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Peroxisome proliferator–activated receptor γ agonist improves arterial stiffness in patients with type 2 diabetes mellitus and coronary artery disease

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Abstract

Arterial stiffness is an independent risk factor for cardiovascular events in diabetic patients, and it can be assessed by measuring pulse wave velocity (PWV). We investigated the degree of arterial stiffness in diabetic patients with coronary artery disease (CAD) and the effect of the proliferator-activated receptor γ (PPAR-γ) agonist rosiglitazone on arterial stiffness in the potential mechanism of anti-arteriosclerosis in patients with type 2 diabetes mellitus and CAD. The 123 participants were divided into 3 groups: healthy controls (n = 36), diabetic patients (n = 41), and diabetic patients with CAD (n = 46). Forty-six diabetic patients with CAD were randomly divided into 2 groups: untreated diabetic patients with CAD and diabetic patients with CAD treated with 4 mg/d of rosiglitazone (n = 25) for 12 weeks. Pulse wave velocity was measured before treatment and at 12-week follow-up. Baseline PWV was significantly higher in patients with diabetes, diabetes and CAD, and diabetes and CAD with treatment as compared with the healthy control group (1633 ± 37.3, 1669 ± 53.8, 1615 ± 44.4, and 1360 ± 39.9 cm/s, respectively, $P < .001$). Pulse wave velocity in the rosiglitazone-treated group was significantly reduced, from 1615 ± 44.4 to 1525 ± 43.1 cm/s, after 12-week treatment, Furthermore, PWV was significantly decreased in the rosiglitazone-treated group compared with untreated group after 12 weeks (1525 ± 43.1 and 1670 ± 41.3 cm/s, respectively). Pulse wave velocity in the untreated group did not differ from baseline levels after 12 weeks. In addition, plasma C-reactive protein level was decreased significantly in the rosiglitazone-treated group compared with values at baseline and for the untreated group after 12 weeks (0.73 ± 0.09, 1.71 ± 0.24, and 1.33 ± 0.29 mg/L, respectively). Plasma level of monocyte chemoattractant protein 1 was decreased in the rosiglitazone group compared with the level at baseline (392 ± 42 and 273 ± 40 pg/mL, respectively). Moreover, the decrease in PWV was associated linearly both with improved homeostasis model assessment of insulin resistance and with decreased C-reactive protein level after PPAR-γ agonist treatment. In conclusion, PPAR-γ agonist rosiglitazone treatment may significantly decrease arterial stiffness in diabetic patients with CAD. Proliferator-activated receptor γ agonists may play an important role in protecting against arteriosclerosis by normalizing the metabolic disorders and depressing chronic inflammation of the vascular system in patients with type 2 diabetes mellitus and serious vascular disease.

1. Introduction

Epidemiological and clinical studies have shown that increased arterial stiffening is associated with increased risk for cardiovascular events and death. Vascular stiffening is influenced by hemodynamic and extrinsic factors such as diabetes, hypertension, and atherosclerosis. Elastic fiber fragmentation and structural dysregulation represent, at least in part, an inflammatory response in the arterial wall, leading to degradation of normal elastin, which can increase vascular stiffness [1]. Pulse wave velocity (PWV), a marker of arterial rigidity, has been identified as an independent predictor of cardiovascular risk in subjects with hypertension and metabolic syndrome [2].

Type 2 diabetes mellitus is characterized by insulin resistance and impaired glucose tolerance. Insulin resistance is often associated with dyslipidemia, hypertension, and atherosclerosis. Although the exact cause of atherosclerosis is not clear, improving the features of metabolic disorders characterized by insulin resistance can significantly decrease

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its risk. Peroxisome proliferator–activated receptors (PPARs) are ligand-activated transcription factors that are a subfamily of the nuclear receptor gene family. In various animal models, PPAR-γ agonists have been shown to decrease the risk of atherosclerosis by directly affecting the formation of atherosclerotic lesions through regulation of the gene expression of glucose, lipid metabolism, and inflammation [3,4]. Arterial stiffening related to insulin resistance may be modified by PPAR-γ agonists. Peroxisome proliferator–activated receptor γ ligands may exert beneficial protective effects on the artery wall by improving metabolism. Peroxisome proliferator–activated receptor γ is expressed in vascular tissue and can contribute to vascular homeostasis. They have been shown to decrease vascular remodeling and inhibit arterial wall inflammation in rats [5]. Moreover, the PPAR-γ agonist pioglitazone improves artery wall elasticity and reduces aortic wall stiffness by, at least in part, an anti-inflammatory mechanism [6].

