Endocrine Journal 2011, **58** (6), 425-432

ORIGINAL

Comparison of metabolic profile and adiponectin level with pioglitazone *versus* voglibose in patients with type-2 diabetes mellitus associated with metabolic syndrome

Keisuke Fujitaka, Hajime Otani, Fusakazu Jo, Hiromi Jo, Emiko Nomura, Masayoshi Iwasaki, Mitsushige Nishikawa and Toshiji Iwasaka

Second Department of Internal Medicine, Kansai Medical University, Moriguchi, Japan

Abstract. Type 2 diabetes mellitus (T2DM) associated with metabolic syndrome (MetS) represents a high risk of cardiovascular disease. We compared the effect of early intervention with pioglitazone *versus* voglibose on physical and metabolic profiles and serum adiponectin level in patients with T2DM associated with MetS. Sixty patients who were diagnosed for the first time as T2DM associated with MetS were analyzed for insulin sensitivity, lipid profile, serum adiponectin and systemic inflammation. Those patients were randomly assigned to oral pioglitazone group (n = 30) or voglibose group (n = 30) in addition to conventional diet and exercise training. Body mass index and waist circumference did not change in the pioglitazone group, whereas these physical parameters significantly decreased in the voglibose group during a 6-month follow-up period. However, glycosylated hemoglobin, fasting plasma glucose, and HOMA-IR more significantly decreased in the pioglitazone group. The level of serum adiponectin especially high-molecular weight adiponectin markedly increased in the pioglitazone group. Moreover, high sensitive CRP significantly decreased only in the pioglitazone group. These results suggest that voglibose is superior in improving obesity, while pioglitazone is superior in ameliorating insulin sensitivity and increasing serum adiponectin in patients with an early stage of T2DM associated with MetS.

Key words: Type-2 diabetes mellitus, Metabolic syndrome, Pioglitazone, Voglibose, Adiponectin

METABOLIC syndrome (MetS) is characterized by accumulation of visceral fat associated with the clustering of metabolic and pathophysiological cardiovascular risk factors; impaired glucose tolerance or type-2 diabetes mellitus (T2DM), dyslipidemia and hypertension [1], and has a strong impact on the global incidence of the life-threatening cardiovascular disease such as stroke and myocardial infarction [2, 3]. The prevalence of MetS is rapidly increasing worldwide not only in industrialized countries but also in developing countries associated with a change in the lifestyle including the increase in food intake and the decrease in exercise.

Therapeutic opportunities for MetS comprise lifestyle modification in conjunction with drug treatment for the MetS-associated complications. Caloric restriction (CR) and regular exercise greatly reduce waist circumference and body mass index (BMI), lower blood pressure and improve lipid profile. Lifestyle modification has been shown to prevent T2DM development. Nevertheless, appropriate treatment of cardiovascular risk factors in MetS often requires pharmacologic interventions against T2DM with insulin-sensitizing agents, such as thiazolidinediones (TZDs) and metformin, or

Received Nov. 4, 2010; Accepted Mar. 8, 2011 as K10E-327
Released online in J-STAGE as advance publication Apr. 17, 2011

Correspondence to: Hajime Otani, M.D., Second Department of Internal Medicine, Kansai Medical University, 10-15 Fumizono-cho, Moriguchi City 570-8507, Japan.
E-mail: otanih@takii.kmu.ac.jp

Abbreviations: AMPK, AMP-activated protein kinase; BMI, body mass index; CR, caloric restriction; HDL, high-density lipoprotein; HbA1c, glycosylated hemoglobin A1c; HMW, high-molecular weight; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high sensitive C-reactive protein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; MetS, metabolic syndrome; PPAR, peroxisome proliferator activated receptor; TZDs, thiazolidinediones; TGs, triglycerides; T2DM, type-2 diabetes mellitus

α-glucosidase inhibitors.

