Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 491–496
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Effect of simvastatin and/or pioglitazone on insulin resistance, insulin secretion, adiponectin, and proinsulin levels in nondiabetic patients at cardiovascular risk—the PIOSTAT Study

Thomas Forst[a,b,*], Andreas Pfützner[a], Georg Lübben[c], Matthias Weber[b], Nikolaus Marx[d], Efstrathios Karagiannis[c], Carsta Koehler[e], Werner Baurecht[f], Cloth Hohberg[a], Markolf Hanefeld[e]

[a]*Institute for Clinical Research and Development, Medical Department, D-55116 Mainz, Germany*
[b]*Department of Endocrinology, Johannes Gutenberg University, D-55130 Mainz, Germany*
[c]*TAKEDA Pharma GmbH Medical, D-52066 Aachen, Germany*
[d]*Department of Cardiology, University Ulm, D-89081 Ulm, Germany*
[e]*GWT-TUD, D-01307 Dresden, Germany*
[f]*Acromion, D-50226 Frechen, Germany*

Received 16 May 2006; accepted 20 November 2006

Abstract

We investigated the effect of pioglitazone in comparison with and in combination with simvastatin on insulin resistance, plasma adiponectin, postprandial plasma glucose, insulin, and intact proinsulin levels in a nondiabetic population at cardiovascular risk. One hundred twenty-five nondiabetic patients at cardiovascular risk were randomized to pioglitazone (PIO), pioglitazone and simvastatin (PIO/SIM), or simvastatin (SIM) treatments. Blood samples were taken for the measurement of adiponectin and lipid levels. In addition, an oral glucose load with the measurements of glucose, insulin, and intact proinsulin levels was performed. Adiponectin levels increased from 14.0 ± 8.2 to 27.6 ± 14.5 μg/mL ($P < .0001$) during PIO treatment and from 11.7 ± 10.0 to 26.7 ± 15.7 μg/mL ($P < .0001$) during PIO/SIM treatment. A decrease in adiponectin levels from 15.5 ± 12.7 to 11.6 ± 7.0 μg/mL ($P < .05$) was observed during SIM treatment. Although fasting intact proinsulin levels remained unchanged, the increase in postprandial intact proinsulin levels could be reduced from 29.5 ± 21.4 to 22.1 ± 17.5 pmol/L ($P < .01$) during PIO treatment and from 24.3 ± 27.4 to 21.1 ± 16.5 mmol/L ($P < .05$) during PIO/SIM treatment. Lipid parameters improved during SIM treatment but not during PIO treatment. Combined treatment with PIO/SIM was superior in improving overall cardiovascular risk profile than every single drug.

1. Introduction

Several studies have shown a significant impact on glucose metabolism and insulin resistance or coronary heart disease even in patients without diabetes [1-7]. Two laboratory parameters, adiponectin and intact proinsulin, have received increasing attention for the characterization of insulin resistance, beta-cell function, and cardiovascular risk [8-11]. Increased intact proinsulin levels and reduced adiponectin plasma levels were shown to be highly predictive for cardiovascular disease and type 2 diabetes mellitus [12-15].

Recently, new drugs for intervention of insulin resistance, the peroxisome proliferator-activated receptors (PPARs), were introduced in the treatment of patients with type 2 diabetes mellitus. Beyond their effects on insulin resistance and glucose metabolism, peroxisome proliferator-activated receptor γ (PPARγ) agonists were shown to interact with several cardiovascular risk factors such as dyslipidemia, intact proinsulin, or adiponectin levels in patients with diabetes and to reduce the risk for myocardial infarction and stroke [16-18]. On the other hand, the most common and clinically applied drug intervention in the treatment of patients with increased cardiovascular risk with or without diabetes is the inhibition of 3-hydroxy-3-methylglutaryl

* Corresponding author. Institute for Clinical Research and Development, Parcusstrasse 8, D-55116 Mainz, Germany. Tel.: +49 6131 5763613; fax: +49 6131 5763611.
E-mail address: thomasf@ikfe.de (T. Forst).

