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RESEARCH ARTICLE

CARDIOVASCULAR SAFETY PROFILE OF PIOGLITAZONE ALONG WITH VITAMIN E

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ABSTRACT

The increase incidence of obesity, stress and aging in genetically predisposed population has lead to an increase in the incidence of type 2 diabetes mellitus. This led to the development of new drugs such as thiazolidinediones (TZDs) which is a agonist of Peroxisome Proliferator-Activated Receptor (PPARgamma).Pioglitazone is a TZD have recently been identified for its severe cardiovasculara complication. Pioglitazone is oral hypoglycemic agent which has been shown to be effective by lowering insulin resistance.Due to its cardiovasculaqr risk factor it is combined with adjunct vitamin E,an antioxidant in the present study. The safety and efficacy of pioglitazone are increased several fold along with vitamin E.

Keywords: Vitamin E,Pioglitazone, PPARγ, diabetes

INTRODUCTION

Diabetes is a chronic disease, which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. This leads to an increased concentration of glucose in the blood (hyperglycaemia or Type 1 diabetes, previously known as insulin-dependent or childhood-onset diabetes) is characterized by a lack of insulin production. Type 2 diabetes (formerly called non-insulin-dependent or adult-onset diabetes) is caused by the body's ineffective use of insulin. It often results from excess body weight and physical inactivity. Gestational diabetes is hyperglycemia that is first recognized during pregnancy.

A total of 57 million deaths occurred in the world during 2008; 36 million (63%) were due to NCDs, principally cardiovascular diseases, diabetes, cancer and chronic respiratory diseases. Nearly 80% of these NCD deaths (29 million) occurred in low- and middle-income countries. NCDs are the most frequent causes of death in most countries in the Americas, the Eastern Mediterranean, Europe, South-East Asia, and the Western Pacifi c. In the African Region, there are still more deaths from infectious diseases than NCDs. Even there, however, the prevalence of NCDs is rising rapidly and is projected to cause almost three-quarters as many deaths as communicable, maternal, perinatal, and nutritional diseases by 2020, and to exceed them as the most common causes of death by 2030. WHO projections show that NCDs will be responsible for a signifi cantly increased total number of deaths in the next decade. NCD deaths are projected to increase by 15% globally between 2010 and 2020 (to 44 million deaths).

Pioglitazone is a prescription drug of the class thiazolidinedione (TZD) with hypoglycemic action to treat diabetes. As Pioglitazone and Rosiglitazone are the same class of drugs, Rosiglitazone is already banned in India due to their cardiotoxcity activity causing MI

Thiazolidinediones, such as pioglitazone, are synthetic ligands for peroxisome proliferator-activated receptors (PPARs). They alter the transcription of genes influencing carbohydrate and lipid metabolism, resulting in changed amounts of protein synthesis and, therefore, metabolic changes. Pioglitazone improves glycaemic control in people with Type 2 diabetes by improving insulin sensitivity through its action at PPAR gamma 1 and PPAR gamma 2, and affects lipid metabolism through action at PPAR alpha. The results of these interactions include increases in glucose transporters 1 and 4, decreased free fatty acids, enhanced insulin signalling, reduced tumour necrosis factor alpha (TNF alpha) and remodelling of adipose tissue. Together, these can increase glucose uptake and utilisation in the peripheral organs and decrease gluconeogenesis in the liver, thereby decreasing insulin resistance.

The incidence of type 2 diabetes is at epidemic proportions throughout the world. Patients with diabetes have a 2–3 fold increased risk of cardiovascular disease when compared to the general population. They also have a greatly increased risk for microvascular disease. Hence medications that successfully control hyperglycemia in type 2 diabetes patients are of utmost importance. The underlying primary pathology in type 2 diabetes is insulin resistance. Drugs that address insulin resistance are effective in controlling hyperglycemia. Thiazolidinediones (TZD) are one such class of drugs that work through PPAR gamma activation. Pioglitazone is a TZD which is widely used for treating patients with type 2 diabetes.

