Insulin-Sensitizers beyond Glycaemic Control

AK Agarwal*, Pushpa Yadav**

***Consultant in Medicine and HOD, Dr. Ram Manohar Lohia Hospital, New Delhi – 110001; **Senior Physician, Department of Medicine, Dr. Ram Manohar Lohia Hospital, New Delhi – 110001**

59

ABSTRACT

Insulin - resistance precedes type 2 diabetes by many years and plays a fundamental role in pathogenesis of type 2 diabetes and its complications. Insulin-resistance affects one-fourth of the population and is the fundamental defect linking each component of metabolic syndrome. Such patients have markedly increased risk of cardiovascular disease.

To improve diabetic care of our population, primary care must have an understanding of the role of insulin-resistance in the pathogenesis of diabetes mellitus and in producing the increased risk of cardiovascular disease. There is an argument for using insulin-sensitizers as it targets whole risk of cardiovascular disease rather than just hyperglycaemia. Although thiazolidinediones lower glucose concentrations and increase insulin sensitivity, their non-glycaemic effects on body weight, lipids, and blood pressure have been a disappointment, implying that this class of drugs will not reduce the need to treat dyslipidaemia and hypertension with separate therapies.

INTRODUCTION

The prevalence of type 2 diabetes mellitus is becoming of epidemic proportion in past several decades owing to advancing age of population, increased prevalence of obesity, and decreased physical activity. It is estimated by World Health Organization that the global prevalence of type 2 diabetes mellitus will be more than double - from 135 million in 1995 to 300 million by 2025. In the United States, 8% of adult population and 19% of population older than 65 years age have diabetes. [1] India bears a sizeable burden of epidemic of diabetes and it is estimated that one out of every five diabetics in the world would be an Indian by the year 2005.

Type 2 diabetes is considered a multifaceted state usually characterised by variable degree of insulin-resistance, impaired insulin secretion, and increased glucose production. Insulin-resistance is a fundamental cause of type 2 diabetes : 92% people with type 2 diabetes have insulin-resistance. It has been suggested that insulin-resistance develops 20-30 years before the onset of type 2 diabetes.[3] With average delay of four to seven years in diagnosing type 2 diabetes,[4] approximately 20% of patients with type 2 diabetes have some evidence of microvascular or neurologic diabetic complication at the time of diagnosis.[5] To reduce the number of people developing type 2 diabetes and the accompanying complications, strategies should be developed to target insulin- resistance at primary care level.

Insulin-resistance is a decrease in sensitivity of tissues like liver, adipose tissue, and skeletal muscles to the action of insulin; leading to increased hepatic glucose production and decreased uptake of glucose by adipose tissue and skeletal muscles. There is rise in blood glucose levels leading to increased secretion of insulin by beta cells. So, the initial step in the development of type 2 diabetes is compensatory hyperinsulinaemia and increased post-prandial glucose concentration. Most patients remain in this hyperinsulinaemic state for a considerable time. However, with passage of time beta cells are unable to produce sufficient insulin to maintain normoglycaemia leading to development of type 2 diabetes. Insulin-resistance affects about one-fourth of the population and one in seven adults have impaired glucose tolerance (IGT),[6] 50% of whom develop diabetes within 10 years. Type 2 diabetics remain hyperinsulinaemic until they are in an advanced stage of the disease.[7]

Gerald Reaven was the first scientist to name the cluster of hypertension, central upper body or android obesity, and dyslipidaemia as syndrome X in 1988[8] to highlight co-occurrence of risk factors for coronary heart disease and type 2 diabetes mellitus. The true prevalence of the deadly quartet of central obesity, hypertension, dyslipidaemia, and glucose intolerance varies widely in different studies because of lack of universally accepted criteria defining the syndrome. The clinical definition of insulin resistance or metabolic syndrome was proposed by WHO[9] in 1999 as given in Table 1. The name of the syndrome was changed to metabolic syndrome because Reaven didn't include central obesity in the original description. Subjects who fulfill the criteria of the syndrome have a major consequence : a

Table 1 : WHO working definition of metabolic syndrome.[8]

(a) Impaired glucose regulation or diabetes.
(b) Insulin-resistance (under hyperinsulinaemic euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation).
(c) Raised arterial pressure ≥ 140/90 mmHg.
(d) Raised plasma triglyceride (≥ 150 mg/dl) and/or low HDL cholesterol (<35 mg/dl for men; < 39 mg/dl for women).
(e) Central obesity (men: waist to hip ratio > 0.90; females; waist to hip ratio > 0.85) and/or BMI > 30 mg/m^2.
(f) Microalbuminuria (urine albumin excretion rate ≥ 20 µg/min or albumin; creatinine ratio ≥ 30 mg/g.