0026-0495/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2006.11.007

coenzyme A reductase by statins (3-hydroxy-3-methylglutaryl coenzyme A inhibitors) [19,20].

Up to now, no information is available about the clinical effects of PPARγ stimulation in comparison with or in combination with statins on the previously described metabolic predictors of cardiovascular risk in nondiabetic patients. The aim of this investigation was to evaluate the effects of pioglitazone in comparison with simvastatin on adiponectin, proinsulin, and postload glucose metabolism in nondiabetic patients with increased risk for cardiovascular disease.

2. Patients and methods

This study was a 2-center, prospective, double-blinded, double-dummy, 3-arm parallel trial evaluating the effects of pioglitazone in comparison with and in combination with simvastatin on insulin resistance and adiponectin plasma levels, as well as on fasting and postload glucose, insulin, and proinsulin levels in nondiabetic patients with elevated cardiovascular risk. The study was performed according to the Declaration of Helsinki and Good Clinical Practice; it was approved by the local ethical review board.

2.1. Patients

One hundred thirty-five patients with increased cardiovascular risk, as defined by previous medical history of infarction, and/or coronary angiography with proven cardiovascular disease, and/or unstable angina pectoris, and/or duplex sonography of cervical or leg vessels with proven arteriosclerotic alterations, and/or electrocardiogram with ischemia, and/or stroke, and/or transient ischemic attack, and/or peripheral arterial occlusion, and/or vessel surgery, and/or hypertension were selected for the study. Patients with previous statin treatment and/or PPARγ-activator treatment within the last 4 weeks before entering the trial were excluded. All patients provided their written informed consent. According to the inclusion criteria, 135 patients were randomized, 132 patients received at least 1 medication, and 125 patients were followed up for at least 1 follow-up investigation and were available for the efficacy analysis. In a double-blinded, double-dummy technique, patients were randomly assigned to 1 of 3 treatment groups: pioglitazone in combination with placebo, pioglitazone in combination with simvastatin, or simvastatin in combination with placebo. Treatment with study medication was started with 30 mg pioglitazone and/or 20 mg simvastatin, and after 2 weeks, the dosage was increased to 45 mg pioglitazone and/or 40 mg simvastatin. The clinical characteristics and previous treatment of the study participants in the different treatment groups are given in Table 1. Even if slightly more patients in the combined pioglitazone and simvastatin group received β-blockers, no statistically significant difference in any of these parameters were evident among the groups. All concomitant medication was kept constant for the observational period.

At baseline and after 3 months of study treatment, blood was taken for the measurement of glucose, insulin, intact proinsulin, adiponectin, and lipid parameters. Insulin resistance was calculated using the homeostasis model assessment HOMA score (fasting serum insulin [μU/mL] $\times$ fasting plasma glucose [mmol/L]/22.5). Patients with a calculated HOMA score of 2 or higher (>75th percentile) were considered to be insulin resistant [21]. All measurements were obtained in the morning with patients fasting from midnight onward. Patients were asked to refrain from having coffee and tea for at least 8 hours before each study visit.

Table 1
Clinical characteristics of the investigated groups

	Pioglitazone (n = 39)	Simvastatin (n = 43)	Simvastatin and pioglitazone (n = 43)
Age (y)	59.5 ± 7.8	57.3 ± 8.4	59.0 ± 8.6
Body mass index (kg/m^2)	30.8 ± 4.8	30.5 ± 3.7	31.2 ± 4.1
Male/female	13/26	16/27	18/25
Hypertension	92.3	90.7	90.7
RAS inhibition therapy	59.0	48.8	62.8
β-Blocking therapy	30.8	34.9	46.5
Calcium channel blockers	17.9	23.3	16.3
Diuretics	12.8	14.0	18.6

Values are expressed as percentages or mean ± SD; there were no significant differences among the groups. RAS indicates renin angiotensin system inhibition, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers.

