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ORIGINAL ARTICLE

Is there any correlation among adiponectin levels in serum, tumor tissue and normal tissue of the same patients with breast cancer?

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Summary

Purpose: *Adiponectin is secreted from adipose tissue and is characterized by hyperinsulinemia which is related with obesity. Although serum adiponectin levels in patients with breast cancer have been studied previously, adiponectin levels in the serum, tumor and normal tissue of the same patients have not been simultaneously investigated. The aim of this study was thus to evaluate the relationship among serum, tumor and normal tissue adiponectin levels in patients with breast cancer.*

Methods: *Fifty-three patients with breast cancer who were operated at the Dr. Lutfi Kirdar Kartal Education and Research Hospital, Department of Surgery, between February 2008 and June 2008, were analyzed. Their serum adiponectin levels, tumor tissue and normal breast tissue adiponectin levels were compared. The correlation between postoperative histopathological parameters, insulin resistance parameters and adiponectin levels was also examined.*

Results: *The mean adiponectin levels in tumor tissue, normal breast tissue and serum were 56 ± 9.6 ng/ml, 56 ± 10 ng/ml and 43.5 ± 3.1 ng/ml, respectively. The serum adiponectin levels were inversely correlated with tumor tissue adiponectin levels ($p=0.001$, $r=-0.43$). When tumor tissue adiponectin levels were increased, serum adiponectin levels were decreased. On the other hand, there was a positive correlation between normal breast tissue adiponectin levels and tumor tissue adiponectin levels ($p=0.0001$, $r= 0.850$). The tumor tissue adiponectin level was inversely correlated with tumor stage ($p=0.037$, $r= –0.29$). Moreover, in early-stage and low grade tumors, both tumor tissue and normal tissue adiponectin levels were high compared with those of advanced stage or high grade tumors ($p=0.027$, $r= –0.32$ and $p=0.004$, $r= –0.408$, respectively). In the subgroup analyses, no significant relationship was found between insulin resistance parameters and adiponectin levels ($p>0.05$).*

Conclusion: *Our results indicate that serum adiponectin levels were inversely correlated with tumor tissue adiponectin levels, but no relationship between normal breast tissue and tumor tissue adiponectin levels was demonstrated. Adiponectin levels in breast tumor tissue increase while serum adiponectin levels decrease. Adiponectin might play an important role in the prevention of tumor progression by decreasing tissue neovascularization.*

Key words: breast cancer, serum adiponectin, tissue adiponectin

Introduction

Breast cancer is the most common cancer in women [1]. Several risk factors have been identified for this disease, of which being female and elderly are the most important [1,2]. Recent studies have shown that obesity and obesity-related situations play an important role in breast cancer carcinogenesis. Research has also been initiated to identify which obesity-related mechanisms and conditions cause breast cancer and other types of cancer. Adipocytokines, which are produced by adipocytes, are biologically active polypeptides that are associated with obesity, hyperinsulinemia, type-2 diabetes and chronic vascular diseases by influencing the endocrine, paracrine, and autocrine metabolism. In recent studies, it has been proven that both obesity and insulin resistance are risk factors for breast cancer development and that they are poor prognostic factors in advanced

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stage breast cancer. Consequently, increased adipocytokine production and decreased serum adiponectin levels correlated with obesity might result in breast cancer carcinogenesis [3-7].

Adiponectin is a 30k-Da peptide hormone that is secreted from adipose tissue and characterized by hyperinsulinemia which is related with obesity. Unlike the other adipocytokines, angiogenesis is suppressed via a cascade involving activation of apoptotic enzymes. The preventive role of adiponectin in the pathogenesis of atherosclerosis occurs through inhibition of vascular smooth muscle and endothelial cell proliferation. Moreover it has been shown that adiponectin prevents neovascularization and endothelial cell proliferation in chicken chorioallantoic membrane and rat cornea [8-14]. Such evidence suggests that adiponectin inhibits tumor metastases by preventing neovascularization [15]. The adiponectin level is inversely proportional with the malignancies associated with obesity, such as breast, uterus, prostate, colon, and upper gastrointestinal cancers and leukemia. Five studies [15-19] found low serum adiponectin levels in postmenopausal breast cancer patients. Karaduman et al. examined adiponectin levels in breast cancer tissue and found that they were significantly higher than those of the normal breast tissue of the control group (p=0.001). The authors concluded that breast cancer risk might increase due to high adiponectin levels in the tumor tissue [20].