Our previous study demonstrated that PPAR-γ agonists significantly reduced plasma levels of monocyte chemoattractant protein 1 (MCP-1) and C-reactive protein (CRP) in patients with type 2 diabetes mellitus and coronary artery disease (CAD) [7]. Recently, clinical studies demonstrated that treatment with pioglitazone significantly decreased CRP and PWV in patients with or without diabetes [8,9]. However, although PPAR-γ agonists can exert an anti-arteriosclerotic effect on the vascular wall in patients with type 2 diabetes mellitus and serious vascular damage such as CAD, the underlying mechanisms are still unclear. Here, we show that treatment with 4 mg/d of the PPAR-γ agonist rosiglitazone for 12 weeks decreased not only insulin resistance but also PWV—a direct parameter of arterial stiffness in patients with diabetes and CAD. Furthermore, plasma levels of CRP and MCP-1 were decreased by rosiglitazone treatment, which suggests that PPAR-γ agonists may exert beneficial effects on the artery by, at least in part, improving metabolism and anti-inflammatory mechanisms in diabetic patients with vascular damage.

2. Materials and methods

2.1. Subjects

Patients were selected from the cardiovascular internal medicine department at the Peking University Third Hospital (Beijing, PR China) from October 2005 to March 2007. We enrolled 123 participants, aged 40 to 78 years, including 36 healthy controls, 41 type 2 diabetic patients, and 46 type 2 diabetic patients with CAD (>50% stenosis as shown on angiography). Patients with acute myocardial infarction during the preceding 12 weeks, heart failure, renal function impairment, liver function impairment, systemic inflammatory disease, infectious disease, cancer, or a serious illness or were undergoing insulin treatment that would affect their participation were excluded.

2.2. Study design

The study participants were divided into 3 groups: healthy controls (n = 36), diabetic patients (n = 41), and diabetic patients with CAD (n = 46). The diabetic patients with CAD were further randomly divided into 2 groups: diabetic patients with CAD (n = 21) and diabetic patients with CAD treated with 4 mg/d rosiglitazone (n = 25) for 12 weeks. All patients had undergone angiography. Blood samples were drawn before angiography and at 12 weeks after the diabetic patients with CAD were treated with rosiglitazone for the analysis of clinical chemistry and inflammatory factors, and these were then centrifuged immediately. Plasma samples were stored at −70°C for further analysis.

All subjects gave their written informed consent. This study was approved by the ethics committee of the Health Science Center, Peking University.

2.3. Pulse wave velocity measurement

Arterial stiffness was assessed by automatic brachial-ankle PWV measurement using the Colin VP-1000 apparatus (Colin Co, Komaki, Japan). The basic principle of PWV assessment is that pressure pulse generated by ventricular ejection is propagated along the arterial system at a speed determined by elasticity of the arterial wall. Knowing the distance and pulse transit time, the velocity can be calculated. Patients were placed in recumbent position and, after a 10-minute rest, underwent brachial-ankle PWV measurement. The value of PWV increases with age. The normal values of PWV are 1100 to 1460 cm/s in healthy people aged 40 to 75 years.

2.4. Laboratory measurements

Blood samples were drawn from an antecubital vein in the morning after overnight fasting and collected into vacuum tubes containing EDTA for the measurement of plasma lipid and lipoprotein levels. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were analyzed by colorimetric enzymatic assays with the use of an autoanalyzer (HITACHI-7170, Hitachi, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) levels were calculated. Fasting plasma glucose, fasting insulin, and hemoglobin A_{1c} levels were determined at the central chemistry laboratory of the Peking University Third Hospital.

Levels of CRP and MCP-1 were measured using enzyme-linked immunosorbent assay kits following the manufacturer's protocols (R&D Systems, Minneapolis, MN). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: IR = [fasting insulin (μU/mL) × fasting glucose (mmol/L)]/22.5.