In addition, at baseline and after 3 months of treatment, all patients received a standardized oral glucose tolerance test (75 mg glucose in 300 mL solution, Dextro OGT, Hoffmann La Roche, Grenzach, Germany). At baseline and after 30, 60, 90, and 120 minutes, blood was taken for the measurement of insulin and blood glucose concentrations. In addition, intact proinsulin plasma levels were measured at baseline and after 30 and 120 minutes.

Blood pressure was measured with the patient in a seated position for at least 5 minutes with an appropriate cuff on the left arm. Patient height was measured at the first visit, and patient weight and waist-to-hip ratio were determined at baseline and at the end of the study.

2.2. Biochemical parameters

All laboratory measurements for both study sites were analyzed in a central laboratory. Specific insulin levels were measured using an enzyme-linked immunosorbent assay technique (Anthos Mikrosysteme, Krefeld, Germany). Plasma glucose was measured with the glucokinase-dehydrogenase method, cholesterol with the cholesterol oxidase phenol 4 aminoantipyrine peroxidase method, high-density lipoprotein (HDL) cholesterol with the precipitation method, and triglycerides with the glycerolphosphate oxidase phenol 4 aminoantipyrine peroxidase method (DiaSys, Holzheim, Germany). Adiponectin and intact proinsulin (Linco Res, St Charles, MO) concentrations were measured using specific immunoassays.

2.3. Statistical analysis

Data are presented as arithmetic mean ± SD for continuous variables and as the number/proportion of

Table 2
Laboratory parameters and blood pressure at baseline and end point for the different treatment groups (values are expressed as arithmetic mean ± SD)

	Pioglitazone		Simvastatin		Pioglitazone and simvastatin	
	Baseline	12 wk	Baseline	12 wk	Baseline	12 wk
Glucose (mmol/L)	5.63 ± 0.54	5.23 ± 0.51*,†,‡	5.60 ± 0.62	5.56 ± 0.55†	5.70 ± 0.66	5.50 ± 0.70*,‡
Insulin (mU/mL)	12.8 ± 7.4	10.2 ± 3.6*,†	13.8 ± 6.3	14.7± 6.5†,§	14.8 ± 7.1	11.5 ± 4.5*,§
HOMA (mU · mol/mL^2)	3.27 ± 2.21	2.40 ± 0.97*,†	3.52 ± 2.07	3.63 ± 1.60†,§	3.70 ± 1.98	2.81 ± 1.15*,§
Adiponectin (μg/mL)	13.96 ± 8.16	27.64 ± 14.49*,†	15.49 ± 12.66	11.59 ± 7.03*,†,§	11.68 ± 9.96	26.67 ± 15.73*,§
Total cholesterol (mmol/L)	5.60 ± 0.99	5.67 ± 1.17†,‡	5.73 ± 1.10	4.44 ± 0.96*,†	5.67 ± 1.26	4.43 ± 0.95*,‡
HDL cholesterol (mmol/L)	1.41 ± 0.41	1.44 ± 0.42	1.43 ± 0.41	1.52 ± 0.42*	1.44 ± 0.45	1.53 ± 0.45*
LDL cholesterol (mmol/L)	3.50 ± 0.94	3.56 ± 1.04†,‡	3.60 ± 1.01	2.32 ± 0.88*,†	3.68 ± 1.10	2.40 ± 0.91*,‡
Triglycerides (mmol/L)	1.50 ± 0.73	1.46 ± 0.64‡	1.63 ± 1.64	1.36 ± 1.16	1.45 ± 0.59	1.13 ± 0.39*,‡
ASAT (μmol/L)	0.43 ± 0.12	0.39 ± 0.10	0.44 ± 0.14	0.44 ± 0.14	0.46 ± 0.12	0.43 ± 0.11
ALAT (μmol/L)	0.43 ± 0.23	0.40 ± 0.18	0.48 ± 0.25	0.46 ± 0.20	0.46 ± 0.22	0.39 ± 0.16
RR syst (mm Hg)	145 ± 15	139 ± 17*	145 ± 18	140 ± 13	145 ± 20	136 ± 16*
RR diast (mm Hg)	89 ± 10	85 ± 12*	90 ± 11	88 ± 10§	87 ± 9	81 ± 8*,§

LDL indicates low-density lipoprotein; ASAT, aspartate aminotransferase; ALT, alanin aminotransferase; RR syst, systolic blood pressure; RR diast, diastolic blood pressure.