In the present study, we aimed to investigate the relationship between adiponectin levels in the serum, normal breast tissue and tumor tissue, and other insulin resistance parameters, and also some prognostic factors in patients with breast cancer.

Methods

Fifty-three women with breast cancer who were operated between February 2008 and June 2008 at the Dr. Lutfi Kirdar Education and Research Hospital, Department of Surgery, were included. The diagnosis of breast cancer of all patients was confirmed by histopathological examination of tumor tissue samples after the operation. The patients were staged according to the American Chamber of Commerce in Japan (ACCJ). Patients with metastatic disease were excluded from the study. Normal breast tissue of the patients was used as the control group. Before the operation, all patients were examined physically, and blood samples were collected from the antecubital vein, following 12-h fasting to detect plasma adiponectin, c-peptide, insulin, glucose and HbA1c levels.

Samples for plasma adiponectin level measurements were centrifuged at 3000 rpm for 10 min for serum separation and then stored in dry tubes at –70° C until further examination. Tumor tissue and normal breast tissue of patients were collected immediately and all pathology specimens were frozen and stored at –70° C until tissue homogenization. On the day of examination, frozen tissue samples were homogenized in homogenization buffer [50 mM HEPES, 0.2% Triton X-100, 1 mM ethylenediaminetetraacetic acid (EDTA) and 0.1 mM phenylmethylsulfonylfluoride (PMSF), pH 7.4] at 13500 rpm in an Ultraturrax T25 (Janke & Kunkel, IKA® Labortechnic, Staufen, Germany) according to the procedure described by Karaduman et al. [20]. Serum samples were melted at room temperature on the day of homogenization. The whole adiponectin samples (tissue and serum) were studied using an "Assaymax Human Adiponectin (Acrp30) ELISA Kit" (Catalog No: Ea2500-1; Lot No: 0201815) (ASSAYPRO MO 63304, USA) as they were transferred to blank ELISA plate. Informed consent and approval were obtained from the patients and the ethics committee of our hospital, respectively.

Other laboratory tests except that for adiponectin were performed in the biochemistry and microbiology laboratories of our hospital. Body mass index (BMI) was calculated using the Quetelet index as the ratio of body weight to body height squared (kg/m^2). Measuring tape was used to measure the patients' waists and hips. The narrowest angle between the arcus costarum and processus spina iliaca anterior posterior (superior) was used for the waist perimeter, and the widest angle passing through the gluteus maximus at the back and symphysis pubis at the front was used for the hip perimeter. According to the World Health Organization's BMI criteria, patients were classified as thin (<18.5), normal (18.5-24.9), over-weight (25.0-29.9), obese (30-39.9) or morbidly obese (>40). Plasma, tumor tissue and normal tissue adiponectin levels were compared [21]. The relationship between anthropometric measurements, age, menarche, pregnancy, number of deliveries, breast feeding time, oral contraceptive (OCC) usage, HRT (hormone replacement therapy), postoperative histopathological parameters (T stage, tumor size, lymph node status, estrogen receptor [ER] and progesterone receptor [PR] status, and c-erb-B2 expression) and adiponectin levels was examined.

Statistical methods

Statistical analyses were performed using SPSS 11.5.0 (SPSS Inc., Chicago, IL, USA) software [22]. Descriptives of the parameters were defined as mean ± SD and 95% confidence intervals (CI) for continuous

variables. The normality of the data was assessed by the Kolmogorov-Smirnov test. Normally distributed parameters were compared using the Student's t-test. The Mann-Whitney U test was used for non-normally distributed data. For the correlation between adiponectin levels, insulin sensitivity parameters and patients' clinicopathologic parameters, Pearson's and Spearman's correlation analyses were used. P-values less than or equal to 0.05 were considered statistically significant.

