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A REVIEW ON 2, 4- THIAZOLIDINEDIONE IN TYPE-2 DIABETES

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ABSTRACT:
Diabetes mellitus is associated with impaired glucose metabolism that leads to an increase in blood glucose levels and free radicals production. Type II diabetes affects millions of people in the United States, and its incidence are increasing at an alarming rate. A key underlying feature of type 2 diabetes is insulin resistance, which is associated with characteristic clinical features and increased cardiovascular risk. Thiazolidinediones are well known for reduction in blood glucose level. The thiazolidinediones (TZDs) or 'glitazones' are a new class of oral antidiabetic drugs that improve metabolic control in patients with type 2 diabetes through the improvement of insulin sensitivity. TZDs exert their antidiabetic effects through a mechanism that involves activation of the gamma isoform of the peroxisome proliferator-activated receptor (PPAR gamma), a nuclear receptor. Several new 2, 4-TZDs such as pioglitazone, rosiglitazone have been marketed for the treatment of type 2 diabetes and in the prevention of its late complications.

Keywords: Diabetes mellitus, 2, 4-thiazolidinedione, Pioglitazone, Rosiglitazone.

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INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The most common form is Type 2 diabetes, which is characterized by combination of resistance to insulin action and an inadequate compensatory insulin secretion.

The prevalence of diabetes in adults world-wide was estimated to be 4.0% in 1995 and is expected to rise to 5.4% by the year 2025. In the Netherlands, the prevalence of diabetes (type 1 and 2) is estimated at 474.000 patients, 216.00 males and 258.000 females. The prevalence for males between 65-85 years is estimated 16% and for females 12% (source: RIVM). An increase of 35% in the next 20 years is estimated. About 85% of these diabetic patients suffer from type 2 diabetes.

Diabetes may lead to several severe complications such as retinopathy, nephropathy, angiopathy and neuropathy. The development of these complications is dependent on the duration of diabetes and the quality of metabolic control, and can be only partially prevented by intensive (insulin) treatment. In type 2 diabetes, hyperglycaemia may cause pathologic and functional changes in various target tissues (without clinical symptoms) a long time before diabetes is diagnosed[1].

Diabetes mellitus is associated with impaired glucose metabolism that leads to an increase in blood glucose level and free radicals production[2]. Diabetes mellitus is a growing healthcare problem that causes significant morbidity and mortality. Diabetes affects at least 18 million adults in the United States, and this prevalence isexpected to increase further as a result of the growing epidemic of obesity in this country. Type II diabetes is marked by 2 underlying defects: insulin resistance, which manifests as a decrease in uptake of glucose by insulin-sensitive tissues, and the inability of the β cell to

produce enough insulin in response to the insulin resistance. As a result of this resistance to insulin, pancreatic cells release larger amounts of insulin to maintain euglycemia.

However, in susceptible individuals, the β cell response is ultimately not optimal with β cell dysfunction, resulting in a decrease in insulin secretion and development of hyperglycemia. Because hyperglycemia can cause damage to severalorgan systems, diabetes is a chronic disease that results in the development of various microvascular and macrovascular complications. By maintaining tight glycemic control, patients can delay the progression and severity of long-term microvascular complications such as nephropathy, neuropathy, retinopathy, and possibly macrovascular complications such as cardiovascular disease[3].

According to the American Diabetes Association, the direct costs in 2007, of treating the estimated 23.6 million type 2 diabetes mellitus (T2DM) patients and the estimated 57 million prediabetic patients in the United States was approximately $116 billion with an additional $58 billion dollars in indirect costs (Hanrahan et. al., 2012). Most cases will be of type 2 diabetes, which is strongly associated with a sedentary life style and obesity. Early stages of type 2 diabetes mellitus (Type II DM) are characterized by tissue resistance to the effects of insulin secreted by pancreatic β cells[4].

TYPES OF DIABETES

There are three main types of diabetes:

Type I diabetes is sometimes called insulin-dependent, immune-mediated or juvenile-onset diabetes. It is caused by an auto-immune reaction where the body's defense system attacks the insulin-producing cells. The reason why this occurs is not fully understood. People with type 1 diabetes produce very little or no insulin. The disease can affect people of any age, but usually occurs in children or young adults. People with this form of diabetes need injections of insulin every day in order to control the levels of glucose in their blood. If people with Type 1 diabetes do not have access to insulin, they will die.

Type 2 diabetes accounts for at least 90% of all cases of diabetes.