2.5. Statistical analysis

One-way analysis of variance was used for the comparison among the 4 groups. The differences between groups were analyzed by Student t test. Within-treatment changes were analyzed by paired t test. Proportions were analyzed by χ^2 test. Pulse wave velocity and plasma levels of cholesterol,

Table 1
Baseline characteristics of healthy controls and diabetic patients with or without CAD

Characteristics	Control group (n = 36)	Diabetes group (n = 41)	Diabetes with CAD (n = 21)	Diabetes with CAD + RSG (n = 25)
Age	58.2 ± 12.6	58.8 ± 11.5	63.5 ± 9.8	63.6 ± 11.2
Body mass index	23.9 ± 3.7	25.2 ± 3.4	24.7 ± 3.8	26.1 ± 3.1
Sex (M/F)	20/16	23/18	14/7	17/8
No. of risk factors				
Hyperlipidemia		25	15	16
Hypertension		15	9	11
Smoking	6	8	5	5
PWV (cm/s) (mean ± SEM)	1360 ± 39.9	1633 ± 37.3 *	1669 ± 53.8 *	1615 ± 44.4 *

Unless otherwise stated, values are expressed as mean ± SD. RSG indicates rosiglitazone.
* $P < .001$ compared with controls.

triglycerides, glucose, CRP, and MCP-1 are expressed as means ± SEM. Plasma levels of triglyceride are given as medians and ranges. Values for other continuous variables are expressed as means ± SD. $P < .05$ (2-tailed) was considered significant.

3. Results

3.1. Baseline clinical characteristics of participants

The characteristics of patients are summarized in Table 1, including the clinical characteristics of the study participants composed of 36 healthy controls, 41 diabetic patients, 21 diabetic patients with CAD, and 25 diabetic patients with CAD + RSG treatment. Statistical analysis indicates that the control, diabetes, diabetes with CAD, and diabetes with CAD + RSG treatment groups are not significantly different from each other with respect to age, sex, body mass index, and smoking. The prevalence of hypertension and hypercholesterolemia was similar among the diabetes, diabetes with CAD, and RSG treatment groups. Pulse wave velocity was significantly higher in patients with diabetes, diabetes and CAD, and diabetes and CAD with treatment as compared with the healthy control group (1633 ± 37.3, 1669 ± 53.8, 1615 ± 44.4, and 1360 ± 39.9 cm/s, respectively; $P < .001$), but baseline PWV did not differ among the diabetic groups. The 46 diabetic patients with CAD were randomly divided into 2 groups: diabetic patients with CAD (21 patients) and diabetic patients with CAD + rosiglitazone treatment (25 patients) who received 4 mg rosiglitazone daily for 12 weeks. The metabolic parameters, PWV levels, and laboratory findings of the study participants including 21 diabetic patients with CAD and 25 diabetic patients with CAD + RSG treatment before and after 12 weeks of follow-up are summarized in Table 2. Statistical analysis indicates that the metabolic parameters, PWV value, and plasma levels of MCP-1 and CRP of patients with CAD and those with CAD treated with rosiglitazone are not significantly different from values at baseline levels (Table 2). The use of other medications was similar between the groups.

Table 2
Metabolic parameters and PWV before and after 12-week follow-up in diabetic patients with CAD

