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Sulphonylurea, Metformin, TZDs: Potential Drugs to Cure Diabetes

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Abstract: This review introduces the disease state of diabetes mellitus and provides a background of the impact of the disease on the population, its biology and pathophysiology, and the current treatment strategies for treating diabetes. In Europe, the thiazolidinedione derivatives pioglitazone and rosiglitazone have been approved for the treatment of type 2 diabetes mellitus either as monotherapy for patients with intolerance or contraindications to metformin or in combination therapy. Modifications of thiazolidinediones have proven highly effective and do not exhaust the possible changes that can be made to improve potency, safety and efficacy of these thiazolidinedione derivatives. TZDs have been approved for type 2 diabetes mellitus, particularly for overweight patients who are inadequately controlled by diet and exercise alone, for which metformin and sulphonylurea are inappropriate because of contraindications or intolerance. This class of drugs seems particularly suited for obese patients, but is currently not considered as a first choice for monotherapy. The efficacy with respect to blood glucose lowering is comparable with sulphonylurea (SU) derivatives and with metformin. Long-term data with respect to efficacy and side effects are still limited. This is the updated report on thaizolidinediones and explained its efficacy and how it is better than other antidiabetic agents.

Keywords: Type 2 diabetes mellitus; monotherapy; pioglitazone; rosiglitazone; rivoglitazone; troglitazone; thiazolidinedione derivatives; sulphonylurea; biguanides.

1 Introduction

Diabetes means a ‘siphon’ or ‘running through’ and earlier it was used to describe the polyuria. **Mellitus** means sugar. Therefore, diabetes mellitus is a clinical state which is associated with flow of sugar in urine. The disease causes loss of weight as if the body mass is passed through the urine. We know that a primary metabolic action of insulin is to facilitate the postprandial disposition of glucose via its actions on three key target tissues: suppression of glucose output from the liver, stimulation of glucose uptake and metabolism in skeletal muscle and adipose tissue. Defects in insulin secretion and action on its target tissues manifest clinically as diabetes, syndrome X, and insulin resistance. The discovery of insulin was done in the early 1920s. The ultimate unifying theme among diabetes researchers today is to uncover novel targets for which to develop improved therapeutic modalities.[1-6]

2 Classification of Diabetes Mellitus

Diabetes mellitus may be categorized into several types as type 1, Insulin Dependent Diabetes Mellitus (IDDM) and type 2, Non-Insulin Dependent Diabetes Mellitus (NIDDM); other specific types of diabetes are explained in **Table 1**.

Table 1: Classification of Diabetes.

Type 1	**ß-cell destruction with little or no endogenous insulin secretory capacity, autoimmune idiopathic**
Type 2	Ranges from relative insulin deficiency to disorders of insulin secretion and insulin resistance
Other specific types	Genetic defects of ß-cell function; Genetic defects in insulin secretion; Diseases of the exocrine pancreas; Endocrinopathies; Drug-induced or chemical induced infections.

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Type 1 diabetes is usually due to an immune-mediated destruction of pancreatic islet β-cells with consequent insulin deficiency and the need to replace insulin. Type 2 diabetes, the more common type, is usually due to resistance to insulin action in the setting of inadequate compensatory insulin secretory response.

Type 2 diabetes is typically a polygenic disease that results from a complex interplay between genetic predisposition and environmental factors such as diet, degree of physical activity, and age, with resulting hyperglycemia and diabetes, blood pressure elevation, and dyslipidemia.[7,8] In fact, collectively these abnormalities, which often occur together, have been designated the "metabolic syndrome" or more properly the "dysmetabolic syndrome". Ultimately, however, even in type 2 diabetes, there is a progressive loss of pancreatic islet β-cells resulting in insulin deficiency and the need to replace insulin as explained in **Figure 1**.[9-15]

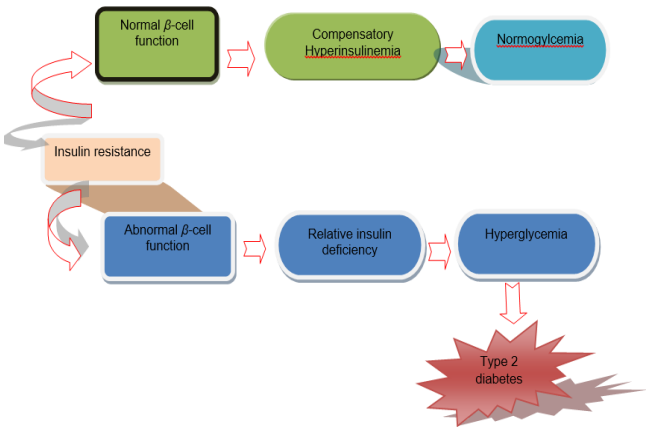

Figure 1 Schematic depiction of the dual defect: insulin resistance in the setting of impaired β-cell function inadequate to compensate for the insulin resistance.