Type 2 diabetes is sometimes called non-insulin dependent diabetes or adult-onset diabetes, and accounts for at least 90% of all cases of diabetes. It is characterized by insulin resistance and relative insulin deficiency, either of which may be present at the time that diabetes becomes clinically manifest. The diagnosis of type II diabetes usually occurs after the age of 40 but can occur earlier, especially in populations with high diabetes prevalence. Type 2 diabetes can remain undetected for many years and the diagnosis is often made from associated complications or incidentally through an abnormal blood or urine glucose test. It is often, but not always, associated with obesity, which itself can cause insulin resistance and lead to elevated blood glucose levels.

Gestational diabetes (GDM) is a form of diabetes consisting of high blood glucose levels during pregnancy. It develops in one in 25 pregnancies worldwide and is associated with complications in the period immediately before and after birth. GDM usually disappears after pregnancy but women with GDM and their offspring are at an increased risk of developing type II diabetes later in life. Approximately half of women with a history of GDM go on to develop Type 2 diabetes within five to ten years after delivery[5].

Symptoms

- ✓ Increased thirst
- ✓ Passing a lot of urine, especially at night
- ✓ Extreme tiredness or lethargy
- ✓ Weight loss
- ✓ Genital itching
- ✓ Itchy skin rash or slow healing wounds
- ✓ Tingling pain and numbness in feet, legs or hands (symptoms of neuropathy)
- ✓ Blurred vision.

Complications

Complications of Type I and Type II diabetes are the same. Prolonged hyperglycaemia causes both microvascular (e.g. retinopathy) and macrovascular (e.g. cardiovascular) damage. Complications include:

- ✓ **Cardiovascular complications** for example, heart attacks, angina, stroke, peripheral artery disease
- ✓ **Kidney damage** (nephropathy) sometimes leading to kidney failure
- ✓ **Eye problems** (retinopathy) which can affect vision and lead to blindness
- ✓ **Nerve damage** (neuropathy) that can cause a range of problems including neuropathic pain, foot problems, limb amputation and erectile dysfunction[6].

About Thiazolidinediones

Thiazolidinedione are well known for reduction in blood glucose level. A number of thiazolidinedione have been approved for clinical use in diabetes. So a series of thiazolidine-2, 4-diones was selected and different models based on MLR, PLS analysis was generated to find out correlation between the physicochemical parameters and the biological activity[4].

2, 4-Thiazolidinediones (2, 4-TZDs) are a new class of antidiabetic agents which are effective in normalizing glucose and lipid metabolism associated with insulin resistance. Several new 2, 4-TZDs such as pioglitazone, rosiglitazone have been marketed for the treatment of

type II diabetes and in the prevention of its late complications. 2, 4-TZDs can be viewed as hydantoin bioisosters potentially free of the hypersensitivity reactions which are linked to the presence of the hydantoin system[7].

Thiazolidinediones (TZDs) are a new class of antidiabetic drugs, having an insulin sensitizing effect in patients with type II diabetes[8].

The thiazolidinediones (TZD), commonly referred to as glitazones, are a relatively new class of oral agents for treating type 2 diabetic patients. Although their mechanism of action is not fully understood, the effects of TZD are mediated, at least in part, through the activation of peroxisome proliferator-activated receptor (PPAR)-γ a specific subclass of nuclear receptors. Thiazolidinediones improve blood glucose control by ameliorating insulin resistance in type 2 diabetes[9].

The development of the thiazolidinediones

The discovery of thiazolidinediones and a substantial amount of the early developmental work occurred in Japan. The first compound, ciglitazone, improved glycaemic control in animal models of insulin resistance, but its mechanism of action was poorly understood and toxicity prevented trials in humans. Other compounds were subsequently developed with less toxicity in animals, and two important findings led to a rapid increase in our understanding of their mode of action. These findings were that thiazolidinediones bind avidly to peroxisome proliferator-activated receptor gamma (PPARϒ) improve insulin sensitivity in parallel with a major change in fat metabolism, including a substantial reduction in circulating free fatty acids.

Three compounds - troglitazone, pioglitazone and rosiglitazone - have entered clinical practice and there has been a steadily increasing understanding of the multiple biological effects of these drugs. Unfortunately, troglitazone caused uncommon but serious liver toxicity, leading to its withdrawal from use. It seems likely that this toxicity was related to the vitamin E-like part of the molecule. Hepatotoxicity does not seem to be associated with the other two compounds, but regular liver function tests are recommended.

Molecular mechanisms of action

PPARϒ is a member of a family of nuclear receptors. Another member of this class, peroxisome proliferator-activated receptor alpha (PPARϒ), is predominantly expressed in the liver and is thought to mediate the triglyceride lowering actions of fibrates. PPARϒ is expressed in many tissues, including colon, skeletal muscle, liver, heart and activated macrophages, but is most abundant in adipocytes.

Thiazolidinediones are selective agonists of PPARϒ. When activated by a ligand, such as a thiazolidinedione, PPARϒ binds to the 9-cis retinoic acid receptor (RXR [retinoid X receptor]) to form a heterodimer. This binds to DNA to regulate the genetic transcription and translation of a variety of proteins involved in cellular differentiation and glucose and lipid metabolism[10].