Parameters	Diabetes with CAD (n = 21)		Diabetes with CAD + RSG (n = 25)	
	Baseline	After 12 wk	Baseline	After 12 wk
Metabolic parameters				
Total cholesterol (mmol/L)	4.49 ± 0.15	4.03 ± 0.17 *	4.50 ± 0.14	3.75 ± 0.11 **
HDL (mmol/L)	1.10 ± 0.06	1.28 ± 0.06 *	1.13 ± 0.05	1.30 ± 0.06 *
LDL (mmol/L)	2.79 ± 0.14	2.33 ± 0.15 *	2.81 ± 0.14	2.0 ± 0.09 **
Triglycerides (mmol/L)	1.85 (1.40-2.33)	1.43 (1.03-1.81)	1.70 (1.48-2.48)	1.43 (1.08-2.08)
Fasting insulin (mIU/L)	10.4 ± 1.22	10.41 ± 1.24	12.4 ± 1.37	9.7 ± 1.11
Fasting plasma glucose (mmol/L)	6.40 ± 0.30	6.73 ± 0.33	6.0 ± 0.4	5.56 ± 0.17 †
HbA_{1c} (%)	6.83 ± 0.27	6.3 ± 0.17	6.45 ± 0.20	5.88 ± 0.10 *,†
HOMA-IR	3.03 ± 0.39	3.28 ± 0.2	3.45 ± 0.30	2.61 ± 0.21 *,†
PWV (cm/s)	1669 ± 53.8	1670 ± 41.3	1615 ± 44.4	1525 ± 43.1 *,†
MCP-1 (pg/mL)	304 ± 54.2	262 ± 50.1	392 ± 42.0	273 ± 40.0 *
CRP (mg/L)	2.04 ± 0.31	1.33 ± 0.29	1.71 ± 0.24	0.73 ± 0.09 **,†
Drug usage (no. of patients)				
Aspirin	19		22	
β-Blocker	18		20	
Lipid-lowering drugs	21		25	
Nitrates	8		8	
Ca antagonists	6		6	
ACE inhibitors	5		7	
Other antidiabetic drugs	18		20	

Values are expressed as mean ± SEM. Triglyceride levels are given as median (range). HbA_{1c} indicates hemoglobin A_{1c}; ACE, angiotensin-converting enzyme.
* $P < .05$ compared with baseline.
** $P < .001$ compared with baseline.
† $P < .05$ compared with controls.

3.2. Effects of rosiglitazone treatment on metabolic parameters

Hemoglobin level and HOMA-IR were significantly decreased in the patients with CAD treated with rosiglitazone for 12 weeks as compared with values at baseline and those for the untreated group (Table 2). Similarly, rosiglitazone significantly decreased the level of fasting plasma glucose after 12 weeks' treatment, as expected. The plasma level of HDL was significantly increased in the 2 groups after 12 weeks. Moreover, the levels of total cholesterol and LDL were significantly decreased in both groups, with no significant differences between the groups in levels.

3.3. Effect of rosiglitazone on PWV

Pulse wave velocity was measured before and after PPAR-γ agonist treatment and was significantly reduced with rosiglitazone, from 1615 ± 44.4 to 1525 ± 43.1 cm/s, after 12 weeks' treatment ($P < .05$) (Table 2). Furthermore, PWV was significantly decreased in the rosiglitazone-treated group as compared with the untreated group after 12 weeks (1525 ± 43.1 vs 1670 ± 41.3 cm/s, $P < .05$). Pulse wave velocity in the untreated group did not differ from that at baseline after 12 weeks (Table 2).

3.4. Effect of rosiglitazone on plasma level of CRP and MCP-1

Plasma CRP level was significantly reduced with rosiglitazone, from 1.71 ± 0.24 to 0.73 ± 0.09 mg/L, after 12-week treatment ($P < .001$) (Table 2) and was significantly decreased in the rosiglitazone-treated group after 12-week treatment as compared with the untreated group (0.73 ± 0.09 vs 1.33 ± 0.29 mg/L, $P < .05$). C-reactive protein level in untreated patients with CAD did not differ from that at baseline after 12 weeks. Plasma MCP-1 level in the rosiglitazone-treated group was significantly reduced, from 392 ± 42 to 273 ± 40 pg/mL, after 12-week treatment.

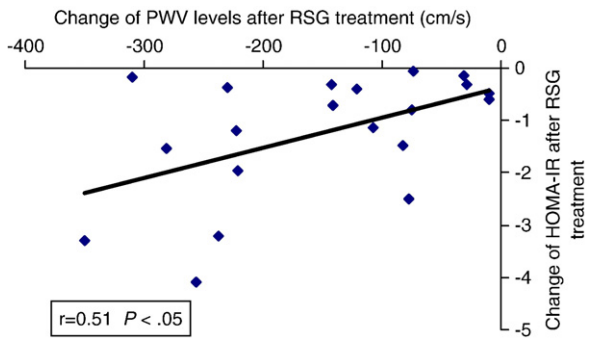

Fig. 1. Correlation between changed PWV and improved HOMA-IR after 12-week PPAR-γ agonist treatment in patients with type 2 diabetes and CAD ($r = 0.51$, $P = .019$; 95% CI, 0.095-0.78).

