Available online at www.sciencedirect.com

SCIENCE DIRECT

Metabolism Clinical and Experimental 54 (2005) 1297–1301

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

Three measures of tumor necrosis factor α activity and insulin resistance in nonobese Japanese type 2 diabetic patients

Michihiro Ohya[a], Ataru Taniguchi[a,*], Mitsuo Fukushima[b], Yoshikatsu Nakai[c], Yukiko Kawasaki[d], Shoichiro Nagasaka[e], Akira Kuroe[a], Yoshiro Taki[a], Satoru Yoshii[a], Masaya Hosokawa[d], Nobuya Inagaki[d], Yutaka Seino[a,d]

[a]*Division of Diabetes and Clinical Nutrition, Kansai-Denryoku Hospital, Osaka 553-0003, Japan*
[b]*Department of Health Informatics Research, Translational Research Informatics Center, Foundation for Biochemical Research and Innovation, Kobe 650-0047, Japan*
[c]*School of Health Sciences Faculty of Medicine, Kyoto University, Kyoto 606-8507, Japan*
[d]*Department of Diabetes and Clinical Nutrition, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan*
[e]*Division of Endocrinology and Metabolism, Jichi Medical School, Tochigi, Japan*

Received 4 December 2004; accepted 5 April 2005

Abstract

The aim of the present study was to investigate the relationship between insulin resistance and tumor necrosis factor α (TNF-α) as well as soluble TNF receptors (sTNF-R), body mass index (BMI), leptin, adiponectin, and serum lipid profile including triglycerides in nonobese Japanese patients with type 2 diabetes. A total of 88 nonobese Japanese type 2 diabetic patients were studied. The duration of diabetes was 11.0 ± 0.8 years. In conjunction with BMI, glycosylated hemoglobin (HbA1c), fasting concentrations of plasma glucose, serum lipids (triglycerides, high-density lipoprotein cholesterol, and total cholesterol), serum leptin, serum adiponectin, serum TNF-α, and soluble TNF receptors (sTNF-R1 and sTNF-R2) were also measured. Insulin resistance was estimated by the insulin resistance index of homeostasis model assessment. Insulin resistance was positively correlated with BMI, triglycerides, leptin, and total cholesterol and negatively correlated with adiponectin and high-density lipoprotein cholesterol. In contrast, insulin resistance was not associated with TNF-α, nor sTNF-R (sTNF-R1 and sTNF-R2) in our diabetic patients. There was no significant relationship between the 3 measures of TNF-α system (TNF-α, sTNF-R1, and sTNF-R2) and BMI, serum triglycerides, leptin, or adiponectin in these patients. From these results, it can be concluded that peripheral levels of TNF-α system activity are not a major factor responsible for insulin resistance in nonobese Japanese type 2 diabetic patients.

1. Introduction

Type 2 diabetes mellitus is a heterogeneous syndrome characterized by insulin resistance and/or defective insulin secretion [1]. In contrast to white populations, nonobese Japanese patients with type 2 diabetes are unique in that they are divided into 2 variants: one with insulin resistance and the other with normal insulin sensitivity [2-9]. The former group is characterized by higher body mass index (BMI), higher triglycerides, higher leptin, and lower adiponectin as compared with the latter group. Whereas serum leptin level is shown to be associated with subcutaneous fat area, serum concentrations of triglycerides and adiponectin are linked to visceral fat areas in nonobese Japanese type 2 diabetic patients [7-9]. Thus, the adipose tissue–linked substances are hypothesized to be associated with insulin resistance in nonobese Japanese type 2 diabetic patients.

Tumor necrosis factor α (TNF-α) is 1 of the most important candidates expressed in human adipocytes [10]. Adipocytes of obese subjects are reported to have higher rates in TNF-α messenger RNA expression and TNF-α protein production as compared with those of nonobese subjects, thus resulting in a greater serum TNF-α concentration in obese subjects [11-13]. The increase in TNF-α messenger RNA levels is positively correlated to the degree

* Corresponding author. Fax: +81 6 6458 6994.
E-mail address: k-58403@kepco.co.jp (A. Taniguchi).