Initially, in type 2 diabetes, insulin-stimulated glucose transport in skeletal muscle is impaired. As compensation, pancreatic β cells display augmented secretion of insulin, resulting in hyperinsulinemia. Peripheral insulin resistance, in combination with impairment in the early phase of insulin secretion, results in hyperglycemia. In end-stage type 2 diabetes, changes in insulin signaling, such as insulin's inability to inhibit hepatic gluconeogenesis, are accompanied by a deterioration of pancreatic β cell function and β cell "exhaustion". In essence, the progression to full-blown type 2 diabetes ensues when the β cell hypersecretion of insulin fails to compensate for insulin resistance. These patients require one to several daily insulin injections for proper glycemic control.

2.1 Clinical features to cure of DM

Clinical presentation of type I and type II diabetes are similar but they vary in their intensity. The symptoms include polyurea, polydipsia, polyphagia, weight loss, fatigue, cramps, constipation, blurred vision, and candidiasis. Longstanding type 1 DM patients are also susceptible to microvascular complications and macrovascular disease. In addition, type 2 DM caries a high risk of large vessel atherosclerosis commonly associated with hypertension, hyperlipidaemia and obesity.

2.2 Genetic factors

Literature reported the relationship between the developments in type 2 diabetes with the history of family having diabetes. Further, a higher concordance rate between monozygotic twins in comparison between dizygotic twins has been found. It indicates that genetic factors play key role. The pathogenesis is involved in the genetic abnormality in the molecules which have relation with the regulatory system of glucose metabolism. [16-20]

2.3 Roles of environmental factors in DM

List of independent factors of pathogenesis has shown risks like aging, obesity, more energy consumption, alcohol consumption, smoking, etc. The changes in food taken in diet mainly increase in fat intake, decrease in starch intake, the increase in the consumption of simple sugars, and the decrease in dietary fiber intake collectively causes obesity. Therefore, it causes worsening of glucose tolerance.

2.4 Impaired insulin secretion

Impaired insulin secretion occurred due decrease in glucose responsiveness and it is usually observed before the clinical onset of disease. In depth, impaired glucose tolerance (IGT) can be induced by a decrease in glucose-responsive early-phase insulin secretion and a decrease in additional insulin secretion after meals causes postprandial hyperglycemia. Literature reported that during the oral glucose tolerance test (OGTT) in IGT cases, an over-response in Western and Hispanic individuals has been observed. Further, they have markedly high insulin resistance. While on the other side, Japanese patients frequently react to this test with decreased insulin secretion. Also, patients in early stages after disease onset mainly show an increase in postprandial blood glucose. It results in increase insulin resistance and decrease early-phase secretion. The succession of the worsening of pancreatic β cell function subsequently causes permanent increase of blood glucose. (**Figure 2**)[21-23]

2.5 Insulin resistance

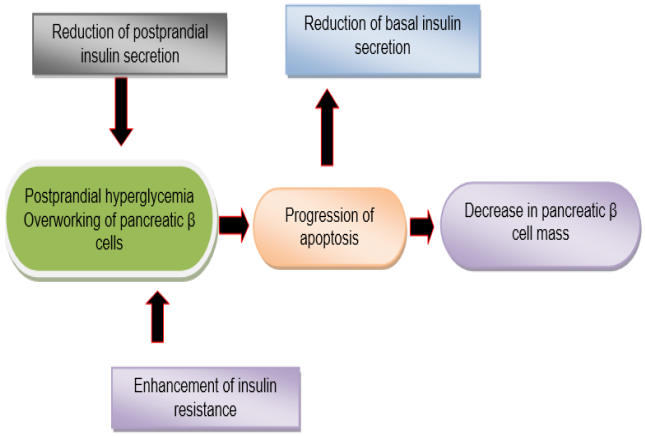

Figure 2 Pathophysiological progression of type 2 diabetes from pancreatic β cell function.

Insulin resistance is a condition, when insulin present in the body does not put forth enough action comparative to its blood concentration. The impairment of insulin action mainly in liver and muscles is a common pathophysiological feature of type 2 diabetes. So, insulin resistance created and increases prior to disease onset. At present, interest of academicians and researchers has emphasized on the involvement of adipocyte-derived bioactive substances (adipokines) in insulin resistance. While TNF-α, leptin, resistin, and free fatty acids act to increase resistance, adiponectin improves resistance.

2.6 Insulin Signal Transduction and Regulation of Glucose Uptake

A primary metabolic role of insulin is to kindle the uptake of circulating glucose in various parts of body like muscle, adipose tissue. In view of the most of the physiological conditions, glucose transport is considered to be the rate-limiting for glucose uptake and it is metabolism by skeletal muscle and adipose tissue. It is reported that the insulin-stimulated glucose uptake is regulated by the muscle- and fat specific, insulin-regulatable glucose transporter isotype 4.[24-29]

2.7 Causes

Diabetes mellitus is primarily a disease due to Insulin deficiency. It is usually associated with hormones which normally have antagonistic actions to insulin; for example, GH, glucagons and glucocorticoids and catecholamines. Predisposing factors as follow:

A **Hereditary** – The most typical form of diabetes is hereditary idiopathic diabetes mellitus.