* $P < .05$ vs baseline (paired t test).

† $P < .05$, pioglitazone vs simvastatin.

‡ $P < .05$, pioglitazone vs simvastatin and pioglitazone.

§ $P < .05$, simvastatin vs simvastatin and pioglitazone (2-sample t tests).

patients with a characteristic for categorical variables. The analysis of safety is based on the intention-to-treat population, which consists of all patients who received at least 1 dose of medication. For efficacy analysis, all patients who underwent baseline assessment and at least 1 examination thereafter were included. All analyses were performed in an exploratory sense, and a P value of less than .05 was considered clinically significant.

Treatment groups were compared at baseline by using the Student t test for continuous variables and the χ^2 test for categorical variables. Changes from baseline for distinct cardiovascular risk parameters were evaluated using Student t tests. Within-group comparisons were analyzed by paired t tests, and between-group comparisons were analyzed by 2-sample t tests. The change from baseline was defined as the absolute change from baseline (actual value minus baseline value) and as the relative change from baseline (actual value minus baseline divided by baseline). Correlation was assessed by using the Spearman rank-order correlation coefficient. Statistical analysis was performed using SAS version 8.2 (SAS Institute, Cary, NC).

3. Results

At baseline, mean fasting blood glucose of the entire study group was 5.64 ± 0.61 mmol/L. According to the oral glucose tolerance test, 16.8% of the patients were found to have an impaired glucose tolerance, and 86.4% of the patients had an impaired insulin sensitivity as defined by a HOMA score of greater than 2. Adiponectin levels at baseline were 13.7 ± 10.5 μg/mL, and an inverse correlation could be obtained between adiponectin plasma levels and insulin resistance (HOMA score: $r = -0.55$, $P < .0001$).

As shown in Table 2, treatment with pioglitazone and the combined treatment with pioglitazone and simvastatin resulted in a reduction of fasting insulin and glucose levels. Fasting insulin levels decreased significantly during pioglitazone treatment by −13% ± 28% and during combined treatment by −16% ± 26%. The HOMA-S score declined by 19% ± 28% during pioglitazone monotherapy and by 17% ± 29% in the combined-treatment group. No significant change in these parameters could be observed with single simvastatin treatment. The improvement in insulin sensitivity was found to correlate with the reduction in fasting glucose levels ($r = 0.52$, $P < .0001$) and with the improvement in blood glucose levels 2 hours after the oral glucose load ($r = 0.26$, $P = .0045$).

As shown in Fig. 1, adiponectin levels increased by 127% ± 105% during pioglitazone monotherapy and by 166% ± 94% during treatment with pioglitazone in