The beneficial effect of TZDs is attributed to activation of peroxisome proliferator activated receptor (PPAR)-γ in the adipose tissue and resultant generation of adiponectin [4, 5], which is known to provide favorable metabolic effects, i.e. greater insulin sensitivity, reduced visceral adipose mass, reduced plasma triglycerides (TGs), and increased high-density lipoprotein (HDL)-cholesterol [6]. On the other hand, α-glucosidase inhibitors have shown to prevent the development of T2DM in people with impaired glucose tolerance (IGT) by inhibiting postprandial hyperglycemia [7]. In addition, an α-glucosidase inhibitor voglibose, can reduce the development of T2DM in high-risk Japanese individuals with IGT [8]. Therefore, both TZDs and α-glucosidase inhibitors are promising anti-diabetic drugs against cardiovascular risk factors in MetS. The purpose of the present study was to compare the effect of pioglitazone, the most commonly employed TZDs, versus voglibose on metabolic profiles and adiponectin in patients with T2DM associated with MetS.

Subjects and Methods

Patients

Between April 2007 and February 2010, 62 patients who were diagnosed for the first time as T2DM associated with MetS were enrolled in the present study. All subjects meet the criteria of T2DM raised by the Japanese Diabetes Society (Treatment Guide for Diabetes 2008-2009). MetS was diagnosed to subjects having one or more of the following criteria for MetS [9]; serum TGs level ≥ 150 mg/dl, serum HDL-cholesterol level < 40 mg/dl, systolic blood pressure ≥ 130 mmHg and / or diastolic blood pressure ≥ 85 mmHg besides waist circumference ≥ 85 cm for male and ≥ 90 cm for female. Those patients were randomly assigned to oral pioglitazone group (n = 31) or matching voglibose group (n = 31) in addition to diet and exercise training during a 6-month follow-up period according to the VICTORY Study [8]. The pioglitazone group and voglibose group of patients received pioglitazone at 30 mg daily and voglibose at 0.9 mg daily for 6 months, respectively. One patient in the pioglitazone group and one patient in the voglibose group were eliminated from the study because of heart failure and intractable diarrhea, respectively. Thus, the data from 60 patients (n = 30 in each group) were analyzed. This study was conducted according to the principles expressed in the Declaration of Helsinki. Informed consent was obtained from each subject after full explanation of the purpose, nature, and risk of all procedures used. The protocol was approved by the ethical review committee at Kansai Medical University, Moriguchi City, Japan.

Measurements

Systolic blood pressure and diastolic blood pressure were measured with automatic electronic sphygmomanometer (HEM-907; Omron, Tokyo, Japan), twice in the sitting position after resting for at least 5 minutes. Height, weight, BMI and waist circumference were measured at the time of physical examination. The value of glycosylated hemoglobin A1c (HbA1c) was estimated as an NGSP equivalent value (%) calculated by the formula HbA1c=HbA1c (JDS) (%) + 0.4 % considering the relational expression of HbA1c (JDS) (%) measured by the previous Japanese standard substance and measurement methods and HbA1c (NGSP) [10]. Fasting plasma glucose, serum TGs, serum HDL-cholesterol, serum low-density lipoprotein (LDL)-cholesterol, serum insulin, serum adiponectin, serum HMW and total adiponectin, and serum high sensitive C-reactive protein (hsCRP) level were measured in the morning after an overnight fasting. Adiponectin was measured according to the method as described previously [11]. True waist circumference was measured midway between the tenth rib and the iliac crest with the subjects in the standing position, recorded at the end of a gentle expiration. Plasma glucose was measured by a glucose oxidase method using GA-1152 (Arkrey, Kyoto, Japan). HbA1c was measured by a high performance liquid chromatography method using HLC-723G8 (Tosoh, Tokyo, Japan). Plasma lipids were assayed by routine automated laboratory methods using COLESTEST (Shimizu Medical, Tokyo, Japan). Serum insulin concentration was measured by the electrochemiluminescence immunoassay using a commercially available kit MODULAR ANALYTICS E170 (Roche Diagnostics GmbH, Mannheim, Germany). Plasma adiponectin concentration was measured as described elsewhere [12]. Serum hsCRP was measured by an ultra high sensitivity latex turbidimetric immunoassay method using CRP Latex X2 (Denka Seiken, Tokyo, Japan). Homeostasis model assessment of insulin resistance (HOMA-IR), an insulin resistance index, was calculated as described elsewhere [13].