Results

The median patient age was 53 years (range 31-72). The median height and weight were 157.8 ± 7.3 cm and 74.3 ± 15.5 kg, respectively, while the median BMI was 29.8 ± 5.9 kg/m². The median chest, hips and waist perimeters were 104.1 ± 13, 107.6 ± 13.7 and 91.3 ± 13.7 cm, respectively. A family history of breast cancer was detected in 8 (15.1%) patients. Twenty-two patients (41.5%) were premenopausal and 29 (54.7%) postmenopausal. The remaining 2 patients (3.8%) were perimenopausal. OCC use was reported by 7 patients and 2 patients had a history of HRT. The median age with respect to the menopause and menarche status of patients was 48 ± 6.7 and 13.5 ± 1.5 years, respectively. Seven of the patients who had children had no breast-feeding history. Patient characteristics are summarized in Table 1.

The laboratory results of patients are shown in Table 2.

The median adiponectin levels of tumor tissue, normal breast tissue and serum were 56 ± 9.6 (range 37.2-63.4), 56 ± 10 (range 32.2-63.4) and 43.5 ± 3.1 (range 36.2-53.1), respectively (Figure 1). According to histopathological evaluation, the majority of patients had a T2 tumor (n=33, 62.2%). Concerning lymph node status, 17 patients had N0, 17 N1, 9 N2 and the remaining 10 patients had N3 status. In total, 66% of the patients had lymph node involvement. While the majority of patients had stage II (n=25, 47.2%), 6 patients had stage I (11.3%), and 22 patients had stage III (41.5%). With regard to hormone receptor status, 33 (62.2%) patients were ER-positive and 29 (54.71%) were PR-positive. Moreover, 17 (32.1%) patients showed overexpression of c-erb-B2.

An inverse correlation between serum adiponectin levels and breast tumor tissue adiponectin levels was found (p=0.001, r= –0.442), such that when the tumor tissue adiponectin level was increased, serum adiponectin was decreased. On the other hand, there was a positive relationship between normal breast tissue adiponectin and tumor tissue adiponectin (p=0.0001, r=0.850). There was no significant relationship between tumor size and adiponectin levels. In contrast, a negative correlation was found between tumor stage and tumor tissue adiponectin levels (p=0.037, r= –0.287), in other words, when the T stage was higher, the tumor tissue adiponectin level was lower. There was a significant relationship between c-erb-B2 and serum adiponectin level (p=0.038). Thus, the patients who had c-erb-B2 overexpression had a high serum adiponectin level. A negative relationship was observed be-

Table 1. Patient characteristics

Characteristics	*Mean±SD*
Age (years, range)	53 (31-72)
Chest perimeter (cm)	104.1 ± 13
Hip perimeter (cm)	107.6 ± 13.7
Waist perimeter (cm)	91.3 ± 13.7
Weight (kg)	74.3 ± 15.5
Height (cm)	157.8 ± 7.3
BMI (kg/m²)	29.8 ± 5.9
Non-breast feeding, n (%)	7 (13.2)
Family history, n (%)	8 (15.1)
Age of menarche (year)	13.5 ± 1.5
Age of menopause (year)	48 ± 6.7
Menopausal status, n (%)	
Premenopause	22 (41.5)
Perimenopause	2 (3.7)
Postmenopause	29 (54.7)
Age at first delivery (year)	20.04 ± 7.5
Number of deliveries	3.5 ± 2.4
Using OCC, n (%)	7 (13.2)
Applying HRT, n (%)	2 (3.7)

BMI: body mass index, OCC: oral contraceptive, HRT: hormone replacement therapy, SD: standard deviation

Table 2. Laboratory values

Values	*Mean±SD (range)*
Glucose (mg/dl)	115 ± 36 (75-273)
Insulin (uU/ml)	12.02 ± 6.8 (0.9-34.5)
C-peptide (ng/ml)	2.8 ± 1.2 (1.12-9.25)
Cortisol (µg/dL)	16.8 ± 7.3 (5.39-44.37)
HbA1c (%)	5.6 ± 0.9 (4.5-8.7)