Rosiglitazone

Rosiglitazone is now licensed for use as monotherapy, combination therapy with metformin or a sulfonylurea, or as part of triple therapy with metformin and a sulfonylurea in the UK. Combination therapy with insulin is not licensed at present. As from January 2008 the European Medicines Agency (EMEA) 114 states that 'rosiglitazone is indicated in the treatment of Type 2 diabetes mellitus:

- as monotherapy in patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance.
- as dual oral therapy in combination with:
  - ✓ metformin in patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin.
  - ✓ a sulfonylurea, only in patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite monotherapy with a sulfonylurea.
- as triple oral therapy in combination with metformin and a sulfonylurea, in patients (overweight patients) with insufficient glycaemic control despite dual oraltherapy.'
- Rosiglitazone is also available in two combination tablet formats (with metformin and

also with glimepiride).

Pioglitazone

Pioglitazone is now licensed for use as monotherapy, combination therapy with metformin or a sulfonylurea, as part of triple therapy with metformin and a sulfonylurea, or in combination therapy with insulin. As from September 2007 the EMEA114 states that, 'pioglitazone is indicated in the treatment of Type 2 diabetes mellitus:

- as monotherapy in patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance
- as dual oral therapy in combination with:
  - ✓ metformin in patients (particularly overweight patients) with insufficient glycaemic control

despite maximal tolerated dose of monotherapy with metformin
- ✓ a sulfonylurea, only in patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulfonylurea

- as triple oral therapy in combination with:
  - ✓ metformin and a sulfonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy
- pioglitazone is also indicated for combination with insulin in Type 2 diabetes mellitus patients with insufficient glycaemic control on insulin for whom metformin isinappropriate because of contraindications or intolerance[13].

Troglitazone (TGZ), a 2, 4 thiazolidinedione (TZD) anti-diabetic agent, has beenassociated with hepatotoxicity in type II diabetic patients. The mechanism of toxicity has not yet been established. However, it has been reported (Kennedy et al., 2003) that the incorporation of a sulphur atom in the cyclic imide structure of N-(3, 5-dichlorophenyl)succinimide (NDPS), analogous to the 2,4-TZD moiety in TGZ, resultedin hepatotoxicity[14].

Dosing

Pioglitazone is taken once daily without regard to meals. Dose can be initiated at 15 mg daily, and titrated up to 45 mg daily.

Rosiglitazone is taken either as a single daily dose or divided dosing without regard to meals. The usual starting dose is 4 mg daily. The maximum recommended dose is 8 mg daily. A dose adjustment in patients with renal insufficiency is not recommended for pioglitazone or rosiglitazone. There are no data on the use of pioglitazone or rosiglitazone in patients under 18 years of age; therefore, use of these products in pediatric patients is not recommended. Pioglitazone is available in 15mg, 30mg, and 45mg tablets. Rosiglitazone is available in 2mg, 4mg, and 8mg tablets.

Adverse effects

Generally, TZDs are well tolerated. The adverse effect profiles are similar between pioglitazone and rosiglitazone.

- Upper respiratory infection,
- Injury
- Headache
- As monotherapy, neither drug caused hypoglycemia, but in combination therapy, hypoglycemia risk is increased, and dose reduction in concomitant agent may be necessary[1,2].
- Dose-dependent weight gain of 0.7 kg to 5.3 kg has been reported in the clinical studies and seems to be a class effect.
- TZDs can cause fluid retention, which may exacerbate or lead to heart failure.
- The incidence of edema is about 3%-5% with TZDs monotherapy; however, when combined with insulin therapy, the incidence of edema can increase to 13%-16%, compared with 5%-7% in patients receiving insulin plus placebo.
- In clinical trials and post-marketing experience, combining pioglitazone or rosiglitazone with insulin resulted in the development of peripheral edema in approximately 16% of patients[15].
- water retention, leading to edema , generally a problem in less than 5% of individuals
- an increased risk of coronary heart disease and heart attacks with rosiglitazone[16].