Table 1 Patients' Characteristics

	Pioglitazone group (n = 30)	Voglibose group (n = 30)	*p* Value
Age (yrs)	61±11	65±9	0.215
Body mass index (kg/m^2)	27.7±4.5	26.9±3.6	0.463
Waist circumference (cm)	98±9	98±8	0.890
Gender (M/F)	20/10	18/12	0.789
Systolic blood pressure (mmHg)	141±26	142±17	0.947
Diastolic blood pressure (mmHg)	83±16	74±14	0.590
Current smokers	8 (26.7%)	9 (30.0%)	> 0.99
HbA1c (%)	6.2±0.8	6.4±0.8	0.312
Fasting plasma glucose (mg/dL)	130±53	129±37	0.977
Fasting serum insulin (μg/mL)	17.9±17.8	15.2±13.9	0.518
HOMA-IR	6.3±8.2	5.6±6.9	0.749
LDL-cholesterol (mg/dL)	128±33	133±52	0.687
HDL-cholesterol (mg/dL)	44±12	48±14	0.206
TGs (mg/dL)	199±87	193±101	0.770
Total adiponectin (μg/mL)	4.9±3.4	4.4±2.1	0.489
HMW adiponectin (μg/mL)	2.3±2.3	1.9±1.3	0.475
hsCRP (mg/dL)	0.194±0.236	0.236±0.217	0.443
ACE inhibitor treatment (n, %)	2 (6.7%)	4 (13.3%)	0.671
ARB treatment (n, %)	23 (76.7%)	19 (63.3%)	0.399
Statin treatment (n, %)	11 (36.7%)	12 (40.0%)	> 0.99
Fibrate treatment (n, %)	1 (3.3%)	3 (10.0%)	0.612

HbA1c, glycosylated hemoglobin A1c; HOMA-IR, homeostasis model assessment for insulin resistance; LDL, low density lipoprotein; HDL, high density lipoprotein; TGs, triglycerides; HMW, high molecular weight; hsCRP, high sensitive C-reactive protein; ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker. Data are expressed as mean ± SD.

Statistical analysis

All analyses were performed with appropriate non-parametrical methods. Treatment groups were compared at baseline by a Wilcoxon rank sum test for continuous variables and chi-square for categorical variables. The difference between treatment groups was assessed by using *t* test statics for the hypothesis that treatment group is a relevant factor in the model. Continuous variables are expressed as mean ± SD. All *p* values < 0.05 were interpreted as statistically significant.

Results

Demographic patients' characteristics of 60 subjects who completed a 6-month follow-up are presented in Table 1. There were no statistically significant differences in any baseline physical and metabolic characteristics between the groups treated with pioglitazone and voglibose. The use of drugs for anti-hypertension and anti-dyslipidemia was similar in both groups.

Changes in the physical and metabolic parameters are shown in Table 2. BMI significantly decreased only in the voglibose group (pioglitazone: -0.3 ± 1.17 kg/m^2; voglibose: -1.2 ± 1.1 kg/m^2; $p < 0.05$ *vs*. baseline). This was associated with a significant decrease in waist circumference in the voglibose group (pioglitazone: 0 ± 5.7 cm; voglibose: -3 ± 5 cm; $p < 0.05$ *vs*. baseline). Systolic and diastolic blood pressures significantly decreased in both groups without a significant intergroup difference.

