Int J Biol Med Res. 2012; 3(2): 1558-1560

Contents lists available at BioMedSciDirect Publications

International Journal of Biological & Medical Research

Journal homepage: www.biomedscidirect.com

Original Article

The effect of Pioglitazone, a PPAR-γ agonist, on cardiovascular risk factors in Type 2 Diabetics

Navjot Kaur [a], Satinder Kaur [a *], Parminder Singh [b], Prerna Goyal [c] and Indu Veerma [a]

Department of Biochemistry [a], Endocrinology [b] and Medicine [c], Dayanand Medical College and Hospital, Ludhiana, India.*

ARTICLE INFO

Keywords:
Pioglitazone
Peroxisome proliferator activated receptor gamma(PPAR-γ)
CRP, fibrinogen.

ABSTRACT

Pioglitazone, a thiazolidinedione (TZD) has an insulin sensitizing action, is being used for long term glycemic control. In addition it has been shown to be having favorable effect on cardiovascular risk factors. To study these effect of TZD, 50 patients of Type 2 Diabetes visiting OPD/IPD of DMC&H, Ludhiana were treated with pioglitazone (15-45 mg/d) for 16 weeks. Biochemical markers of glycemic control (FBS, insulin levels, HbA1c) and cardiovascular risk factors (lipid profile, CRP, fibrinogen) were analyzed at 0 and 16 weeks of treatment. There was significant decrease in FBS, HbA1c and insulin levels after the treatment showing good glycemic control. There was significant decrease in triglyceride levels,10% increase in HDL levels and 55% decrease in CRP levels showing anti-inflammatory and antiatherogenic effect of pioglitazone. But no significant change could be observed in total cholestrol, LDL and fibrinogen levels. These properties seem to make the drug particularly useful in patients with insulin resistant type 2 diabetes.

1. Introduction

Type 2 diabetes is becoming a major health care problem since it is associated with serious progressive micro and macro vascular complications. Therefore, it is of clinical importance to evaluate and treat these complications especially cardiovascular disease (CVD) in these patients beyond glycemic control [1].

Insulin resistance in diabetics stimulate SMC proliferation in arterial wall and put them at high risk of CHD. The insulin sensitizing TZDs, which are selective ligands of nuclear transcription factor peroxisome proliferator activated receptor (PPAR-γ) are the first drugs to address basic problem of insulin resistance [2]. PPAR-γ are expressed in adipose tissue where it promote adipogenesis, lipogenesis and glucose uptake. Activation of these receptors by the drug makes it hypolipidemic and hypoglycemic both [3]. Receptors are also expressed in endothelial cells, vascular smooth muscle cells (VSMC) and macrophages. They regulate recruitment of monocytes to endothelial cells, modulate inflammatory response in these cells and inhibit macrophage foam cell formation, VSMC proliferation and migration. All this may be responsible for antiatherogenic effect of TZD [4-6].

2.Materials and Methods

50 patients of Type 2 Diabetes (age 45-65 years, 33 male and 17 female) visiting Endocrinology OPD of DMC&H were included in the study. Patients with previous history of CVD, hypertension, smoking and those taking insulin, metformin or another TZD were excluded from the study. Only those taking sulfonylurea or diet control for diabetes were included. Patients were put on pioglitazone (15-45 mg/day, depending upon intial FBS levels). During follow up visits dose of pioglitazone was adjusted to achieve desired glycemic control (FBS <110 mg/day) Overnight fasting blood sample was collected for biochemical investigations at 0 and 16 weeks of treatment. FBS, HbA1c, CRP, cholesterol, HDL, LDL and triglyceride were analyzed on autoanalyzer Hitachi 911 (Roche). Plasma insulin was estimated by electrochemiluminiscence on ELECSYS-2010 (Roche) . Fibrinogen was estimated by Clauss method using Sigma diagnostic kits.

* Corresponding Author : Dr Satinder Kaur
Associate Professor
Department of Biochemistry
Dayanand Medical college & Hospital,
Ludhiana, Punjab, india.
Email: satinder_bhari@yahoo.com

Diabetes is associated with chronic low grade inflammation. Inflammatory biomarker of arteriosclerosis, CRP have been shown to predict cardiovascular risk and reflect overall burden of vascular disease in patients [7]. Therapeutic strategies that limit inflammation in vessel wall can be promising tool in diabetics. Fibrinogen, hemorheologically active plasma protein, plays an important role in arterial pathogenesis. It is clinically important as it influence RBC aggregation and blood viscosity after vascular injury. High levels have been associated with diabetes, hypertension, stroke, smoking and CVD [8]. Aim of the present work was to study effect of pioglitazone on glycemic control and CVD risk factors.

3.Results

There was significant decrease in FBS ($p<0.001$), HbA1c was within normal limits (<7.0 %) and insulin levels were also decreased (< 17 U/ml) in all the patients after 16 weeks of treatment with pioglitazone. Some increase in mean body weight (77 kg vs 75 kg) was observed which was not significant. There was significant reduction in TG ($p<0.05$), 10% increase in HDL levels and 55% decrease in CRP levels. No significant change in cholesterol and LDL levels could be observed. Table I

Table I Effect of Pioglitazone on glycemic control and CVD risk markers

Markers	0 weeks	16 weeks
Fasting glucose(mg/dl)	189.2±25.2	108±18.1*
HbA1c (%)	8.2±2.4	6.9±2.1
Insulin(U/ml)	23.5±12.6	17.1±11.9
Body weight (Kg)	75.12±8.14	77.7±7.94
Cholesterol(mg/dl)	144.4±44.7	154.1±48.2
HDL-chol(mg/dl)	33.9±8.1	36.7±10.2
LDL-chol (mg/dl)	76.3±9.5	86±8.5
Triglyceride(mg/dl)	208.4±136.4	158.2±153.1*
CRP (mg/l)	17.2±8.6	7±8.4
Fibrinogen (mg/dl)	397.5±109.7	390.9±114.4

*** P<0.05**

4. Discussion

Effect of glycemic control by pioglitazone on CVD risk factors was studied in Type 2 Diabetes. TZDs are known to increase body weight, as obseved in our study as well, due to expansion of subcutaneous fat, whereas visceral mass remains unchanged or decreases [9].