SD: standard deviation

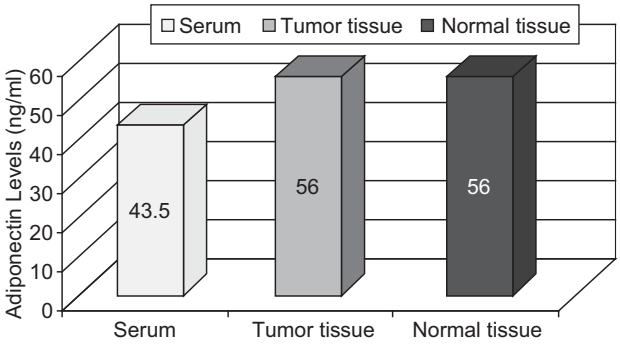

Figure 1. Mean adiponectin levels.

tween nuclear grade and tumor tissue adiponectin level (p=0.027, r= –0.320) and normal breast tissue adiponectin level (p=0.004, r= –0.408). The tumor tissue adiponectin level was inversely correlated with tumor stage (p=0.037, r= –0.29). In early stage and low grade tumors, both tumor tissue and normal tissue adiponectin levels were high compared with those of advanced stage or high grade tumors (p=0.027, r= –0.32 and p=0.004, r= –0.408, respectively). On the other hand, there was no significant relationship between nuclear grade and serum adiponectin levels (p=0.104, r=0.238), or between histological grade and serum adiponectin levels (p=0.126, r=0.224). Spearman's correlation coefficient and p-values between adiponectin levels and other variables are shown in Table 3.

There was no significant correlation between demographic and histopathological characteristics and adiponectin levels in a subgroup analysis of patients who were compared using non-parametric tests (p>0.05).

Discussion

It is known that breast cancer is linked with obesity and obesity-related situations. Insulin resistance is an important factor for type 2 diabetes mellitus. Many factors play a role in the pathogenesis of insulin resistance. Of these issues, adipose tissue and obesity are really important. In order to figure out the mechanism by which breast cancer occurs, attention has been focused on various cytokines secreted by adipose tissue. Adiponectin, almost all of which is secreted by adipose tissue, is a newly defined peptide-structured adipocytokine. It has been shown that adiponectin increases insulin sensitivity and has anti-inflammatory, anti-atherosclerotic, anti-apoptotic and anti-angiogenic effects [8-15].

The plasma adiponectin level decreases significantly in obesity, and increases with weight loss. It has been proved that adiponectin exerts a protective effect against type 2 diabetes mellitus and insulin resistance. In animal models, adiponectin provides glucose transport to muscle tissues and in these tissues it accelerates free fatty acid oxidation, and thus prevents glucose synthesis via its effects on hepatic gluconeogenesis enzymes. In addition, it decreases the level of free fatty acids, triglycerides and glucose in the plasma in the same way. However, insulin resistance caused by adiponectin deficiency has previously been shown in obese mice [23-26].

The adiponectin level is inversely correlated with obesity-related malignancies, such as primary breast, uterus, prostate, colon, upper gastrointestinal system cancers and leukemia. According to 4 retrospective [15-18] and one prospective study [19], the plasma adiponectin level was lower in postmenopausal women with breast cancer compared to women without breast cancer. In the study carried out by Miyoshi et al. in 2003, the authors found that there was a correlation between tumor size and high histological grade and low serum adiponectin level, and that hypoadiponectinemia was an indicator of an aggressive phenotype [16]. In contrast, in our study we found a significant negative correlation between normal and breast cancer tissue adiponectin levels and the histological and nuclear grade of tumors in breast cancer patients. However, this was not reflected by the serum adiponectin level. Therefore, we conclude that low tissue adiponectin levels are an indicator of tumor aggressiveness.