Significant improvement of HbA1c was observed at 6-month follow-up in both groups (pioglitazone: -0.3 ± 0.5 %; voglibose: -0.2 ± 0.6 %, $p < 0.05$ *vs*. baseline in both groups). However, HbA1c was significantly ($p < 0.02$) less in the piogritazone group compared to the voglibose group. Fasting glucose significantly decreased in the pioglitazone group (pioglitazone: -22 ± 40 mg/dL, $p = 0.002$), while it did not significantly decrease in the voglibose group (-6 ± 29 mg/dL, $p = 0.274$). Accordingly, the fasting glucose level was significantly ($p = 0.028$) less in the pioglitazone group compared to the voglibose group. Fasting serum insulin significantly decreased in the pioglitazone group (-4.7 ± 10.2 μU/mL, $p = 0.013$), while it did not significantly change in the voglibose group (-6 ± 29 μU/mL, $p = 0.351$). Similarly, HOMA-IR significantly

Table 2 Changes in the Physical and Metabolic Parameters

Parameters	pioglitazone group (n = 30)			voglibose group (n = 30)			*p* Value (between groups at 6 month)
	Baseline	6 Months	*p* Value	Baseline	6 Months	*p* Value	
Body mass index (kg/m^2)	27.7±4.5	27.4±4.5	0.866	27.4±4.5	26.2±3.8	0.001	0.310
Waist circumference (cm)	98±9	98±13	0.490	98±13	95±9	0.006	0.365
Systolic blood pressure (mmHg)	141±26	132±17	0.032	142±17	129±20	0.011	0.522
Diastolic blood pressure (mmHg)	83±16	74±14	0.002	74±14	71±13	0.008	0.311
HbA1c (%)	6.2±0.8	5.9±0.5	0.002	6.4±0.8	6.2±0.6	0.027	0.020
Fasting plasma glucose (mg/dL)	130±53	108±18	0.002	129±37	123±28	0.274	0.028
Fasting serum insulin (μg/mL)	17.9±17.8	13.2±9.6	0.013	15.2±13.9	18.1±20.1	0.351	0.030
HOMA-IR	6.3±8.2	3.6±2.8	0.037	5.6±6.9	5.6±6.1	0.735	0.017
LDL-cholesterol (mg/dL)	128±33	113±23	0.048	133±52	131±44	0.710	0.055
HDL-cholesterol (mg/dL)	44±12	48±14	0.013	48±14	49±13	0.794	0.947
TGs (mg/dL)	199±87	146±96	0.003	193±101	130±43	0.049	0.091
Total adiponectin (μg/mL)	4.9±3.4	13.5±13.3	0.002	4.4±2.1	5.4±3.5	0.006	0.006
HMW adiponectin (μg/mL)	2.3±2.3	8.7±11.9	0.008	1.9±1.3	2.5±2.1	0.007	0.015
hsCRP(mg/dL)	0.194±0.236	0.084±0.094	0.026	0.236±0.217	0.210±0.241	0.597	0.026

HbA1c, glycosylated hemoglobin A1c; HOMA-IR, homeostasis model assessment for insulin resistance; LDL, low density lipoprotein; HDL, high density lipoprotein; TGs, triglycerides; HMW, high molecular weight; hsCRP, high sensitive C-reactive protein. Data are expressed as mean ± SD.

decreased in the pioglitazone group (-2.7 ± 6.1, p = 0.037), while it remained unchanged in the voglibose group (-0.1 ± 8.1, p = 0.735). LDL-cholesterol significantly decreased in the pioglitazone group (-15 ± 26 mg/dL, p = 0.048), while it remained unchanged in the voglibose group (-2 ± 31 mg/dL, p = 0.710). Subanalysis of LDL-cholesterol data showed that the LDL-cholesterol level significantly decreased in the pioglitazone group of patients who had been receiving statins (127 ± 23 mg/dL from the baseline to 102 ± 29 mg/dL at 6 month) compared to those without statins (130 ± 41 mg/dL from the baseline to 128 ± 19 mg/dL at 6 month). LDL-cholesterol level did not significantly change in the voglibose group of patients with statins (135 ± 63 mg/dL from the baseline to 133 ± 51 mg/dL at 6 month) or without statins (131 ± 44 mg/dL from the baseline to 130 ± 35 mg/dL at 6 month). HDL-cholesterol significantly increased in the pioglitazone group (+4 ± 11 mg/dL, p = 0.013), while it did not increase in the voglibose group (+1 ± 8 mg/dL, p = 0.794). The TGs level significantly decreased in both groups with a trend being lower in the voglibose group (p = 0.091). In both groups, a significant increment of total and HMW adiponectin was observed (pioglitazone: +8.5 ± 12.2μg/mL and +6.1 ± 10.9 μg/mL; voglibose: +0.9 ± 1.5 μg/mL and +0.5 ± 0.9 μg/mL; $p < 0.05$ *vs*. baseline in both groups). However, total and HMW adiponectin was significantly increased in the pioglitazone group compared to the voglibose group.