0026-0495/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2005.04.017

of hyperinsulinemia, and weight loss is accompanied by a decrease in serum TNF-α concentration and an increase in insulin sensitivity [11-13]. It remains, however, unsolved whether the relationships between serum TNF-α and insulin resistance are caused by or are a result of obesity itself. Furthermore, it is suggested that glucose is proinflammatory and may potentially induce TNF-α. To address this, we recruited nonobese well-controlled Japanese type 2 diabetic patients carefully stratified by their resistance to insulin and explored the relationships between insulin resistance and the TNF-α system (serum TNF-α, serum-soluble TNF receptors). This is the first documented case where peripheral levels of TNF-α system activity (TNF-α, soluble TNF receptors) are not a major factor responsible for the evolution of insulin resistance, at least not in nonobese Japanese type 2 diabetic patients.

2. Subjects and methods

Eighty-eight nonobese Japanese type 2 diabetic patients who visited Kansai-Denryoku Hospital were enrolled for the present study. Type 2 diabetes mellitus was diagnosed based on the World Health Organization criteria [14]. The patients showed no evidence of acute infectious illness at the time of the study. The duration of diabetes was 11.0 ± 0.8 years (mean ± SEM) (range, 1-35 years). Seventy-six of 88 diabetic patients were taking sulfonylureas (gliclazide), and the rest were treated on a dietary regimen with no medication to alter blood glucose level. No patients have received insulin therapy. All subjects had ingested at least 150 g of carbohydrate for the 3 days preceding the study. None of the subjects had significant renal, hepatic, or cardiovascular disease. Patients did not consume alcohol or perform heavy exercise for at least 1 week before the study. Blood pressure was also measured.

Blood was drawn in the morning after a 12-hour fast. Plasma glucose was measured with glucose oxidase method. The triglycerides, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) were also measured. Serum insulin was measured using a 2-site immunoradiometric assay (Insulin Riabead II, Dainabot, Osaka, Japan). Coefficients of variation were 4% for insulin greater than 25 μU/mL and 7% for insulin less than 25 μU/mL. Serum leptin and adiponectin concentrations were measured with a radioimmunoassay kit (Linco Research, St Charles, Mo) as described previously [7,8]. The intra-assay and interassay coefficients of variation were less than 5% for leptin and adiponectin. Serum TNF-α concentrations were measured by enzyme immunoassay kit (Quantikine HS Human TNF-α immunoassay kit, R&D Systems, Inc, Minneapolis, Minn), and serum concentrations of sTNF-R1 and sTNF-R2 were measured by enzyme-linked immunosorbent assay (BIOTRAK, Amersham Life Sciences, Uppsala, Sweden), as described previously [15]. The limits of sensitivity for TNF-α, sTNF-R1, and sTNF-R2 were 0.5, 25, and 50 pg/mL, respectively. Samples for insulin, leptin, adiponectin, and TNF-α system (TNF-α, sTNF-R1, and sTNF-R2) were prepared, frozen, and stored at −70°C until the assay.

The estimate of insulin resistance by homeostasis model assessment (HOMA-IR) was calculated with the following formula: fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5 [16]. The HOMA-IR value of normal tolerant subjects was 1.6 ± 0.9 (mean ± SD), and we defined the values greater than 2.5 as an insulin-resistant state and the values less than 2.5 as an insulin-sensitive state [2,5,17]. The threshold value (2.5) for insulin resistance in our study is similar to that (2.77) in nonobese subjects with no metabolic disorders reported by Bonora et al [18]. It may be argued that the use of sulfonylureas in patients with diabetes might significantly affect the estimate of insulin resistance by HOMA, as these drugs are known to decrease fasting plasma glucose without substantially changing fasting plasma insulin [19]. It seems, however, unlikely because Bonora et al [20] and Emoto et al [21] showed that in the validation studies of HOMA, the correlation of insulin sensitivity measured by such method and that measured by the glucose clamp was not substantially different in diet-treated and sulfonylurea-treated type 2 diabetes. Another problem is that pancreatic B-cell function per se might affect HOMA-IR in Japanese type 2 diabetic patients because these patients are accompanied by mild impairments in pancreatic B-cell function [2]. In our present study, however, fasting C-peptide level was greater than 0.8 ng/mL, indicating that their pancreatic function is not severely impaired. Therefore, we used HOMA-IR in diet-treated and sulfonylurea-treated diabetic patients, taking into account pancreatic insulin secretion.