Recently, Karaduman et al. reported that the adiponectin level in breast tumor tissue was significantly higher than in the control group [20] and thus that high tissue adiponectin levels might increase the risk of breast cancer. In their study, patients with fibroadenoma, which is a benign breast tumor, had been enrolled into the study as the control group. This heterogeneous control group might have influenced their results. In our study, the normal breast tissues of the patients with breast cancer were used as the control group in order to provide homogeneity in the breast tissue.

The possibility of a correlation between the other insulin sensitivity parameters and breast cancer occurrence was also investigated by measuring plasma, normal breast tissue and breast tumor tissue adiponectin

Table 3. Spearman's correlation coefficient and p-values between adiponectin levels and other variables

Variable	*Serum adiponectin*		*Tumor tissue adiponectin*		*Normal tissue adiponectin*	
	Coefficient	*p-value*	*Coefficient*	*p-value*	*Coefficient*	*p-value*
Insulin	–0.17	0.224	–0.14	0.301	–0.013	0.927
C-peptide	–0.24	0.084	0.09	0.515	0.149	0.291
Glucose	0.21	0.140	0.04	0.794	0.084	0.552
HbA1c	–0.15	0.263	–0.04	0.773	–0.03	0.824
Nuclear grade	0.23	0.104	–0.32	0.027	–0.408	0.004
Stage	–0.05	0.721	–0.29	0.037	–0.181	0.194
CRP	–0.23	0.102	0.009	0.950	0.055	0.7

levels, unlike in previous studies. In addition, the relationships between various insulin resistance parameters and adiponectin levels were analyzed.

Hou et al. reported that both BMI and waist perimeter were higher in patients with breast cancer compared with healthy control subjects [15]. In our study, parameters such as age, family history, menarche age, menopausal status, breast-feeding history, age at first delivery, BMI, breast, waist and hip perimeter, usage of OCC and HRT were compared between all adiponectin groups. Among these parameters, there was a weak positive correlation between age at first delivery and the adiponectin level in normal breast tissue and a negative correlation between delivery number and serum adiponectin. However, we found no significant relationship between the other anthropometric values and adiponectin levels. In another similar study, a significant relationship between adiponectin levels and anthropometric values such as BMI was indicated [16].

In our study, histopathological parameters were compared with adiponectin levels. We found that there was a negative relationship between tumor stage and adiponectin levels in tumor tissue, i.e. as tumor stage increased, the adiponectin levels in tumor tissue decreased. This suggests that at low adiponectin levels a tumor's aggressiveness increases because of tumor stage. However, further studies are required to clarify this point. In a study performed by Hou et al., although there was no significant relationship between the serum adiponectin level and tumor size, they found a significant relationship between lymph node metastasis and histological grade [15]. In our study we did not identify any correlation between tumor tissue, serum adiponectin level or lymph node status. In contrast to our results, Karaduman et al. did not observe any relationship between tumor size, tumor stage or adiponectin level [20].

In the present study we detected a significant relationship between serum adiponectin level and c-erb-B2 expression or amplification status. Thus, the serum adiponectin level was higher in patients who had c-erb-B2 overexpression (p=0.038). This kind of correlation has not been reported in previous studies [16-18,20]. In contrast to the findings of Karaduman et al. [20], no difference in adiponectin levels between tumor and normal breast tissue was detected in our study. However, serum levels were lower in normal tissue than in tumor tissue, as in the literature.

A reverse relationship between serum and tumor tissue adiponectin levels, but no significant relationship between adiponectin levels in normal breast tissue and tumor tissue were confirmed in this study. However, when we compared adiponectin levels in tumor tissue with those in the serum, the former were significantly higher (p=0.001). Karaduman et al. used fibroadenoma tissue as the control group. A possible limitation of their study stems from the inclusion of fibroadenoma, which is a benign breast tumor, and therefore, does not provide enough homogeneity between groups. In addition, it is possible that the results would have been different if normal breast tissue had been used as the control group instead of fibroadenoma.

In conclusion, our study on adiponectin did not detect significant difference between levels in breast tumor tissue and normal breast tissue. However, the serum adiponectin level was low compared with that in tumor tissue. Adiponectin may prevent tumor progression by decreasing neovascularization in the tissue. In the future, more accurate information will be obtained by comparing normal tissue and tumor tissue in controlled prospective studies with a larger sample size.