Discussion

We compared the change in physical and metabolic profiles after administration with pioglitazone versus voglibose in patients who were diagnosed for the first time as T2DM associated with MetS. Although this study was not placebo-controlled, and the sample size was small, there were several salient differences in these profiles. BMI and waist circumference did not change in the pioglitazone group, whereas these physical parameters significantly decreased in the voglibose group during a 6-month follow-up period. Because these groups of patients equally received diet and physical therapy, these results suggest that voglibose is superior in improving obesity compared to pioglitazone. It has been demonstrated that an α-glucosidase inhibitor, acarbose, decreases waist circumference in human obese subjects associated with T2DM [14], and this effect is attributed to the reduction of visceral fat [15]. Our finding using voglibose supports the anti-visceral obesity effect of α-glucosidase inhibitors. Although we measured waist circumference as a surrogate marker of visceral obesity, waist circumference is not an accurate indicator for visceral adiposity. It has been demonstrated that TZDs cause a major redistribution of body fat with a decrease in visceral fat content [16]. Thus, it is possible that abdominal subcutaneous fat but not visceral fat was increased by pioglitazone tratement. Analysis of abdominal fat content by com-

puted tomography will be necessary to evaluate actual visceral fat volumes.

The present study demonstrated that systolic and diastolic blood pressures similarly decreased in both groups. This decrease in blood pressure is at least in part attributed to the improvement of lifestyle. In addition, the reduction of visceral adipose tissue may also be an important factor in the blood pressure lowering effect of voglibose. We found that HbA1c, fasting plasma glucose, and HOMA-IR more significantly decreased in the pioglitazone group. These results suggest that pioglitazone is superior in ameliorating insulin sensitivity compared to voglibose. The previous study [17] demonstrated that pioglitazone was capable of improving insulin sensitivity in patients with T2DM without a change in intra-abdominal fat, and the improved insulin sensitivity was correlated with an increase in serum adiponectin level. The present study also demonstrated that pioglitazone is superior in increasing the level of serum adiponectin especially HMW adiponectin. A similar effect of pioglitazone on the serum HMW adiopnectin level has already been reported by Aso *et al*. who demonstrated that low-dose pioglitazone significantly increased HMW adiponectin and improved glycemic control in patients with advanced T2DM [18]. It is now apparent that adiponectin exerts diverse effects on glucose and lipid metabolism, thereby improving insulin sensitivity and lowering TGs [19].

Adiponectin is also known to act as an anti-inflammatory molecule [20]. The present study indeed demonstrated that pioglitazone-induced increase in adiponectin was associated with a significant decrease in hsCRP, which has been implicated in a valuable marker for atherosclerosis [21-23]. This anti-inflammatory effect may play a crucial role in preventing the development of atherosclerosis and cardiovascular disease. It has been demonstrated that in a large, placebo-controlled, outcome study in secondary prevention, PROactive study, the use of pioglitazone in addition to an existing optimized macrovascular risk management resulted in a significant reduction of macrovascular endpoints within a short observation period that was comparable to the effect of statins and angiotensin-converting enzyme inhibitors in other trials [24]. In addition, the efficacy of TZDs in preventing atherosclerosis in patients with T2DM has been confirmed by subsequent clinical trials [25]. However, a recent study lack of association between adiponectin levels and atherosclerosis in preclinical rodent models [26]. A follow-up period in our present study was too short to evaluate macrovascular endopoints. Further research is warranted to elucidate the exact mechanism of action by which adiponectin confers the anti-atherosclerotic effect.