Table 1
Clinical characteristics in insulin-resistant and insulin-sensitive diabetic patients

	Insulin-resistant	Insulin-sensitive	*P*
No. of subjects	32	56	
Age (y)	61.9 ± 1.7	63.2 ± 1.1	.252
Men/women	25/7	38/18	.155
HOMA-IR	3.58 ± 0.22	1.58 ± 0.07	<.001
Diabetes duration (y)	10.7 ± 1.5	11.2 ± 0.8	.376
Smoking (no/yes)	25/7	42/14	.307
SU/diet	27/5	49/7	.343
BMI (kg/m^2)	23.7 ± 0.3	22.4 ± 0.3	.003
HbA1c (%)	7.4 ± 0.2	6.8 ± 0.1	.007
Triglycerides (mg/dL)	153 ± 12	104 ± 5	<.001
Total cholesterol (mg/dL)	214 ± 6	198 ± 5	.026
Leptin (ng/mL)	6.4 ± 0.8	4.7 ± 0.4	.018
HDL-C (mg/dL)	54 ± 2	61 ± 2	.012
Adiponectin (μg/mL)	10.7 ± 1.1	16.9 ± 1.6	.005
Fasting glucose (mg/dL)	150 ± 4	135 ± 3	.003
Fasting insulin (μU/mL)	9.8 ± 0.6	4.7 ± 0.2	<.001
Systolic blood pressure (mm Hg)	139 ± 3	135 ± 3	.107
Diastolic blood pressure (mm Hg)	86 ± 2	79 ± 1	.001
TNF-α (pg/mL)	3.70 ± 0.49	3.15 ± 0.19	.107
sTNF-R1 (pg/mL)	1132 ± 55	1208 ± 55	.185
sTNF-R2 (pg/mL)	2025 ± 88	2073 ± 67	.333

3. Statistical analysis

Data are presented as mean values ± SEM. Statistical analyses were conducted using the StatView 5 system (Statview, Berkeley, Calif). The mean values of the 2 groups were compared with Student *t* test. Spearman rank correlation coefficient analysis was also performed to calculate a correlation. $P < .05$ was considered as significant.

4. Results

The subjects studied were all Japanese type 2 diabetic patients (63 men and 25 women) with an age range of 43 to 84 years (62.8 ± 1.0 years) and a BMI of 17.1 to 26.7 kg/m^2 (21.0 ± 0.8 kg/m^2). They were all nonobese [22]. The fasting plasma glucose was 141 ± 3 mg/dL, and glycosylated hemoglobin (HbA1c) was 7.0% ± 0.1%. Fasting insulin level was 6.56 ± 0.39 μU/mL. Serum triglycerides, total cholesterol levels, and HDL-C levels were 121 ± 6, 204 ± 4, and 59 ± 2 mg/dL, respectively. Serum leptin and adiponectin concentrations were 5.3 ± 0.4 ng/mL and 14.6 ± 1.2 pg/mL, respectively. There was a wide variation in insulin resistance calculated by HOMA in our diabetic patients (range, 0.51-7.17; mean ± SD, 2.30 ± 0.15). Thirty-two (36%) of 88 patients had HOMA-IR greater than 2.5, indicating that they are insulin-resistant [4,5]. On the other hand, serum TNF-α, soluble TNF-R1(sTNF-R1), and soluble TNF-R2 (sTNF-R2) were 3.35 ± 0.22 (range, 1.6-15.7), 1180 ± 43 (range, 699-2920), and 2055 ± 56 pg/mL (range, 1250-3860 pg/mL), respectively.