Pioglitazone profile

Cardiovascular safety

There has been much discussion about the cardiovascular safety of TZDs over the last few years since the findings of a meta-analysis of 42 trials, in which Nissen et al compared the risk for MI associated with rosiglitazone with that of placebo or other antihyperglycemic agents. Rosiglitazone was associated with a significant 42% increased risk for MI.Since then several studies have shown some risk of increased myocardial infarction associated with rosiglitazone use.

Anti-inflammatory effects

Thiazolidinediones have been shown to decrease post angioplasty neointimal hyperplasia in both animals and humans PPAR-γ ligands have been shown to inhibit and stimulate angiogenesis. Pioglitazone has been shown to have anti-proliferative effects in humans, decreasing in-stent neointimal proliferation.

Weight gain

Pioglitazone causes dose-dependent and time-dependent weight gain alone and in combination with other hypoglycemic agents. The mechanism of weight gain is unclear but probably involves a combination of fluid retention and fat accumulation.

Eeffects on liver

There was no evidence of pioglitazone-induced hepatotoxicity or elevation of ALT levels in the pre-approval clinical studies

Edema

It is unknown whether or not there is a causal relationship between pioglitazone and macular edema. Concern for TZD associated macular edema has risen due to multiple case reports.

Effect on skeletal system

Thiazolidinediones have been associated with low bone density and increased fracture risk. A 4y observational study in older diabetic population showed that pioglitazone (and rosiglitazone) lowered bone density at trochanter, spine and whole body compared to those not taking TZDs.Separately pioglitazone has been shown to increase peripheral fractures in women compared to control groups (1.8 fracture vs. 1.15 per 100 patient years), but not in men, in the PROactive trial. Similar findings have been reported in other trials. There is insufficient data to suggest that pioglitazone increases risk of hip or spine fracture.

Interactions studies

In vivo drug-drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP 450 isoform 3 A4 substrate. An enzyme inhibitor of CYP2C8 (such as gemfibrozil) may significantly increase the AUC of pioglitazone and an enzyme inducer of CYP2C8 (such as rifampin) may significantly decrease the AUC of pioglitazone. Therefore, if an inhibitor or inducer of CYP2C8 is started or stopped during treatment with pioglitazone, changes in diabetes treatment may be needed based on clinical response.

ADR

Adverse effects of pioglitazone occurring in at least 5% of patients include upper respiratory tract infection, headache, sinusitis, myalgia, tooth disorder, aggravation of diabetes mellitus, and pharyngitis A postmarketing safety study of pioglitazone from 2008 showed that malaise and vomiting were the most frequently reported adverse reactions. Other adverse reactions included dizziness, headache, diarrhea, weight gain and abnormal liver function tests.

Pioglitazone effectiveness:

Prevention of type 2 diabetes

TZDs have been shown to prevent the onset of type 2 diabetes, which appears to be a class effect. Most recent data from Defronzo et al has shown that use of pioglitazone 45 mg reduced the incidence of type 2 diabetes by around 62%.Separately rosiglitzone and troglitazone have also been shown to be effective in prevention of type 2 diabetes. It is plausible that this effect is mediated by preservation of beta cell function as shown in studies of pioglitazone and troglitazone in the prevention of type 2 diabetes in insulin resistance Hispanic women.

Treatment of type 2 diabetes

Pioglitazone is approved to be used as monotherapy or in combination with metformin, sulfonylurea or insulin. It has been shown to be moderately effective in achieving glycemic control in placebo-controlled studies of patients with type 2 diabetes, either as monotherapy or in combination with metformin, sulfonylurea or insulin. Scherbaum et al showed that pioglitazone, both 17.5 and 35 mg/day, in addition to dietary control, was associated with significant reductions (vs. placebo) in mean levels of both glycosylated haemoglobin (HbA1C) and fasting blood glucose.