Interestingly, pioglitazone significantly decreased LDL-cholesterol in the presence of statins. Theoretically, improvement of insulin sensitivity and reduction of TGs are associated with a decrease in small dense LDL particles and an increase in HDL and LDL-cholesterol. Leonhardt *et al*. [27] reported that pioglitazone alone or in combination with simvastatin had no significant effect on LDL-cholesterol level. We administered pioglitazone in patients who continued statins (pitavastatin, rosuvastatin or atorvastatin) and other lipid-altering therapies maintaining stable serum LDL-cholesterol level. Although the number of patients who administered statins was small, there was no tendency to show a difference in a drug effect between these statins on LDL-cholesterol level in combination with pioglitazone. To the best of our knowledge, there has been no report which analyzed the change in the LDL-cholesterol level in patients with T2DM and high LDL-cholesterolemia. Whatever the mechanism of increase in the efficacy of statins after administration of pioglitazone, the statin-sensitizing effect of pioglitazone in subjects complicated with high-LDL cholesterolemia may be favorable in preventing high dose statin-induced side-effects such as rhabdomyolysis and reducing medical cost.

The effect of voglibose on physical and metabolic parameters appears to be attributed to the improvement of obesity and reduction of visceral fat. Voglibose is a CR-mimetic drug. CR primary affects energy stores in visceral adipose tissue [28]. Indeed, a substantial improvement in all aspects of MetS with only a moderate degree of weight loss by CR has been observed in a randomized clinical trial [29]. The favorable effect of adipose tissue reduction could be due to increased production of adiponectin and decreased production of pro-inflammatory adipocytokines such as tumor necrosis factor-α, interleukin-6, monocyte chemoattractant protein-1, plasminogen activator inhibitor-1 [20, 30, 31]. Imbalance between adiponectin and pro-inflammatory cytokines is responsible for oxidative stress especially to endothelial cells and underlies the pathogenesis of the obesity-associated insulin resistance, T2DM, dyslipidemia and hypertension. We found that voglibose improved visceral obesity, reduced HbA1c and serum TGs level and modestly increased total and HMW adi-

ponectin, suggesting that the decrease in visceral fat stimulated the production of adiponectin. A similar effect on serum adiponectin level has been observed in other α-glucosidase inhibitors, miglitol and acarbose, in patients with T2DM [32, 33]. Therefore, it is possible that voglibose could improve insulin resistance as has been proposed by Satoh *et al*. [34]. However, insulin resistance and systemic inflammation were not significantly improved by administration of voglibose during a 6-month follow-up period. The question as to whether the inferiority of voglibose in improving insulin resistance and systemic inflammation is due to lower adiponectin level compared to pioglitazone remains unknown at present. Longer follow-up may be necessary to improve insulin resistance and systemic inflammation in the voglibose group.

Pioglitazone and other TZDs are associated with fluid retention and edema that may exacerbate existing or developing congestive heart failure [35]. Pioglitazone increases diurnal proximal sodium retention in diabetic and hypertensive individuals [36]. Pioglitazone was associated with a rapid increase in body weight and an increase in diurnal proximal sodium reabsorption, without any changes in renal hemodynamics or in the modulation of the renin-angiotensin aldosterone system to changes in salt intake. In spite of sodium retention, pioglitazone dissociated the blood-pressure response to salt and abolished salt sensitivity in salt-sensitive individuals. These effects cause fluid retention and may contribute to the increased incidence of congestive heart failure with TZDs. In the present study, we encountered one patient who discontinued pioglitazone due to overt heart failure. However, because surrogate end points used to indicate fluid retention (body weight, hematocrit, total protein, and albumin) may not change [35], careful follow-up is necessary not to overlook latent heart failure in patients receiving pioglitazone.

In conclusion, our present data suggest that voglibose is superior in improving obesity, while pioglitazone is superior in ameliorating insulin sensitivity in patients with an early stage of T2DM complicated by MetS. In addition, pioglitazone exerted more favorable effects on serum adiponectin and systemic inflammation at 6-month follow-up. Long term follow-up would unmask the ultimate superiority of these drugs with respect to the development of T2DM and atherosclerotic cardiovascular disease.

Conflict of Interest

The authors declare no conflicts of interest.