Diagnosis of metabolic syndrome is made when two or more of the above-mentioned components are present in presence of impaired glucose regulation or diabetes mellitus and/or insulin resistance.

Table 2 : ATP III criteria for identification of metabolic syndrome.[10]

(a) Abdominal obesity (waist circumference): men > 102 cm (40 in); women > 88 cm (35 in).
(b) Triglycerides ≥ 150 mg/dl.
(c) HDL cholesterol: men < 40 mg/dl; women < 50 mg/dl.
(d) Blood pressure ≥ 130/≥ 85 mmHg.
(e) Fasting glucose ≥ 110 mg/dl.

Diagnosis of metabolic syndrome is made when 3 or more of the risk determinants shown above are present.

markedly increased risk of cardiovascular disease (CVD). The criteria of the National Cholesterol Education Program adult treatment panel guidelines (NCEP ATPIII),[10] laid in 2001, are more clinically relevant because those measurements are readily available (Table 2) and waist circumference is a better indicator of central obesity,[10] is simpler to measure, and culturally more acceptable to our population. In future, a number of prothrombotic and pro-inflammatory states will be included in the definition of metabolic syndrome, since the definition is incomplete. Insulin-resistance is the fundamental defect linking each component of metabolic syndrome and manifests as resistance to insulin-mediated glucose disposal.[11] There is compensatory hyperinsulinaemia and abnormalities associated with hyperinsulinaemia and insulin resistance (listed in Table 3).[11,12]

INSULIN-SENSITIZERS IN MANAGEMENT OF INSULIN- RESISTANCE

It is now understood that insulin resistance poses a major risk in type 2 diabetes and metabolic syndrome. Is there any advantage in treating insulin resistance *per se* in the absence of hyperglycaemia or in patients with impaired fasting glucose ? These questions need to be answered. By effectively targeting insulin resistance much can be achieved in primary care to reduce an excess risk of diabetes in our population and it may be possible to prevent some complications associated with insulin-resistance.

Some oral antidiabetic agents go far beyond controlling glucose level only. These are known as insulin-sensitizers and belong to the groups; biguanides and thiazolidinediones. Their mechanism of action is shown in Table 4.

Table 3 : Abnormalities associated with hyperinsulinaemia/insulin resistance[11,12]

I. Glucose intolerance
   Impaired fasting glucose
   Impaired glucose tolerance
   Type 2 diabetes mellitus
II. Major risk factor for cardiovascular disease in type 2 diabetes
III. Hypertension - 50% of patients of hypertension are insulin-resistant
   - Vasodilatation impaired in insulin resistant state
   - ↑ Resorption of Na and water by kidney tubule
   - Overactive sympathetic system
IV. Dyslipidaemia
   ↑ Triglycerides
   ↓ HDL-C
   ↓ LDL - particle diameter
   ↑ Post-prandial lipaemia
V. Obesity
   Risk factor for cardiovascular disease
   Risk factor for development of type 2 diabetes
VI. Acceleration and increase in severity of atherosclerosis directly via pathways in vascular smooth muscles.
VII. Hyperuricaemia
   Abnormal uric acid metabolism
   ↓ Renal uric acid clearance
VIII. Haemostatic
   ↑ Plasminogen activator inhibitor - 1
   ↑ Fibrinogen leading to ↑ blood coagulability
IX. Endothelial dysfunction
   ↑ Mononuclear cell adhesion
   ↑ Plasma concentration of cellular adhesion molecules
   ↑ Plasma concentration of asymmetric dimethyl arginine
   ↓ Endothelial-dependent vasodilatation
X. Reproductive
   Polycystic ovary syndrome
XI. Liver
   NASH

Table 4 : Mechanism of anti-hyperglycaemic effect of metformin and thiazolidinediones.

Metformin	Thiazolidinediones
1. Suppression of hepatic glucose output.	1. Affinity for PPARγ correlates with its glucose lowering potency by increase in cellular uptake of glucose in skeletal muscle
2. Also enhances suppression of gluconeogenesis by insulin and reduced glucagons-stimulated gluconeogenesis.	2. Decrease hepatic glucose production.
3. Increased insulin-mediated glucose disposal with muscle, implicated as the main site of action.	3. Prolong pancreatic β-cell function by preventing apoptosis of β-cells.
4. Increases the binding of insulin to its receptors.	
5. Increased intestinal glucose use	
6. Decreased fatty acid oxidation.	