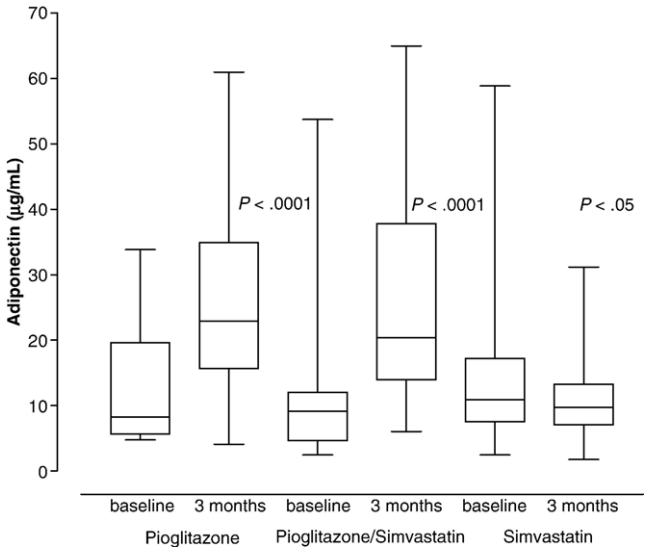

Fig. 1. Adiponectin plasma levels at baseline and after 12 weeks of treatment with pioglitazone, pioglitazone and simvastatin, or simvastatin.

combination with simvastatin. Surprisingly, treatment with simvastatin alone resulted in a small but significant reduction in adiponectin levels by 12% ± 30%. An inverse correlation was obtained between the improvement in HOMA-S score and the change in adiponectin plasma levels ($r = -0.32$, $P = .0004$). After 3 months of treatment, adiponectin levels were significantly higher in both pioglitazone-treated groups compared with the simvastatin group.

Pioglitazone treatment and the combined treatment were found to significantly improve glucose and insulin profile during the oral glucose tolerance test, whereas no significant effect could be observed during simvastatin monotherapy. As illustrated in Fig. 2A to C, fasting intact proinsulin levels were found in the upper normal limit. After the glucose load, a pronounced increase in intact proinsulin levels could be observed in all treatment groups. Although no significant change in fasting intact proinsulin levels could be observed in any treatment group, pioglitazone and the combination of pioglitazone with simvastatin significantly reduced the increase in postprandial intact proinsulin levels.

As shown in Table 2, single treatment with simvastatin and the combined treatment with simvastatin and pioglitazone resulted in a significant improvement in total cholesterol, HDL, and low-density lipoprotein levels.

A significant decrease in systolic and diastolic blood pressures could be observed in pioglitazone-treated patients and in the group receiving both study drugs, whereas only a nonsignificant decrease in blood pressure could be observed with single simvastatin treatment.

3.1. Safety and tolerability

All 3 kinds of treatment were generally well tolerated. There was no significant difference in the number of adverse events among the study groups. Treatment with pioglitazone was associated with a higher number of peripheral edema in the pioglitazone monotherapy (11.4%) and in the combined-treatment group (22.2%) compared with the simvastatin monotherapy group (7.0%). There was 1 serious adverse event in the pioglitazone monotherapy group, where a patient needed to be hospitalized because of nephrolithiasis.

As shown in Table 2, no adverse effect could be found on liver function in any of the observed groups.

Body weight increased significantly in the pioglitazone-treated (1.8 ± 3.6 kg, $P = .003$) and the combination-treated patients (1.2 ± 2.2 kg, $P < .001$). No significant changes could be observed in the waist-to-hip ratio.

4. Discussion

In our study, 16.8% of nondiabetic patients with increased cardiovascular risk were found with impaired glucose tolerance, and 86.4% of the patients were identified with an impaired insulin sensitivity according to a HOMA-S score of higher than 2. None of the included patients had diabetes according to the definition of the American Diabetes Association.

Consistent with previous studies showing a strong effect of pioglitazone treatment on adiponectin plasma levels in diabetic patients [22,23], our study revealed a striking improvement in adiponectin levels also in nondiabetic patients at cardiovascular risk. Besides increasing adiponectin levels, PPARα and PPARγ stimulations were shown to increase the expression of adiponectin receptors in macrophages and might therefore evolve substantial therapeutic effects in the development and progression of arteriosclerosis [24]. Treatment with pioglitazone or the combined treatment with pioglitazone and simvastatin for 3 months resulted in a 127% and 166% increase in adiponectin plasma levels, respectively. In contrast to the results obtained by Chu et al [25] in patients with type 2