References

1. Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S (1987) Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. *Metabolism* 36: 54-59.
2. Alba AC, Delgado DH (2009) Optimal medical treatment of cardiovascular risk factors: can we prevent the development of heart failure? *Expert Rev Cardiovasc Ther* 7: 147-157.
3. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, Culebras A, DeGraba TJ, Gorelick PB, Guyton JR, Hart RG, Howard G, Kelly-Hayes M, Nixon JV, Sacco RL (2006) Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 113: e873-923.
4. Choi KC, Ryu OH, Lee KW, Kim HY, Seo JA, Kim SG, Kim NH, Choi DS, Baik SH, Choi KM (2005) Effect of PPAR-alpha and -gamma agonist on the expression of visfatin, adiponectin, and TNF-alpha in visceral fat of OLETF rats. *Biochem Biophys Res Commun* 336: 747-753.
5. Sharma AM, Staels B (2007) Review: Peroxisome proliferator-activated receptor gamma and adipose tissue--understanding obesity-related changes in regulation of lipid and glucose metabolism. *J Clin Endocrinol Metab* 92: 386-395.
6. Lara-Castro C, Luo N, Wallace P, Klein RL, Garvey WT (2006) Adiponectin multimeric complexes and the metabolic syndrome trait cluster. *Diabetes* 55: 249-259.
7. Hanefeld M, Karasik A, Koehler C, Westermeier T, Chiasson JL (2009) Metabolic syndrome and its single traits as risk factors for diabetes in people with impaired glucose tolerance: the STOP-NIDDM trial. *Diab Vasc Dis Res* 6: 32-37.
8. Kawamori R, Tajima N, Iwamoto Y, Kashiwagi A, Shimamoto K, Kaku K (2009) Voglibose for prevention