Treatment of polycystic ovary syndrome

Therapy with pioglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women.As a result, these patients may be at an increased risk for pregnancy while taking pioglitazone. Thus, adequate contraception in premenopausal women should be recommended.

Treatment of diabetic nephropathy (Effect on kidney)

Small studies have suggested that TZDs may have protective effects on the kidney. A recent systematic review and meta-analysis comparing the use of TZDs (pioglitazone and rosiglitazone) to placebo or other anti-diabetic agents concluded that thiazolidinedione treatment was associated with a significant decrease in urinary albumin clerearance. Limitations of this study included significant heterogeneity across included studies in several subgroup analyses and unavailable patient-level data. In a small 1-year open labeled randomized controlled trial of 34 normoalbuminuric patients with type 2 diabetes, rosiglitazone appeared to exert nephroprotective effects beyond glycemic control.Future clinical trials looking into hard renal outcomes should be conducted to further delineate the potential benefits of thiazolidinediones on diabetic nephropathy.

VITAMIN E

It refers to a group of eight fat-soluble compounds that include both tocopherols and tocotrienols. Of the many different forms of vitamin E, γ-tocopherol is the most common in the North American diet. γ-Tocopherol can be found in corn oil, soybean oil, margarine, and dressings. In the North American diet, α-tocopherol, the most biologically active form of vitamin E, is the second-most common form of vitamin E. This variant can be found most abundantly in wheat germ oil, sunflower, and

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safflower oils. As a fat-soluble antioxidant, it stops the production of reactive oxygen species formed when fat undergoes oxidation.

Functions

Vitamin E has many biological functions, the antioxidant function being the most important and/or best known other functions include enzymatic activities, gene expression, and neurological function(s). The most important function of vitamin E has been suggested to be in cell signaling (and it may not have a significant role in antioxidant metabolism)

- As an antioxidant, vitamin E acts as a peroxyl radical scavenger, preventing the propagation of free radicals in tissues, by reacting with them to form a tocopheryl radical, which will then be reduced by a hydrogen donor (such as vitamin C) and thus return to its reduced state.[12] As it is fat-soluble, it is incorporated into cell membranes, which protects them from oxidative damage
- Vitamin E also plays a role in neurological functions and inhibition of platelet aggregation
- As an enzymatic activity regulator, for instance, protein kinase C (PKC), which plays a role in smooth muscle growth, can be inhibited by α-tocopherol. α-Tocopherol has a stimulatory effect on the dephosphorylation enzyme, protein phosphatase 2A, which in turn, cleaves phosphate groups from PKC, leading to its deactivation, bringing the smooth muscle growth to a halt
- Vitamin E also protects lipids and prevents the oxidation of polyunsaturated fatty acids.

So far, most human supplementation studies about vitamin E have used only α-tocopherol. This can affect levels of other forms of vitamin E, e.g. reducing serum γ- and δ-tocopherol concentrations. Moreover, a 2007 clinical study involving α-tocopherol concluded supplementation did not reduce the risk of major cardiovascular events in middle-aged and older me

Deficiency

Vitamin E deficiency can cause:

- spinocerebellar ataxia
- myopathies
- peripheral neuropathy
- ataxia
- skeletal myopathy
- retinopathy
- impairment of the immune response
- red blood cell destructio] Supplementation

While vitamin E supplementation was initially hoped to have a positive effect on health, research has not supported this hope. Vitamin E does not decrease mortality in adults, even at large doses, and may slightly increase it. It does not improve blood sugar control in an unselected group of people with diabetes mellitus or decrease the risk of stroke. Daily supplementation of vitamin E does not decrease the risk of prostate cancer and may increase it. Studies on its role in age-related macular degeneration are ongoing as, though it is of a combination of dietary antioxidants used to treat the condition, it may increase the risk. A Japanese study in 2012 found vitamin E may contribute to osteoporosis.