Very effective glycemic control could be achieved within 16 weeks of treatment as shown by decreased HbA1c levels (<7.0%) in all the patients. Stimulation of PPAR-γ receptors present in liver and muscles also contributes to antihyperglycemic effects of the drug. Similar control has been reported by other workers as well [10-11]. High insulin levels as seen in diabetics can itself be atherogenic. High insulin levels can cause thickening and stiffness of arterial wall contributing to narrowing of coronary blood vessels. Insulin levels also decreased in our study, indicating TZDs act as an insulin sensitizer, increases sensitivity in liver, adipose tissue and peripheral tissues [9,12].

HDL cholesterol has antiatherogenic effect such as removal of cholesterol from atherosclerotic plaque and body cells. It works as scavenger clearing cholesterol that build up in blood vessels.It also has antioxidant effect. Pioglitazone treatment resulted in 10% increase in HDL levels. Triglyceride levels decreased significantly because of increased fatty acid metabolism. Similar beneficial effect of pioglitazone on lipid profile have been reported by other workers as well [3,13].

Raised fibrinogen levels in diabetes contribute significantly to thrombus formation due to increased blood viscosity and sluggish blood flow. High fibrinogen results from increased synthesis not compensated by proportional increase in its clearance [14]. No influence of pioglitazone could be observed on fibrinogen levels. Earlier studies on PAI-1 and pioglitazone were also negative showing that it is not having any beneficial role in coaggulation parameters [15-16].

CRP is not only a cardiovascular risk factor but does contribute in its pathogenesis. Native CRP can bind oxidised LDL, partly degraded LDL, as found in atheromatous plaque and then activate complement system causing inflammation in the plaque. By triggering complement activation it may exacerbate tissue damage leading to more severe disease [7]. CRP levels were decreased by 55% after the treatment showing anti-inflammatory effect of pioglitazone. Other studies have also reported similar effect [15].

5.Conclusion

Present study gives evidence of anti-inflammatory and anti-atherogenic effect of pioglitazone as indicated by improvement in CVD risk markers along with long term glycemic control.

6. References

[1] Sheetz MJ, Kin GL. Molecular understanding of hyperglycemia's adverse effects for diabetes complications. JAMA. 2002; 288: 2579-2588.

[2] Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferators-activated receptor gamma (PPAR-γ). J Biol Chem. 1995; 270: 12953-59.

[3] Goldberg RB, Kendall DM, Deeg MA. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care. 2005; 28: 1547-54.

[4] Ricorte M, Li AC, willson TM, Kelly CJ, Glass CK. The peroxisome proliferators-activated receptor -γ is a negetive regulator of macrophage activation. Nature. 1998; 391: 79-82.

[5] Hsueh WA, Jackson S, Law RE. Control of vascular cell proliferation and migration by PPAR-γ : a new approach to macrovascular complications of diabetes. Diabetes Care. 2001; 24: 392-397.

[6] Noriko S, Yoshihiro O, Takeshi U, Tetsuya T, Shigeo K, Hiroko U et al. Antiatherogenic effect of pioglitazone in Type 2 Diabetic patients irrespective of the responsiveness to its antidiabetic effect. Diabetes Care. 2003; 26(9): 2493-99.

[7] Pepys MB and Hirschfield GM. C-reactive protein: a critical update. J Clin Inves. 2003; 111(12): 1805-1812.

[8] Khan TM, Marwat MA, Khan P, Wazir F, rehman A. Plasma fibrinogen levels in diabetics with complications- a prospective study. Gomel J med Sci. 2005; 3(2): 48-50.

[9] 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: 2784-2791.

[10] Scherbaum WA, Goke B. Metabolic efficacy and safety of once-daily pioglitazone monotherapy in patients with type 2 diabetes: a double-blind, placebo-controlled study. Horm Metab Res. 2002; 34: 589-595.

[11] Aronoff S, Rosenblatt S, Braithwaite S, Egan JM, Mathisen AL, Schneider RL. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes. Diabetes Care 2000; 23: 1605-1611.

[12] Miyazaki Y, Mahankali A, Matsuda M et al. Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. Diabetes Care 2001; 24: 710-719.

[13] Van Wijk JPH, de Koning EJP, Martens EP, Rabelink TJ. Thiazolidinediones and blood lipids in type 2 diabetes. Arterioscler Thromb Vasc Biol. 2003; 23: 1744-1749.

[14] Festa Ad, Agostino R jr, Tracy RP, Haffner SM. The insulin resistance atherosclerosis study, elevated levels of acute phase protein and plasminogen activator inhibitor predict the development of type 2 diabetes. Diabetes 2002; 4: 1131-1137.

[15] 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: 1925-1931.

[16] Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Circulation 2002; 106: 679-684.