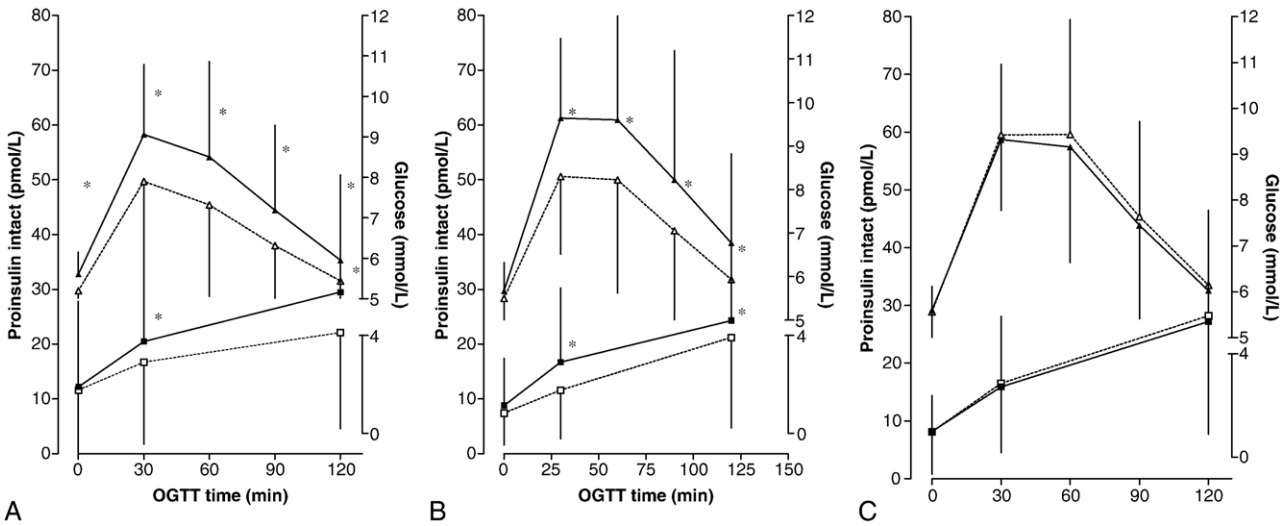

Fig. 2. Time course of postprandial glucose and proinsulin intact plasma levels at baseline and 12 weeks after treatment with pioglitazone (A), pioglitazone and simvastatin (B), or simvastatin (C). Values are expressed as mean ± SD. ■ indicates proinsulin at baseline; □, proinsulin after 12 weeks of treatment; ▲, glucose at baseline; △, glucose after 12 weeks of treatment; OGTT, oral glucose tolerance trial. *$P < .001$.

diabetes mellitus, in our study, single treatment with simvastatin slightly, but significantly, reduced adiponectin plasma levels. The reason for this discrepancy might be caused by the different patient populations investigated in the 2 studies (diabetic vs nondiabetic patients).

In our study, treatment with pioglitazone and the combination of pioglitazone with simvastatin significantly improved the time course of glucose and insulin levels after an oral glucose load.

Intact proinsulin plasma concentrations were found to be elevated in obese patients and in patients with insulin resistance and were shown to be a strong predictor for type 2 diabetes mellitus and cardiovascular disease [8,26-28]. In addition, an association between increased proinsulin levels and a sympathoadrenal imbalance of the autonomic nervous system is described for diabetic and nondiabetic subjects [29]. Heretofore, nothing is known about the release of intact proinsulin in the postprandial state in nondiabetic patients at increased cardiovascular risk. In contrast to the only moderately elevated intact proinsulin levels at baseline, a remarkable increase in intact proinsulin levels could be observed after the oral glucose load. Treatment with the PPARγ agonist pioglitazone in patients with type 2 diabetes mellitus were shown to significantly reduce intact proinsulin levels [30], which was found to be associated with an improvement in other cardiovascular risk markers such as intima-media thickness of the carotid artery [31]. In our recent study, treatment with pioglitazone and the combination of pioglitazone with simvastatin did not affect fasting intact proinsulin levels but significantly decreased the increase in postprandial intact proinsulin levels. No effect of simvastatin monotherapy on intact proinsulin levels could be observed in this patient population. The finding of a considerable increase of intact proinsulin levels in the postprandial state is new, and might have important clinical implications. Pursuing research has to clarify the role of the postprandial increase in intact proinsulin levels as a independent cardiovascular risk factor in patients with insulin resistance.