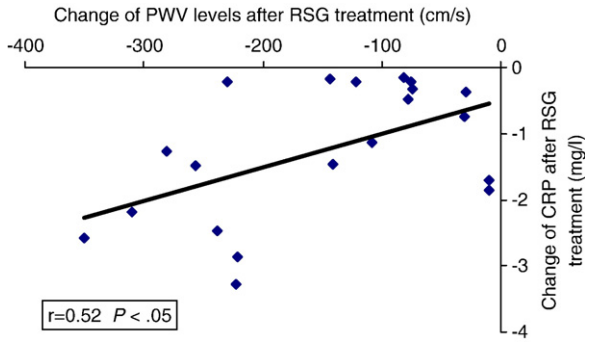

Fig. 2. Correlation between the changed PWV and decreased plasma CRP level after 12-week PPAR-γ agonist treatment in patients with type 2 diabetes and CAD ($r = 0.52$, $P = .017$; 95% CI, 0.1- 0.78).

3.5. Correlation between changed PWV and improved insulin resistance with PPAR-γ agonist treatment

To test whether change in PWV after PPAR-γ agonist treatment is related to improved metabolic parameters, we tested the correlation between changed PWV and improved insulin resistance. Decreased PWV was correlated linearly with improved HOMA-IR after 12-week PPAR-γ agonist treatment ($r = 0.51$, $P = .019$; 95% confidence interval [CI], 0.095-0.78) (Fig. 1).

3.6. Correlation between changed PWV and inflammatory marker levels with PPAR-γ agonist treatment

Arterial stiffness may be caused and promoted by chronic inflammation in the vascular wall, and PPAR-γ agonists may have a direct benefit on vascular stiffening through anti-inflammation. We tested the correlation between changed PWV and CRP level in the vascular wall and found that decreased PWV correlated linearly with decreased plasma level of CRP after PPAR-γ agonist treatment for 12 weeks ($r = 0.52$, $P = .017$; 95% CI, 0.1-0.78) (Fig. 2).

4. Discussion

Our study demonstrates that 12-week rosiglitazone treatment significantly improved metabolic parameters, including levels of fasting plasma glucose, hemoglobin A_{1c}, and HOMA-IR, in patients with type 2 diabetes mellitus and CAD. In addition to improving metabolic parameters, the levels of the inflammatory markers CRP and MCP-1 were also significantly decreased by rosiglitazone treatment as compared with that at baseline and those of controls. Furthermore, PPAR-γ agonist treatment significantly reduced the hyperstiffness of the vascular wall related to insulin resistance in these patients. Finally, improved PWV was correlated linearly with decreased HOMA-IR and plasma level of CRP after rosiglitazone treatment.

Pulse wave velocity measurement offers a way to evaluate vascular stiffness. Studies have shown that PWV is a marker

of cardiovascular risk and an independent predictor of mortality. Vascular wall structure and function are mainly influenced by blood pressure, glucose, and age-associated alterations [10]. Arterial stiffening is consistently observed in patients with metabolic syndrome or diabetes [11]. Hyperglycemia and insulin resistance increase the expression of angiotensin type 1 receptor in vascular tissue, thus promoting wall stiffness [12,13]. Arterial stiffness is also caused by advanced glycation end products, produced by hyperglycemia to form a cross-link with collagen, which results in an accumulation of collagen molecules.

As a regulator of glucose metabolism, PPAR-γ decreases the plasma level of glucose and increases insulin resistance, which contribute to major risk factors for diabetes. Peroxisome proliferator–activated receptor γ is expressed in most cells of the vascular wall and atherosclerotic lesions [3,4]. We hypothesized that arterial stiffness could be decreased by PPAR-γ agonist treatment by improving the metabolic profile. In the present study, we demonstrated that treatment with the PPAR-γ agonist rosiglitazone significantly decreased PWV and improved the metabolic profile in patients with diabetes and CAD. Moreover, the decreased PWV was correlated linearly with improved HOMA-IR in these patients after rosiglitazone treatment. Given that PWV is important in assessing arteriosclerosis, reducing PWV levels by rosiglitazone might have beneficial effects in patients with type 2 diabetes mellitus and CAD. A study with the PPAR-γ agonist pioglitazone showed significantly decreased aortic PWV, but this antiatherogenic effect was independent of the improved glucose metabolism [8]. In our study, because decreased PWV correlated linearly with improved HOMA-IR, the antiatherogenic effect of the PPAR-γ agonist may be associated with the mechanism of improved metabolism, even in type 2 diabetic patients with serious vascular damage such as CAD.