Dietary sources

Sunflower oil

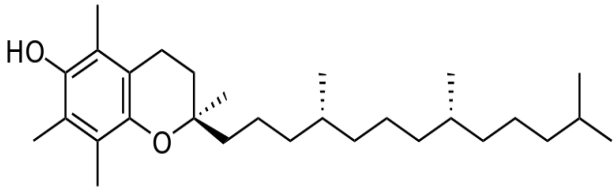
Safflower oil

Nuts and nut oils, such as almonds and hazelnuts

Palm oil

High-value green, leafy vegetables: spinach, turnip, beet greens, collard greens, and

One IU of vitamin E is defined as equivalent to either: 0.67 mg of the natural form, RRR-α-tocopherol, also known as d-α-tocopherol; or 0.45 mg of the synthetic form, all-rac-α-tocopherol, also known as dl-α-tocopherol.[6]



Structure-Vitamin E

MATERIALS AND METHOD

Animals

Wistar albino rats (150–200 g) were obtained from Central Animal Facility, Hamdard University and kept at 25±1 °C, 55±5% humidity alongwith 12 h light/dark cycle. The animals were given standard pellet diet (Lipton rat feed, Ltd., Pune) and water ad libitum throughout the experimental period. The experiment was approved by the 'Institutional Animal Ethics Committee'. Both the drug pioglitazone and vitamin E were administered orally.

36 Wistar rats of either sex is taken.It is divided into 6 groups with 6 rats in each group.

Animal will be kept overnight fasting, and drugs will be administered according to treatment schedule.

Drug	Trade name
Doxorubicin	Oncordia
Pioglitazone	Glit
Vitamin E.	Evion

Statistical analysis

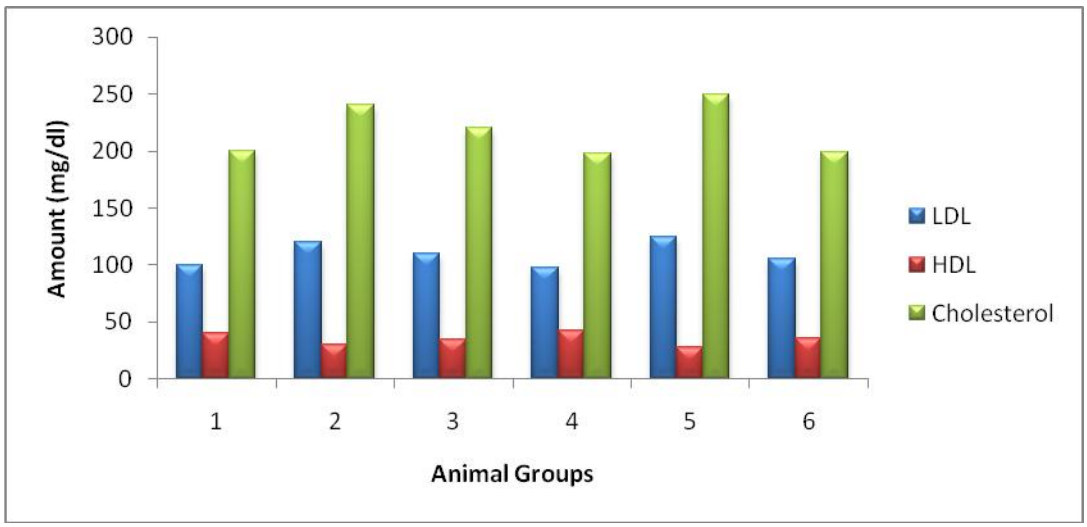
Data are analyzed by Post-Hock test & Dunnet test.