The insulin sensitizing thiazolidinediones, which are selective ligands of the nuclear transcription factor peroxisome - proliferator - activated receptor γ (PPARγ), are the first drugs to address the basic problem of insulin resistance in patients with type 2 diabetes. This class of drugs may be useful in the treatment of patients even with non-diabetic insulin-resistant conditions.

PPARγ is expressed most abundantly in adipose tissue but is also found in pancreatic beta cells, vascular endothelium, and macrophages. In January 1997, the first thiazolidinedione, troglitazone, was approved as a glucose-lowering therapy for patients in the United States with type 2 diabetes. Troglitazone was subsequently withdrawn from the market, in March 2000, because of hepatotoxicity. The two currently available PPARγ agonists, rosiglitazone and pioglitazone, were approved in the United States in 1999.[13]

Insulin-sensitivity increased in all non-diabetic persons with upper body obesity who were treated either with diet control, exercise, and weight reduction or were treated with pioglitazone.[14] Those on diet and exercise had weight loss with decreased visceral and total body fat, whereas subjects on pioglitazone had no change in visceral or body fat and had weight gain. They both increase insulin-sensitivity by different mechanisms. Long term effectiveness of diet and exercise in reducing insulin-resistance are disappointing. Whether pharmacotherapy should be used for insulin-sensitization remains to be answered.

Type 2 diabetes can be prevented or delayed in persons at high risk of the disease as shown in a recent study. It was found that the incidence of diabetes was reduced by 31% on treatment with metformin, and by 58% with lifestyle changes as compared to placebo in subjects with increased risk of diabetes and those effects is similar in all races and in men and women.[15] Metformin has the potential advantage of targeting insulin resistance, which is an early feature of the disease, and reducing plasma insulin concentration.

There are a number of reports of beneficial effects on risk factors and surrogate end-points of cardiovascular disease (CVD), although no studies are currently available showing reduction of insulin resistance by pharmacotherapy being beneficial on clinical cardiovascular end-points; such trials are going on. Long-term therapy with metformin particularly in patients with hyperglycaemia results in moderate reduction in plasma triglyceride concentration, due to decreased hepatic synthesis of very low density lipoproteins.[16,17] Plasma total cholesterol also is lowered a little and there is some rise in HDL-C.[17] All three glitazones raise HDL-C[18,19] and change small, dense, more atherogenic LDL particles to larger, less atherogenic ones. Pioglitazone is also most effective in lowering triglyceride levels, rosiglitazone being the least effective. Rosiglitazone also decreases blood pressure in diabetic subjects,[20] which is proportional to its effect on decreasing insulin resistance.

Insulin-sensitizers also have a favourable effect on prothrombotic and proinflammatory states which have been implicated in pathogenesis for CVD. Metformin therapy leads to decreased platelet sensitivity to aggregating possibly due to reduced blood glucose concentrations.[17] A significant fall in t-PA and VWF antigen levels is also reported with metformin therapy. Some studies have also reported increased fibrinolytic activity and small reductions in plasma concentrations of fibrinolytic inhibitor plasminogen activator inhibitor type 1,[16] reversing the prothrombotic state. Similar effects have been shown by troglitazone[21] and rosiglitazone. C-reactive protein, a marker of proinflammatory state, has also been shown to be reduced by all the glitazones, pioglitazone lowering it even when blood sugar was not reduced by this drug.[22] Endothelial dysfunction related to insulin resistance independent of glycaemic control is ameliorated by insulin sensitization by rosiglitazone[23] (Fig. 1).

There is some evidence that in type 2 diabetes progression of carotid artery atherosclerosis might be reversed with thiazolidinediones.[24] If one considers the additional effect on insulin sensitivity, haematocrit, and blood pressure and the evidence that thiazolidinediones suppress the proliferation and migration of vascular smooth muscles and inhibit macrophage activation, their anti-atherosclerotic potential might be useful. Troglitazone lowered E-selectin, ICAM, and MCP-1 and rosiglitazone decreased E-selectin, cytokines, and adhesion molecules involved in the pathogenesis of atherosclerosis. In atherosclerotic plaque rupture, a precipitating event in acute coronary syndrome, matrix-degrading metalloproteinases (MMP-9)[25] has been implicated. It was decreased in type 2 diabetic subjects with CVD by troglitazone and rosiglitazone.