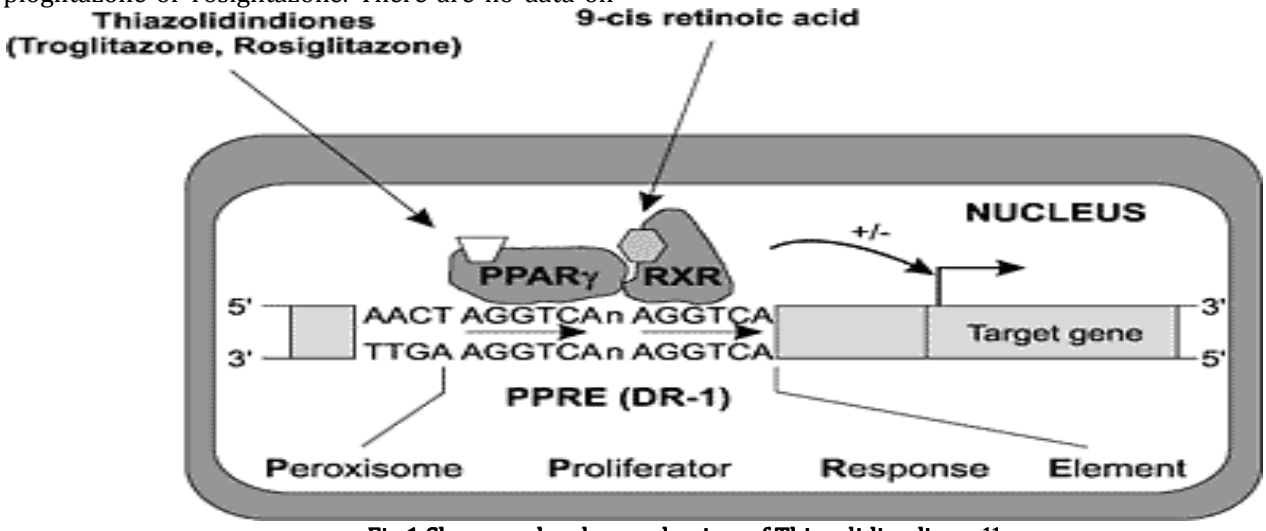

Fig.1 Shows molecular mechanism of Thiazolidinediones[11]

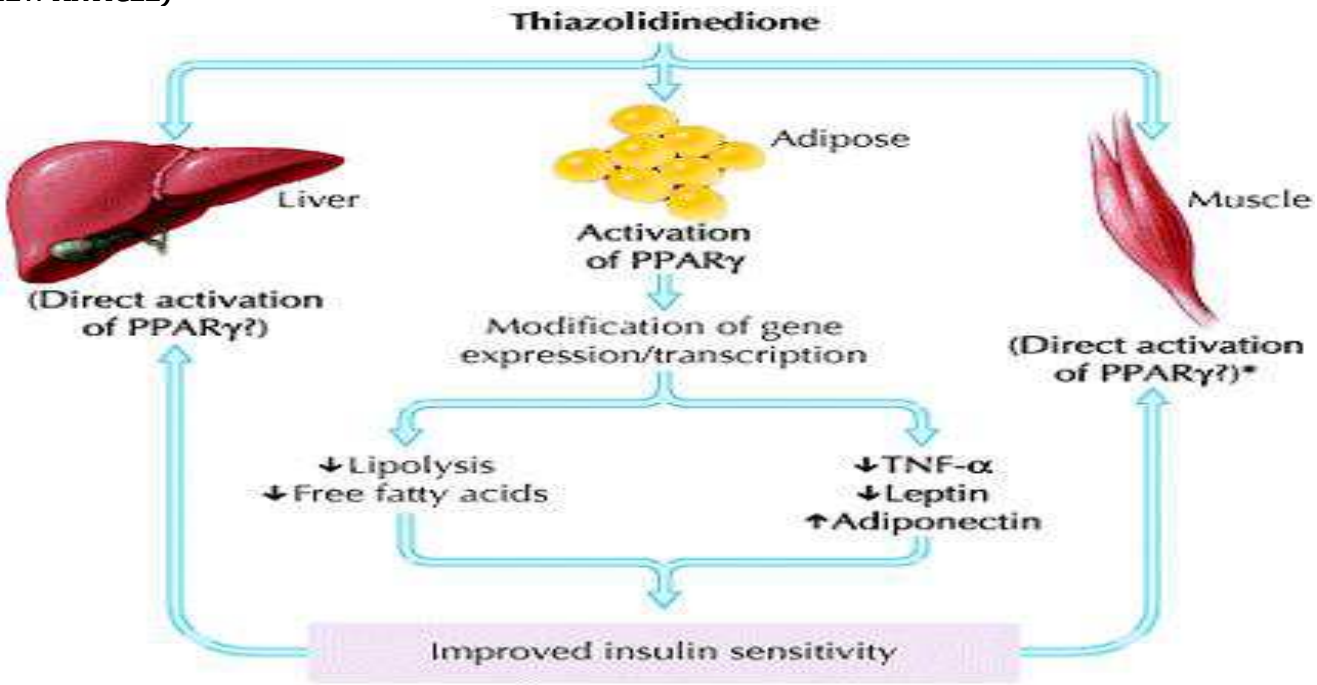

Fig. 1 Shows mechanism of Thiazolidinediones

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