In our study, treatment with simvastatin and the combination of simvastatin and pioglitazone significantly improved total cholesterol, HDL, and low-density lipoprotein plasma levels. In contrast to previous studies on diabetic patients [32], no significant effect on these lipid parameters could be observed during treatment with pioglitazone alone.

In conclusion, this is the first study that investigated the effect of pioglitazone in comparison with and in combination with simvastatin on several markers of the metabolic syndrome in nondiabetic patients with increased cardiovascular risk. Despite the specific beneficial action of each single drug on distinct cardiovascular risk factors, the combined treatment with both study drugs was able to provide an overall improvement of all risk markers observed in our study. The results of the study also prove additional protective effects of PPARγ agonists on the cardiovascular system in patients pretreated with statins. Further studies need to evaluate the clinical significance of these beneficial effects of combining PPARγ agonist and statin treatments in reducing the cardiovascular risk in patients without diabetes.

Acknowledgment

This study was supported by a grant from TAKEDA Pharma GmbH, Aachen, Germany.

Appendix A

This study was performed at 2 sites:

1. GWT-TUD, Center for Clinical Studies, Dresden, Germany
2. Institute for Clinical Research and Development, Mainz, Germany.

References

[1] Balkau B, Shipley M, Jarrett RJ, et al. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study [see comments]. Diabetes Care 1998;21:360-7.

[2] Modan M, Meytes D, Rozeman P, et al. Significance of high HbA_1 levels in normal glucose tolerance. Diabetes Care 1988;11:422-8.

[3] de Vegt F, Dekker JM, Ruhe HG, et al. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. Int J Obes Relat Metab Disord 1999;42:926-31.

[4] Jadhav S, Petrie J, Ferrell W, et al. Insulin resistance as a contributor to myocardial ischaemia independent of obstructive coronary atheroma: a role for insulin sensitisation? Heart 2004;90:1379-83.

[5] Tenerz A, Norhammar A, Silveira A, et al. Diabetes, insulin resistance, and the metabolic syndrome in patients with acute myocardial infarction without previously known diabetes. Diabetes Care 2003;26:2770-6.

[6] Rewers M, Zaccaro D, D'Agostino R, et al. Insulin sensitivity, insulinemia, and coronary artery disease: the Insulin Resistance Atherosclerosis Study. Diabetes Care 2004;27:781-7.

[7] Sasso FC, Carbonara O, Nasti R, et al. Glucose metabolism and coronary heart disease in patients with normal glucose tolerance. JAMA 2004;291:1857-63.

[8] Zethelius B, Lithell H, Hales CN, et al. Insulin sensitivity, proinsulin and insulin as predictors of coronary heart disease. A population-based 10-year, follow-up study in 70-year old men using the euglycaemic insulin clamp. Int J Obes Relat Metab Disord 2005;48:862-7.

[9] Oh JY, Barrett-Connor E, Wedick NM. Sex differences in the association between proinsulin and intact insulin with coronary heart disease in nondiabetic older adults: the Rancho Bernardo Study. Circulation 2002;105:1311-6.

[10] Shimabukuro M, Higa N, Asahi T, et al. Hypoadiponectinemia is closely linked to endothelial dysfunction in man. J Clin Endocrinol Metab 2003;88:3236-40.

[11] Lam KS, Xu A. Adiponectin: protection of the endothelium. Curr Diabet Rep 2005;5:254-9.

[12] Schondorf T, Maiworm A, Emmison N, et al. Biological background and role of adiponectin as marker for insulin resistance and cardiovascular risk. Clin Lab 2005;51:489-94.