DOSAGE REGIMEN

Group	Animal Rat			No. of Animals	Drug Treatment	Dosage (mg/kg) rate of administration and duration
	Wt. (Kg)	Age (Days)	Strain			
1	150	55	Wistar albino rats	6	Control	Nornal saline 0.9 %
2	160	60	Wistar albino rats	6	Doxorubicin	15 mg/kg,I.P
3	155	57	Wistar albino rats	6	Pioglitazone (Per se)	0.4 mg/kg,p.o
4	165	65	Wistar albino rats	6	Vit. E(Per se)	0.15 mg/kg ,p.o
5	170	70	Wistar albino rats	6	Doxorubicin + Pioglitazone	15 mg/kg,I.P+0.4 mg/kg,p.o
6	163	64	Wistar albino rats	6	Doxorubicin + Pioglitazone + Vit. E	15 mg/kg,I.P+0.4 mg/kg,p.o+0.15 mg/kg ,p.o

RESULT

Group of animal		Drug administered	LDL (mg/dl)	HDL (mg/dl)	Cholesterol (mg/dl)
1	Normal Control	Nornal saline 0.9 %	100	40	200
2	Doxorubicin	15 mg/kg,I.P	120	30	240
3	Pioglitazone (Per se)	0.4 mg/kg,p.o	110	35	220
4	Vit. E(Per se)	0.15 mg/kg ,p.o	98	42	198
5	Doxorubicin + Pioglitazone	15 mg/kg,I.P+0.4 mg/kg,p.o	125	28	250
6	Doxorubicin + Pioglitazone + Vit. E	15 mg/kg,I.P+0.4 mg/kg,p.o+0.15 mg/kg ,p.o	105	36	199



It is clear from the table and graph that the level of LDL cholesterol is significantly decreased in a group that is administered a combination of doxorubicin,pioglitazone and vitamin E,while it is moderate in group which is administerd with pioglitazone alone.Same events repeated with total cholesterol level.The events is reversed in HDL level i.e the group with triple combination have significantly higher level of HDL cholesterol in comparision to pioglitazone alone.Vitamin E treating group is still having highest level of HDL cholesterol.

DISCUSSION

Studies show that pioglitazone has anti-inflammatory, anti-proliferative effects. But at the same time pioglitazone also has proangiogenic and proliferative properties in certain situations. The overall effect of the vascular effects of pioglitazone is likely tissue specific and depends on the pathophysiological process. E.g, its anti-proliferative, anti-inflammatory effects effects may be beneficial in terms of decreasing post angioplasty restenosis or damage post-stroke ischemia. These mechanisms may also be beneficial in the setting of NASH. However, its proangiogenic, proliferative properties exerted through VEGF, may be beneficial in wound healing in type 2 diabetes patients who lack adequate vascular supply to chronic wounds such as ulcers. Congestive heart failure may be one of the detrimental effects of pioglitazone mediated by a stimulation of VEGF expression.

Weight gain is one of the main issues with pioglitazone treatment. This is may be due to fluid gain as well as fat accumulation. However fat accumulation has been observed to be subcutaneous and not intra-abdominal. Moreover there may be a transfer of fat from the intra-abdominal compartment to the subcutaneous compartment. This might lead to decreased cardiovascular risk as increased visceral fat is strongly linked to adverse cardiovascular outcomes.

Newer detrimental effects on bone health and macular edema are yet to be characterized by perfectly powered

and designed studies. Mechanisms by which these occur are not clear at this time. In terms of efficacy, along with vitamin E,overall reduction of insulin resistance and hyperglycemia shows that pioglitazone is clinically efficacious in type 2 diabetes.

In conclusion current evident suggests that pioglitazone has an acceptable safety profile along with Vitamin E, may have beneficial cardiovascular and pleotropic effects and is efficacious in patients with type 2 diabetes.

CONCLUSION

It can be concluded from present study that pioglitazone alone if given to a potient of type 2 diabetes,it worsen cardiovascular complication of diabetes and it worsen lipid profiles by decreasing HDL and by increasing LDL cholesterol .Rosiglitazone,a member of thiozolidine dione is already withdrawn from market due to severe cardiovascular ADR. But when Pioglitazone is combined with Vitamin E,an antioxidant it reduces the complication and ADR,So by present study it can be deduced that combination of pioglitazone and Vitamin E is beneficial for diabetic patient regarding cardiovascular complication and other ADR. Drugs safety and efficay profile is increased and ADR profile is decreased along with vitamin E.

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