Table 1 shows the clinical profile between insulin-resistant and insulin-sensitive type 2 diabetic patients. Compared with insulin-sensitive type 2 diabetic patients, insulin-resistant patients had significantly higher levels of BMI, HbA1c, triglycerides, total cholesterol, leptin, and diastolic blood pressure and lower concentrations of HDL-C and adiponectin. No significant difference was observed in age, sex, duration of diabetes, smoking, systolic blood pressure, and the 3 measures of TNF-α system (TNF-α, sTNF-R1, and sTNF-R2) between the 2 groups.

Table 2
Correlation of TNF-α, sTNF-R1, and sTNF-R2 to measures of variables in diabetic patients

	TNF-α		sTNF-R1		sTNF-R2	
	r	*P*	r	*P*	*r*	*P*
BMI	−0.062	.563	−0.013	.904	−0.159	.137
Systolic blood pressure	0.042	.712	0.208	.682	0.154	.177
Diastolic blood pressure	0.136	.233	0.006	.956	−0.009	.940
HbA1c	0.028	.790	−0.031	.769	−0.128	.233
Fasting glucose	−0.067	.948	−0.073	.496	−0.161	.133
Fasting insulin	0.048	.653	0.026	.811	−0.012	.908
HOMA-IR	0.026	.806	−0.008	.938	−0.061	.571
Triglycerides	0.082	.442	0.011	.920	−0.041	.705
Leptin	−0.204	.059	−0.004	.968	−0.093	.389
Adiponectin	−0.188	.089	0.111	.314	0.148	.180

The correlation between the 3 measures of TNF-α system (TNF-α, sTNF-R1, and sTNF-R2) and the factors associated with insulin resistance (BMI, systolic blood pressure, diastolic blood pressure, HbA1c, fasting glucose, fasting insulin, HOMA-IR, triglycerides, leptin, and adiponectin) was next investigated in our diabetic patients (Table 2). Peripheral levels of the 3 measures of the TNF-α system (TNF-α, sTNF-R1, and sTNF-R2) were not associated with these variables.

5. Discussion

Type 2 diabetes is a heterogenous syndrome characterized by insulin resistance and/or defective insulin secretion [1]. There seems to be racial difference in insulin resistance in type 2 diabetes. Haffner et al [23] surveyed the prevalence of white type 2 diabetic patients and found that 92% of type 2 diabetic patients were insulin-resistant. Chaiken et al [24] reported that 60% of type 2 diabetic patients with BMI less than 30 kg/m^2 were insulin-resistant in African-American populations. We recently demonstrated that 40% of type 2 diabetic patients are insulin-resistant in nonobese Japanese type 2 diabetic patients [4,5]. Whereas the patients with type 2 diabetes already manifest some elements of inflammation, the intriguing feature that nonobese Japanese type 2 diabetic patients are divided into 2 variants enables us to explore whether some inflammatory markers such as TNF-α participated in the worsening of insulin resistance. We therefore investigated TNF-α and sTNF-R in nonobese Japanese type 2 diabetic patients stratified into 2 different groups: one with insulin resistance and the other with normal insulin sensitivity.

The reason why Japanese type 2 diabetic patients are not always associated with insulin resistance is unclear, but it may be due to the fact that mean BMI in our type 2 diabetic patients is 21.0 kg/m^2 less than that in white populations (average BMI 30 kg/m^2). Chang et al [25] recently reported that only 23.6% of Korean type 2 diabetic patients are insulin-resistant. Their mean level of BMI was 22.6 kg/m^2.