of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. *Lancet* 373: 1607-1614.
9. (2005) [Definition and the diagnostic standard for metabolic syndrome--Committee to Evaluate Diagnostic Standards for Metabolic Syndrome]. *Nippon Naika Gakkai Zasshi* 94: 794-809 (In Japanese).
10. The Committee of Japan Diabetes Society on the diagnostic criteria of diabetes mellitus (2010). Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. *J Jpn Diabetes Sos* 53: 450-467 (In Japanese).
11. Tonelli J, Li W, Kishore P, Pajvani UB, Kwon E, Weaver C, Scherer PE, Hawkins M (2004) Mechanisms of early insulin-sensitizing effects of thiazolidinediones in type 2 diabetes. *Diabetes* 53: 1621-1629.
12. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T, Matsuzawa Y (1999) Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 257: 79-83.
13. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28: 412-419
14. Yamagishi S, Nakamura K, Takeuchi M (2005) Inhibition of postprandial hyperglycemia by acarbose is a promising therapeutic strategy for the treatment of patients with the metabolic syndrome. *Med Hypotheses* 65: 152-154.
15. Kobatake T, Matsuzawa Y, Tokunaga K, Fujioka S, Kawamoto T, Keno Y, Inui Y, Odaka H, Matsuo T, Tarui S (1989) Metabolic improvements associated with a reduction of abdominal visceral fat caused by a new alpha-glucosidase inhibitor, AO-128, in Zucker fatty rats. *Int J Obes* 13: 147-154.
16. Campbell IW (2005) The Clinical Significance of PPAR Gamma Agonism. *Curr Mol Med* 5: 349-363.
17. Shadid S, Jensen MD (2003) Effects of pioglitazone versus diet and exercise on metabolic health and fat distribution in upper body obesity. *Diabetes Care* 26: 3148-3152.
18. Aso Y, Hara K, Ozeki N, Yatsuka C, Nakano T, Matsumoto S, Suetsugu M, Nakamachi T, Takebayashi K, Haruki K, Inukai T (2009) Low-dose pioglitazone increases serum high molecular weight adiponectin and improves glycemic control in Japanese patients with poorly controlled type 2 diabetes. *Diabetes Res Clin Pract* 85: 147-152.
19. Kadowaki T, Yamauchi T (2005) Adiponectin and adiponectin receptors. *Endocr Rev* 26: 439-451.
20. Berg AH, Scherer PE (2005) Adipose tissue, inflammation, and cardiovascular disease. *Circ Res* 96:939-949.
21. Yeh ET (2005) High-sensitivity C-reactive protein as a risk assessment tool for cardiovascular disease. *Clin Cardiol* 28: 408-412.
22. Athyros VG, Kakafika AI, Karagiannis A, Mikhailidis DP (2008) Do we need to consider inflammatory markers when we treat atherosclerotic disease? *Atherosclerosis* 200: 1-12.
23. Fruchart JC, Nierman MC, Stroes ES, Kastelein JJ, Duriez P (2004) New risk factors for atherosclerosis and patient risk assessment. *Circulation* 109: III15-19.
24. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J (2005) Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 366: 1279-1289.
25. Goldberg RB (2007) The new clinical trials with thiazolidinediones--DREAM, ADOPT, and CHICAGO: promises fulfilled? *Curr Opin Lipidol* 18: 435-442.
26. Nawrocki AR, Hofmann SM, Teupser D, Basford JE, Durand JL, Jelicks LA, Woo CW, Kuriakose G, Factor SM, Tanowitz HB, Hui DY, Tabas I, Scherer PE (2010) Lack of association between adiponectin levels and atherosclerosis in mice. *Arterioscler Thromb Vasc Biol* 30: 1159-1165.
27. Leonhardt W, Pfutzner A, Muller J, Pietzsch J, Forst T, Karagiannis E, Lubben G, Hanefeld M (2008) Effects of pioglitazone and/or simvastatin on low density lipoprotein subfractions in non-diabetic patients with high cardiovascular risk: A sub-analysis from the PIOSTAT study. *Atherosclerosis* 201: 155-162.
28. Das M, Gabriely I, Barzilai N (2004) Caloric restriction, body fat and ageing in experimental models. *Obes Rev* 5: 13-19.
29. Seshadri P, Iqbal N, Stern L, Williams M, Chicano KL, Daily DA, McGrory J, Gracely EJ, Rader DJ, Samaha FF (2004) A randomized study comparing the effects of a low-carbohydrate diet and a conventional diet on lipoprotein subfractions and C-reactive protein levels in patients with severe obesity. *Am J Med* 117: 398-405.
30. Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S (2005) Adipokines: molecular links between obesity and atheroslcerosis. *Am J Physiol Heart Circ Physiol* 288: H2031-2041.
31. Maury E, Brichard SM (2010) Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. *Mol Cell Endocrinol* 314: 1-16.
32. Yokoyama H, Kannno S, Ishimura I, Node K (2007) Miglitol increases the adiponectin level and decreases

urinary albumin excretion in patients with type 2 diabetes mellitus. *Metabolism* 56: 1458-1463.

33. Ochiai H, Ooka H, Shida C, Ishikawa T, Inoue D, Okazaki R (2008) Acarbose treatment increases serum total adiponectin levels in patients with type 2 diabetes. *Endocr J* 55: 549-556.
34. Satoh N, Shimatsu A, Yamada K, Aizawa-Abe M, Suganami T, Kuzuya H, Ogawa Y (2006) An alpha-glucosidase inhibitor, voglibose, reduces oxidative stress markers and soluble intercellular adhesion molecule 1 in obese type 2 diabetic patients. *Metabolism* 55: 786-793.
35. Kavanagh K, Brown KK, Berquist ML, Zhang L, Wagner JD (2010) Fluid compartmental shifts with efficacious pioglitazone therapy in overweight monkeys: implications for peroxisome proliferator-activated receptor-gamma agonist use in prediabetes. *Metabolism* 59: 914-920.
36. Zanchi A, Maillard M, Jornayvaz FR, Vinciguerra M, Deleaval P, Nussberger J, Burnier M, Pechere-Bertschi A (2010) Effects of the peroxisome proliferator-activated receptor (PPAR)-gamma agonist pioglitazone on renal and hormonal responses to salt in diabetic and hypertensive individuals. *Diabetologia* 53: 1568-1575.