C-reactive protein may reflect the body's response to inflammation in vessels. Chronic subclinical inflammation may act as part of the insulin resistance syndrome, and CRP is independently related to insulin sensitivity [14]. Moreover, CRP may exert a direct effect in promoting the progression of atherosclerosis [15,16]. The stability of the vascular wall depends on the balance between production and degradation of collagen and elastin. A disorder of this balance, mainly by stimulation of inflammatory factors, leads to diminished elastin, which contributes to vascular stiffness. Examination of arteriosclerotic vessels shows infiltration of macrophages and increased level of matrix metalloproteinases and cytokines [17]. Hence, arteriosclerosis could represent, at least in part, a chronic subclinical inflammatory response of the vascular wall. Pasceri et al [16] reported that increased CRP level induced the expression of MCP-1 in human umbilical vein endothelial cells, which was also decreased by the PPAR-γ ligand. Early studies of pioglitazone in vascular fibrosis identified its anti-inflammatory and potentially antiatherogenic activities in rats [18]. In addition, rosiglitazone reduced matrix metalloproteinase 9 serum levels and modulated vascular inflammation in type 2 diabetic patients with CAD [16,19]. An animal study has shown that vascular wall calcification is associated with monocyte/macrophage infiltration and induction of tumor necrosis factor α in rats; pioglitazone decreases the level of tumor necrosis factor α, blunts aortic calcification, and reduces aortic wall stiffness [1]. A recent clinical study has shown that pioglitazone treatment reduces inflammation, improves markers of endothelial function, and reduces arterial stiffness in obese men [20]. These results suggest that rosiglitazone regulates the expression of inflammatory factors involved in vascular stiffness and may exert beneficial effect on vascular wall in arteriosclerosis via anti-inflammation. We previously showed that PPAR-γ agonists significantly reduced the homocysteine-induced formation of reactive oxygen species and expression of MCP-1 in human monocytes and MCP-1 plasma level in patients with diabetes mellitus and CAD [7,21]. In the present study, we demonstrate further that rosiglitazone significantly decreases the plasma levels of CRP and MCP-1 in patients with diabetes and CAD. Moreover, the improved PWV was correlated linearly with the decreased plasma level of CRP after PPAR-γ agonist treatment. Given that chronic inflammation may be important in arteriosclerosis, inhibiting inflammatory markers by a PPAR-γ agonist such as rosiglitazone might exert potentially beneficial effects in vascular stiffness.

Patients with insulin resistance have enhanced risk for arteriosclerosis. Rosiglitazone appears to enhance insulin action by modulating the expression of a number of genes that are critically involved in glucose and lipid metabolism. Clinical studies have shown that troglitazone decreases the intimal and medial thickness of carotid arteries [22]. Furthermore, Takagi et al [23] demonstrated that troglitazone reduces intimal hyperplasia after coronary stent implantation in patients with type 2 diabetes mellitus. A recent study showed that pioglitazone inhibits in-stent restenosis in atherosclerotic rabbits by limiting the local inflammatory pathway [24]. Our present results show that metabolic disorders and CRP levels were all decreased significantly by 12-week rosiglitazone treatment. Thus, the reversal of the metabolic disorder and reduced inflammatory marker levels are associated with improved arteriosclerosis risk factors and reduced arterial stiffness in patients with diabetes and CAD. Precisely how the PPAR-γ agonist decreases arterial stiffness is unclear; however, its effect on improved metabolism and anti-inflammation most likely contributes to its vascular beneficial effect.

In conclusion, these results indicate that PPAR-γ agonists may influence several key steps of arteriosclerosis, such as metabolic disorders and chronic inflammatory response in vessels. Rosiglitazone may play an important role in protecting against arteriosclerosis by normalizing the metabolic disorders of diabetes mellitus and depressing chronic inflammation of the vascular wall in patients with type 2 diabetes mellitus and serious vascular damage.

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