Using HOMA-IR and/or minimal model analysis, we have investigated the factors underlying insulin resistance in nonobese Japanese type 2 diabetic patients [2-9]. Whereas BMI and triglycerides are considered to be the most important factors responsible for the evolution of insulin resistance, regional abdominal adipose tissue distribution per se contributes to insulin resistance in nonobese Japanese type 2 diabetic patients [19]. In contrast to white and African-American populations, subcutaneous and visceral fat areas are independently associated with insulin resistance in nonobese Japanese type 2 diabetic patients [26,27]. Not only serum triglycerides but also serum leptin and adiponectin levels are shown to be associated with insulin resistance in our populations [4,5,7,8]. Serum triglycerides level is positively correlated to visceral fat area [9]. Serum leptin level is positively correlated to subcutaneous fat areas, whereas serum adiponectin level is negatively correlated to

visceral fat areas [7,8]. Furthermore, we recently demonstrated that inflammation per se is independently associated with insulin resistance in nonobese Japanese type 2 diabetic patients [6]. We subsequently found that C-reactive protein, 1 of the inflammatory markers, is not only associated with insulin resistance but also with BMI and adipocytokine such as leptin and adiponectin (data not shown). Thus, the factors underlying insulin resistance in nonobese Japanese type 2 diabetic patients are hypothesized to be linked to adipose tissue–related insulin resistance.

Another candidate that is associated with adipose tissue–related insulin resistance is TNF-α, a potent proinflammatory cytokine [10]. Hotamisligil and Spiegelman [28] were the first workers who proposed that TNF-α represents a key mediator of obesity-linked insulin resistance. Overexpression of TNF-α from adipose tissue is shown in different rodent models of obesity. Dandona et al [12] showed that plasma concentration of TNF-α is increased among obese subjects, and it decreases with weight loss. In vitro studies have shown that TNF-α inhibits insulin-stimulated glucose uptake in adipocytes in vitro by decreasing phosphorylation of the insulin receptor [29].

In the present study, we used serum TNF-α, soluble TNF-R1, and soluble TNF-R2 as an index of TNF-α system activity since peripheral levels of TNF receptor remain elevated for a longer time than TNF-α itself and reflect the degree of TNF-α activation more accurately than the measurement of TNF-α itself. Using the 3 measures of TNF-α system activity, we first demonstrated that TNF-α system activity is not responsible for insulin resistance, at least not in nonobese Japanese type 2 diabetic patients. This is a surprising finding because TNF-α is suggested to have a key role in the assessment of insulin resistance of obese and type 2 diabetic patients [10,28]. Thus, the reason why we could not find the relationship between insulin resistance and peripheral levels of TNF-α system in our patients is not known, but it may be due to the difference in clinical characteristics studied. The previous studies supporting the relationship between insulin resistance and TNF-α are derived from the studies dealing with the obese diabetic patients [10-13]. Obese subjects are shown to have higher concentration of TNF-α than nonobese subjects. Moreover, adipose tissue TNF-R2 messenger RNA is shown to be correlated with BMI and hyperinsulinemia in obese diabetic patients. Weight loss is accompanied by a decrease in serum TNF-α concentration and an increase in insulin sensitivity.

On the other hand, there is some literature supporting our present finding that peripheral levels of TNF-α system activity are not associated with insulin resistance in human subjects. Kellerer et al [30] found no correlation between plasma TNF-α and insulin resistance in the offspring of type 2 diabetic patients. Two investigators [31,32] have shown that administration of antibodies or antagonists to TNF-α have not improved insulin sensitivity in insulin-resistant individuals. Zavarotoni et al [33] recently demonstrated that differences in TNF-α activity do not appear to contribute to the marked variation in insulin action that occurs in healthy individuals. Ghanim et al [34] very recently showed that TNF-α is not related to HOMA-IR in obese subjects. Thus, it may be speculated that adipose tissue–linked TNF-α system activity might function locally at the level of the adipocyte in a paracrine or autocrine fashion in our study's diabetic patients. Alternatively, adipose tissue may not play a major role in the determination of peripheral levels of TNF-α system activity in our nonobese, well-controlled, unique Japanese type 2 diabetic patients.