By reducing insulin-resistance, morphologic, physiologic, and clinical outcomes of CVD in type 2 diabetic patients can be improved. The IMT (intima - media thickness) of carotid arteries morphologically correlates with extent of coronary artery atherosclerosis, and has been shown to be reduced by both troglitazone[26] and pioglitazone[24] within 3 months of administration. Physiologically endothelial dysfunction which is part of atherosclerotic disease, improved by troglitazone and rosiglitazone.[23] Pioglitazone is also shown to decrease pulse wave velocity which is a direct measure of arterial distensibility, and correlates well with IMT and is a good marker of vascular damage.[22] Clinically, in type 2 diabetic patients detected less than 8 years ago, rosiglitazone improved myocardial blood flow measured by positron emission tomography scanning. But in patients, who had long-standing diabetes, the results were not significant suggesting that only early recognition and treatment of insulin resistance is likely to prevent or delay CVD. Restenosis rate of stents placed in coronary arteries was markedly reduced by rosiglitazone,[27] independent of glycaemic control. Similar results have been shown with pioglitazone. In summary, thiazolidinediones and metformin improve the metabolic, vasoactive, inflammatory, and thrombogenic *milieu* to potentially retard the atherosclerotic process and reduce insulin resistance and components of insulin resistance syndrome.

Metformin inhibits TNFα and several TNF-inducible responses which are likely to promote hepatic steatosis and necrosis. Metformin, when administered to insulin resistant obese non-alcoholic steatohepatitis (NASH) patients, resulted in normalization of transaminase levels; improvement in insulin sensitivity, and decrease in liver volume. Larger studies are needed to confirm that metformin could be a promising agent in treatment of NASH patients.

Both rosiglitazone and pioglitazone have been shown to normalise ALT levels in subjects with NASH. Hepatic fat content and size,

