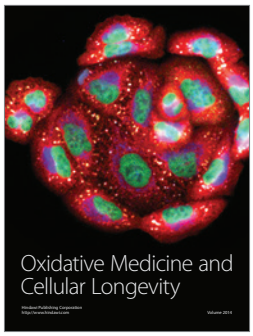

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