In summary, we demonstrated for the first time that although the number of patients with type 2 diabetes is limited, peripheral levels of TNF-α system activity do not appear to be a major explanation of the mechanisms underlying insulin resistance at least in nonobese well-controlled Japanese type 2 diabetic patients. This idea can be inferred from our present study that peripheral levels of TNF-α system activity are not associated with serum leptin and adiponectin which are another index of insulin resistance in human beings [10].

Acknowledgment

The authors thank Ms Ikuko Yoshioka, Ms Naomi Kitatani, Ms Tomoko Tsuji, Ms Yuhko Nakanishi, Mr Yasuhiko Tsukamoto, and Mr Takahide Okumura, Division of Diabetes and Clinical Nutrition at the Kansai-Denryoku Hospital for encouraging this study.

References

[1] Gerich JE. The genetic basis of type 2 diabetes mellitus: impaired insulin secretion versus impaired insulin sensitivity (Review). Endocr Rev 1998;19:491-503.
[2] Taniguchi A, Nakai Y, Fukushima M, et al. Pathogenic factors responsible for glucose tolerance in patients with NIDDM. Diabetes 1992;41:1540-6.
[3] Nagasaka S, Tokuyama K, Kusaka I, et al. Endogenous glucose production and glucose effectiveness in type 2 diabetic subjects derived from stable-labeled minimal model approach. Diabetes 1999;48:1054-60.
[4] Taniguchi A, Fukushima M, Sakai M, et al. The role of the body mass index and triglyceride levels in identifying insulin-sensitive and insulin-resistant variants in Japanese non–insulin-dependent diabetic patients. Metabolism 2000;49:1001-5.
[5] Taniguchi A, Fukushima M, Sakai M, et al. Remnant-like particle cholesterol, triglycerides, and insulin resistance in nonobese Japanese type 2 diabetic patients. Diabetes Care 2000;23:1766-9.
[6] Taniguchi A, Nagasaka S, Fukushima M, et al. C-reactive protein and insulin resistance in non-obese Japanese type 2 diabetic patients. Metabolism 2002;51:1578-81.
[7] Okumura T, Taniguchi A, Nagasaka S, et al. Relationship of regional adiposity to serum leptin level in nonobese Japanese type 2 diabetic male patients. Diabetes Metab 2003;29:15-8.
[8] Yatagai T, Nagasaka S, Fukushima M, et al. Hypoadiponectinemia is associated with visceral fat accumulation and insulin resistance in subjects with type 2 diabetes mellitus. Metabolism 2003;52:1274-8.
[9] Taniguchi A, Nakai Y, Sakai M, et al. Relationship of regional adiposity to insulin resistance and serum triglyceride levels in non-obese Japanese type 2 diabetic patients. Metabolism 2002;51:544-8.