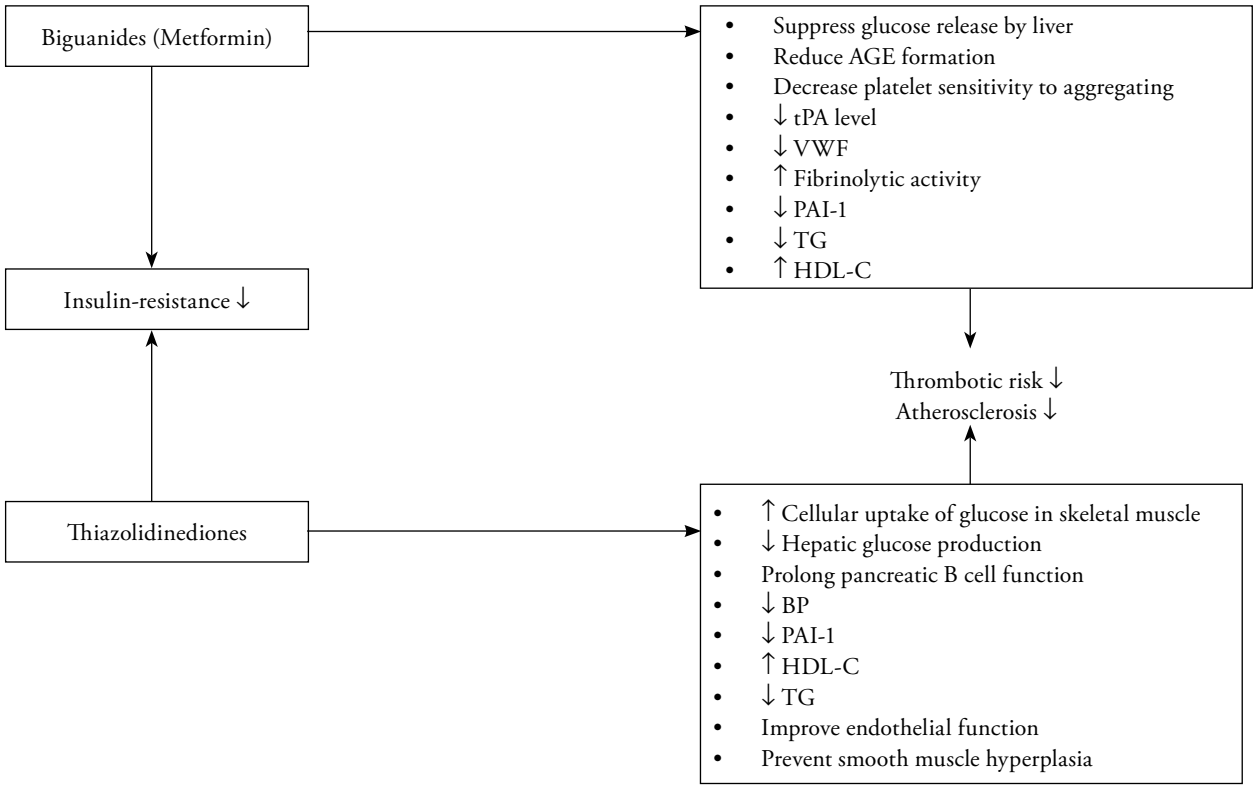

Fig. 1 : Therapeutic approach in the prevention and treatment of insulin-resistance. Metformin and thiazolidinediones go far beyond the glucose control.

as well as glucose and FFA sensitivity to insulin were consistently improved along with histological signs of steatosis. Whether the observed liver effects were caused by improved insulin sensitivity or by anti-inflammatory actions of this class of compounds remains to be determined.

Thiazolidinediones may be an ideal therapy for insulin-resistance and lipoatrophy associated with highly active antiretroviral therapy, because the drugs increase both insulin sensitivity and subcutaneous fat mass. However, in the only placebo-controlled trial in which patients with lipodystrophy associated with highly active antiretroviral therapy were treated (rosiglitazone, 8 mg per day for 6 months),[28] there was no evidence of an increase in adiposity or body weight, in contrast to studies in patients with type 2 diabetes.[29,30]

Metformin is a useful adjunct to lifestyle changes in women with PCOS as it improves insulin-resistance and hyperandrogenism. It modestly increases menstrual regularity and ovulation and decreases weight. Thiazolidinediones are also very effective for PCOS symptoms and insulin resistance and improvement in those parameters may lead to increased ovulation. These agents must be used cautiously except in women who are sterile.

The success of metformin use in Diabetes Prevention Program and use of metformin and thiazolidinediones in PCOS suggests that these medications or drug class could be used to treat the entire syndrome. Precise identification of patients at risk plays a determining role because of efficacious intervention. Unfortunately, the precision of tools for evaluating risk leaves a lot to be desired.

Although, it remains unclear whether insulin resistance *per se* is a primary cause of some or all of the components of metabolic syndrome, common treatment strategies that improve insulin resistance also improve other components of metabolic syndrome and should reduce the risk of vascular disease.

There is enough and very suggestive evidence that reducing insulin- resistance by insulin-sensitizers may be beneficial independent of glycaemic control. There appear to be situations in which treatment directed at insulin resistance in euglycaemic or mildly hyperglycaemic patients may be of value. Certainly, treatment with proper nutrition and exercise is advisable. But a lot of questions still need to be answered before pharmacotherapy with insulin sensitizers can be started. When do we start pharmacological treatment? As soon as the metabolic syndrome is diagnosed or later on and how long it should be continued? At present, the evidence for beneficial effects is not direct and rests on surrogate end-points and intermediate outcomes. Further studies are required to demonstrate reduction in hard clinical events to formulate strategies to start pharmacotherapy for treating insulin resistance by insulin sensitizers in the absence of hyperglycaemia.

REFERENCES

1. Harris MI, Flegal KM, Cowie OC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults. *Diabetes Care* 1998;21:518-24.
2. Haffner SM. Epidemiological studies on the effects of hyperglycaemia and improvement of glycaemic control on macrovascular events in type 2 diabetes. *Diabetes Care* 1999;22 (Suppl):3:54-6.