References

1. Hortobagyi GN, de la Garza Salazar J, Pritchard K et al. The global breast cancer burden: variations in epidemiology and survival. Clin. Breast Cancer 2005; 6: 391-401.
2. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007, Ca Cancer J Clin 2007; 57: 43-66.
3. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004; 4: 579-591.
4. Ursin G, Longnecker MP, Haile RW, Greenland SA. Meta-analysis of body mass index and risk of premenopausal breast cancer. Epidemiology 1995; 6: 137-141.
5. Van den Brandt PA, Spiegelman D, Yaun SS et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol 2000; 152: 514-527.
6. Rose DP, Komninou D, Stephenson GD. Obesity, adipocytokines, and insulin resistance in breast cancer. Obes Rev 2004; 5: 153-165.
7. Stephenson GD, Rose DP. Breast cancer and obesity: an update. Nutr Cancer 2003; 45: 1-16.
8. Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (adipose most abundant gene transcript 1). Biochem Biophys Res Commun 1996; 221: 286-289.
9. Nakano Y, Tobe T, Choi-Miura NH, Mazda T, Tomita M. Isolation and characterization of GBP28, a novel gelatin-binding protein purified from human plasma. J Biochem 1996; 120: 803-812.
10. Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem 1996; 271: 10697-10703.
11. Stefan N, Vazarova B, Funahashi T et al. Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. Diabetes 2002; 51: 1884-1888.
12. Arita Y, Kihara S, Ouchi N et al. Adipocyte-derived plasma protein, adiponectin, acts as a platelet growth factor-BB-

binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle cell. Circulation 2002; 105: 2893-2898.
13. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to Clq, produced exclusively in adipocytes. J Biol Chem 1995; 270: 26746-26749.
14. Brakenhielm E, Veitonmaki N, Cao R et al. Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. Proc Natl Acad Sci USA 2004; 101: 2476-2481.
15. Hou W, Xu Y, Yu T et al. Adipocytokines and breast cancer risk. Chin Med J 2007; 120: 1592-1596.
16. Miyoshi Y, Funahashi T, Kihara S et al. Association of serum adiponectin levels with breast cancer risk. Clin Cancer Res 2003; 9: 5699-5704.
17. Mantzoros C, Petridou E, Dessypris N et al. Adiponectin and breast cancer risk. J Clin Endocrinol Metab 2004; 89: 1102-1107.
18. Chen DC, Chung YF, Yeh YT et al. Serum adiponectin and leptin levels in Taiwanese breast cancer patients. Cancer Lett 2006; 237: 109-114.
19. Tworoger SS, Eliassen HA, Kelesidis T et al. Plasma Adiponectin Concentrations and Risk of Incident Breast Cancer. J Clin Endocrinol Metab 2007; 92: 1510-1516.
20. Karaduman M, Bilici A, Ozet A, Sengul A, Musabak U, Alomeroglu M. Tissue levels of adiponectin in breast cancer patients. Med Oncol 2007; 24: 361-366.
21. Marshak DR. Strategies for protein purification and characterization: a laboratory course manual. Plainview, NY: Cold Spring Harbor Laboratory Press; 1996.
22. SPSS Inc. SPSS for Windows. Version 11.5.0, Chicago: SPSS Inc., 2001.
23. Yamauchi T, Kamon J, Waki H. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001; 7: 941-946.
24. Hollenbeck C, Reaven GM. Variations in insulin stimulated glucose uptake in healthy individuals with normal glucose tolerance. J Clin Endocrinol Metab 1987; 64: 1169-1173.
25. Berg AH, Combs TP, Du X, Brownlee M, Schererv PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. Nat Med 2001; 7: 947-953.
26. Menzaghi C, Ercolino T, Di Paola R. A haplotype at the adiponectin locus is associated with obesity and other features of the insulin resistance syndrome. Diabetes 2002; 51: 2306-2312.