[10] Pittas AG, Joseph NA, Greenberg AS. Adipocytokines and insulin resistance. J Clin Endocrinol Metab 2004;89:447-52.
[11] Hotamisligil GH, Arner P, Caro JF, et al. Increased adipose tissue expression of tumor necrosis factor-α in human obesity and insulin resistance. J Clin Invest 1995;95:2409-15.
[12] Dandona P, Weinstock R, Thuse A, et al. Tumor necrosis factor-α in sera of obese patients: fall with weight loss. J Clin Endocrinol Metab 1998;83:2907-10.
[13] Katsuki A, Sumida Y, Murashima S, et al. Serum levels of tumor necrosis factor-α are increased in obese patients with non–insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1998;83:859-62.
[14] World Health Organization. Diabetes mellitus: report of a WHO study group. Geneva: World Health Org; 1985 [Tech. Rep. Ser., no. 727].
[15] Nakai Y, Hamagaki S, Takagi R, et al. Plasma concentrations of tumor necrosis factor-α (TNF-α) and soluble TNF receptors in patients with bulimia nervosa. Clin Endocrinol 2000;53:383-8.
[16] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28: 412-9.
[17] Taniguchi A, Nakai Y, Doi K, Fukushima M, et al. Glucose effectiveness in two subtypes within impaired glucose tolerance: a minimal model analysis. Diabetes 1994;43:1211-7.
[18] Bonora E, Kiechl S, Willeit J, Oberhollenzer F, et al. Prevalence of insulin resistance in metabolic disorders: the Bruneck study. Diabetes 1998;47:1643-9.
[19] Groop LC. Drug treatment of non–insulin-dependent diabetes mellitus. In: Pickup J, Williams G, editors. Textbook of diabetes, vol. 38. Oxford (UK): Blackwell; 1997. p. 1-18.
[20] Bonora E, Targher G, Alberiche M, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity. Diabetes Care 2000;23:57-63.
[21] Emoto M, Nishizawa Y, Maekawa K, et al. Homeostasis model assessment as a clinical index of insulin resistance in type 2 diabetic patients treated with sulfonylureas. Diabetes Care 1999;22:818-22.
[22] Taniguchi A, Nakai Y, Doi K, et al. Insulin sensitivity, insulin secretion, and glucose effectiveness in obese subjects: a minimal model analysis. Metabolism 1995;44:1397-400.
[23] Haffner SM, D'Agostino Jr R, Mykkanen L, et al. Insulin sensitivity in subjects with type 2 diabetes: relationship to cardiovascular risk factors: the Insulin Resistance Atherosclerosis Study. Diabetes Care 1999;22:562-8.
[24] Chaiken RL, Banerji MA, Pasmantier RM, et al. Patterns of glucose and lipid abnormalities in black NIDDM subject. Diabetes Care 1991;14: 1036-42.
[25] Chang SA, Kim HS, Yoon KH, et al. Body mass index is the most important determining factor for the degree of insulin resistance in non-obese type 2 diabetic patients in Korea. Metabolism 2004;53: 142-6.
[26] Abate N, Garg A, Peshock RM, et al. Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. Diabetes 1996;45:1684-93.
[27] Banerji MA, Chaiken RL, Gordon D, et al. Does intra-abdominal adipose tissue in black men determine whether NIDDM is insulin-resistant or insulin-sensitive? Diabetes 1995;44:141-6.
[28] Hotamisligil GS, Spiegelman BM. Tumor necrosis factorα: a key component of the obesity-diabetes link. Diabetes 1994;43:1271-8.
[29] Liu LS, Spelleken M, Rohrig K, et al. Tumor necrosis factor-α acutely inhibits insulin signaling in human adipocytes. Implication of the p80 tumor necrosis factor receptor. Diabetes 1998;47:515-22.
[30] Kellerer M, Rett K, Renn W, et al. Circulating TNF-alpha and leptin levels in offsprings of NIDDM patients do not correlate to individual insulin sensitivity. Horm Metab Res 1997;29:111-4.
[31] Ofei F, Hurel S, Newkirk J, et al. Effects of an engineered human anti–TBF0-alpha antibody (CDP571) on insulin sensitivity and glycemic control in patients with NIDDM. Diabetes 1996;45:881-5.
[32] Paquot N, Castillo MJ, Lefebvee PJ, et al. No increased insulin sensitivity after a single administration of a recombinant human tumor necrosis factor receptor: Fc fusion protein in obese insulin resistant patients. J Clin Enodocrinol Metab 2000;85:1316-9.
[33] Zavarotoni I, Numeroso F, Dongiovanni P, et al. What is the contribution of differences in three measures of tumor necrosis factor-alpha activity to insulin resistance in healthy volunteers? Metabolism 2003; 52:1593-6.
[34] Ghanim H, Aljada A, Hofmeyer D, et al. Circulating mononuclear cells in the obese are in a proinflammatory state. Circulation 2004;110: 1564-71.