3. Beck-Nielsen H and the European Group for the study of insulin resistance (EGIR). General characteristics of the insulin resistance syndrome. Prevalence and heritability. *Drugs* 1999;58 (Suppl 1):7-10.
4. Harris MI, Klein R, Welborn TA et al. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care* 1992;15:815-9.
5. Complications in newly diagnosed type 2 diabetic patients and their association with different clinical and biochemical risk factors. *Diabetes Res* 1990;13:1-11.
6. Reaven GM. Syndrome X: 6 years later. *J Intern Med* 1994;736:13-22.
7. Boden G. Pathogenesis of Type 2 diabetes - insulin resistance. *Endocrinol Metab Clin North Am* 2001;11:437-41.
8. Reaven G. Banting Lecture : Role of insulin-resistance in human disease. *Diabetes* 1988;37:1595-1607.
9. World Health Organization: Report of a WHO consultation : definition of metabolic syndrome in definition, diagnosis, and classification of diabetes and its complications. Geneva. World Health Organization, Department of Noncommunicable Disease Surveillance, 1999.
10. Executive summary of the third report of the National Cholesterol Education Program (NECP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001;285:2847-97.
11. Reaven G. Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease. *Circulation* 2002;107:287-8.
12. Michael Mead. Ten key facts on insulin resistance - Review Diabetes and Primary Care: Summer 2003.
13. Jarvinen HY. Thiazolidinediones. *N Engl J Med* 2004;351:1106-18.
14. Shahid S, Jensen MD. Effects of pioglitazone versus diet and exercise on metabolic health and fat distribution in upper body obesity. *Diabetes Care* 2003;26:3148-52.
15. Knowler WC, Fowler SE, Hamman RF. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:6:393-403.
16. Nagi DK, Yudkin JS. Effects of metformin on insulin-resistance, risk factors for cardiovascular disease, and plasminogen activator inhibitor in NIDDM subjects : a study of two ethnic groups. *Diabetes Care* 1993;16: 621-9.
17. Bailey CJ. Biguanides and NIDDM. *Diabetes Care* 1992;15:755-72.
18. Fonseca VA, Valiquett TR, Huang SM et al. the Troglitazone study group. Troglitazone monotherapy improves glycaemic control in patients with type 2 diabetes mellitus: A randomised, controlled study. *J Clin Endocrinol Metab* 1998;83:3169-76.
19. Peters Harmel AL, Kendall DM, Buse JB, et al. Impact of adjunctive thiazolidinedione therapy on blood lipid levels and glycaemic control in patients with type 2 diabetes. *Curr Med Res Opin* 2004;20:215-23.
20. Raji A, Seely EA, Bekins SA, et al. Rosiglitazone improves insulin sensitivity and lowers blood pressure in hypertensive patients. *Diabetes Care* 2003;26:172-8.
21. Fonseca VA, Reynolds T, Hemphill D, et al. Effect of troglitazone on fibrinolysis and activated coagulation in patients with non-insulin dependent diabetes mellitus. *J Diabetes Complications* 1998;12:181-6.
22. Satoh N, Ogawa Y, Usui T, et al. Antiatherogenic effect of pioglitazone in type 2 diabetes, irrespective of responsiveness to its antidiabetic effect. *Diabetes Care* 2003;26:2493-99.
23. Pistroch F, Passauer J, Fischer S, et al. In type 2 diabetes, rosiglitazone therapy for insulin-resistance ameliorates endothelial dysfunction independent of glycaemic control. *Diabetes Care* 2004;27:2, 484-90.
24. Koshiyama H, Shimono D, Kuwamura N, et al. Rapid communication: inhibitory effect of pioglitazone on carotid arterial wall thickness in type 2 diabetes. *J Clin Endocrinol Metab* 2001;86:3452-56.
25. Wakino S, Lawre Hsueh WA. Vascular protective effects by activation of nuclear receptor PPARγ. *J Diabetes Complications* 2002;16:49-9.
26. Minikawa J, Tanaka S, Yamanchi M, et al. Potent inhibitory effect of troglitazone on carotid arterial wall thickness in type 2 diabetes. *J Clin Endocrinol Metab* 1998;83:1818-20.
27. Choi SH, Choi DH, Ko YK, et al. Preventive effects of rosiglitazone on restenosis after coronary stenting in patients with type 2 diabetes (Abstract). *Diabetes* 2003;52 (Suppl, 1.):A19.
28. Sutinen J, Hakkinen AM, Westerbacka J, et al. Rosiglitazone, in the treatment of HAART - associated lipodystrophy a randomized double blind placebo - controlled study. *Antivir Ther* 2003;8:199-207.
29. Miyazaki Y, Glass I, Triplitt C, et al. Effect of rosiglitazone on glucose and non-esterified fatty acid metabolism in type 2 diabetic patients. *Diabetologia* 2001;44:2210-9.
30. Miyazaki Y, Mahankali A, Matsuda M, et al. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. *J Clin Endocrinol Metab* 2002;87:2784-91.