[13] Maahs DM, Ogden LG, Kinney GL, et al. Low plasma adiponectin levels predict progression of coronary artery calcification. Circulation 2005;111:747-53.

[14] Pfutzner A, Pfutzner AH, Larbig M, et al. Role of intact proinsulin in diagnosis and treatment of type 2 diabetes mellitus. Diabetes Technol Ther 2004;6:405-12.

[15] Zethelius B, Byberg L, Hales CN, et al. Proinsulin and acute insulin response independently predict type 2 diabetes mellitus in men—report from 27 years of follow-up study. Int J Obes Relat Metab Disord 2003;46:20-6.

[16] Dormandy JA, Charbonnel B, Eckland DJ, et al. 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 2005;366:1279-89.

[17] Khan MA, St Peter JV, Xue JL. A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. Diabetes Care 2002;25:708-11.

[18] Forst T, Lubben G, Hohberg C, et al. Influence of glucose control and improvement of insulin resistance on microvascular blood flow and endothelial function in patients with diabetes mellitus type 2. Microcirculation 2005;12:543-50.

[19] Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005;352:20-8.

[20] Schaefer EJ, McNamara JR, Asztalos BF, et al. Effects of atorvastatin versus other statins on fasting and postprandial C-reactive protein and lipoprotein-associated phospholipase A2 in patients with coronary heart disease versus control subjects. Am J Cardiol 2005;95:1025-32.

[21] Hedblad B, Nilsson P, Janzon L, et al. Relation between insulin resistance and carotid intima-media thickness and stenosis in non-diabetic subjects. Results from a cross-sectional study in Malmo, Sweden. Diabet Med 2000;17:299-307.

[22] Pfutzner A, Marx N, Lubben G, et al. Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: results from the pioneer study. J Am Coll Cardiol 2005;45:1925-31.

[23] Miyazaki Y, Mahankali A, Wajcberg E, et al. Effect of pioglitazone on circulating adipocytokine levels and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 2004;89:4312-9.

[24] Qi Y, Takahashi N, Hileman SM, et al. Adiponectin acts in the brain to decrease body weight. Nat Med 2004;10:524-9.

[25] Chu CS, Lee KT, Lee MY, et al. Effects of rosiglitazone alone and in combination with atorvastatin on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Am J Cardiol 2006;97:646-50.

[26] Alssema M, Dekker JM, Nijpels G, et al. Proinsulin concentration is an independent predictor of all-cause and cardiovascular mortality: an 11-year follow-up of the Hoorn Study. Diabetes Care 2005;28:860-5.

[27] Pfutzner A, Kunt T, Hohberg C, et al. Fasting intact proinsulin is a highly specific predictor of insulin resistance in type 2 diabetes. Diabetes Care 2004;27:682-7.

[28] Wallander M, Bartnik M, Efendic S, et al. Beta cell dysfunction in patients with acute myocardial infarction but without previously known type 2 diabetes: a report from the GAMI study. Int J Obes Relat Metab Disord 2005;48:2229-35.

[29] Haffner SM, D'Agostino R, Mykkanen L, et al. Proinsulin and insulin concentrations in relation to carotid wall thickness: Insulin Resistance Atherosclerosis Study. Stroke 1998;29:1498-503.

[30] Kubo K. Effect of pioglitazone on blood proinsulin levels in patients with type 2 diabetes mellitus. Endocr J 2002;49:323-8.

[31] Forst T, Hohberg C, Fuellert SD, et al. Pharmacological PPARgamma stimulation in contrast to beta cell stimulation results in an improvement in adiponectin and proinsulin intact levels and reduces intima media thickness in patients with type 2 diabetes. Horm Metab Res 2005;37:521-7.

[32] Hanefeld M, Brunetti P, Schernthaner GH, et al. One-year glycemic control with a sulfonylurea plus pioglitazone versus a sulfonylurea plus metformin in patients with type 2 diabetes. Diabetes Care 2004;27:141-7.