B **Age** – The disease is common with increasing age.

C **Obesity** – A reliable indicator for body fat is Body Mass Index (BMI). Individuals with values of 25-30 are overweight and with values >30 are obese. [4,6-10, 15, 30-35]

3 Current Treatments for Diabetes

In the present scenario, approaches for the treatment of type 2 diabetes include diet, exercise, and different pharmacologic agents including insulin, biguanides, sulfonylureas, and thiazolidinediones (TZDs). These biological potent molecules act by different mechanisms or routes to try to normalize the blood glucose levels. It also avoids the well-recognized, serious complications of diabetes which can affect different organ systems like kidneys, cardiovascular, ophthalmic, and nervous systems. Adverse effects of these or "first-generation" therapies are hypoglycemia, high weight gain, and edema. Miniperspectives which make up this series focus clearly on diabeted. It gives exceptional surveys of some of the most potent areas of diabetes research are PPARα/β receptor agonists, GLP-1 analogues, dipeptidyl peptidase 4 (DPP4) and protein tyrosine phosphatase 1B (PTP1B) inhibitors. The subsequent miniperspective concisely concludes the severe nature of type 2 diabetes, potency of present treatments and identifies desirable characteristics of new agents.[36-45]

Another approach to increase the GLP-1 activity is used to decrease its deprivation by the enzyme dipeptidyl peptidase 4 (DPP4), a non-classical serine protease. Many DPP4 inhibitors are available and they are in phase III evaluation. DPP4 inhibitors are effective and safely decrease the blood glucose in diabetic patients. Another merit linked with both of the GLP- 1-based therapies is weight loss, it contribute to their definitive clinical potency. It stands in difference to the weight gain linked with both insulin and TZD use. Dietary changes and exercise are considered to the first line of treatment for type 2 diabetics.

Hypocaloric diets to induce weight loss result in lowering of plasma glucose, in some cases normalizing blood sugar levels. The mechanism for improved glucose homeostasis following weight loss includes amelioration of hepatic and peripheral insulin resistance. Weight loss and exercise enhance insulin sensitivity and glucose utilization and improve lipid and lipoprotein profiles. There are mainly five categories of orally active antidiabetic drugs on the market: metformin, a biguanide for type 2 diabetes; thiazolidinediones, including pioglitazone and rosiglitazone, peroxisome proliferator-activated receptor gamma (PPARɣ) activators; the R-glucosidase inhibitors that delay intestinal carbohydrate absorption and blunt postprandial glucose excursions; and sulfonylureas (SU) and non-sulfonylurea (non-SU) insulin secretagogues that stimulate insulin secretion by pancreatic β cells.

3.1 Sulfonylureas

Sulfonylureas have been used for the treatment of NIDDM. An NIDDM patient is characterized by a low response in insulin secretion toward increased blood glucose levels. The use of these agents, as with extra insulin from outside the body, typically prevents achieving good glucose

control; people usually keep their blood glucose elevated above optimal in order to reduce the frequency and severity of hypoglycemia. Other, infrequent side effects that can occur are nausea, skin reactions, and abnormal liver function tests. Weight gain can also occur unless the diabetic diet and exercise program are followed.[46-55]

3.2 Biguanides

Biguanides, including phenformin and metformin, were introduced in 1957 as oral antidiabetic drugs. Phenformin was later withdrawn in many countries due to its side effect of lactic acidosis. Metformin is now a widely used biguanide for the therapy of type 2 diabetes. The main side effect of metformin monotherapy is gastrointestinal (GI) symptoms. At 2550 mg daily dosage, patients experienced abdominal discomfort, bloating, and metallic taste. The GI side effects are the primary reason for discontinuation but can be lessened by gradual dose titration and administration with food.[56-68]

3.3 Thiazolidinediones (TZDs)

Pioglitazone, troglitazone and rosiglitazone, three oral blood glucose lowering drugs for the treatment of type 2 diabetes mellitus, have been marketed since 2000. All belong to the class of thiazolidinedione derivatives (TZDs), also referred to as **Glitazones**. It should be realised that compounds other than the TZDs can also stimulate the PPARγ receptor. TZDs have been approved for type 2 diabetes mellitus, particularly for overweight patients who are inadequately controlled by diet and exercise alone, for which metformin is inappropriate because of contraindications or intolerance. TZDs have also been approved for use in combination therapy.

The weight gain associated with the use of thiazolidinediones is the increase in subcutaneous adipose tissue and the concomitant decrease in visceral fat, which alters the distribution of adipose tissue. Fluid retention and the induced increase in plasma volume are another potential cause of increased body weight. The incidence of weight gain is greater when thiazolidinediones are used in combination with insulin and lower when it is coadministered with metformin, sulfonylurea, or used as monotherapy.[42-47, 52-59, 69-75]

3.3.1 Mechanism of action of thiazolidinediones

The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptors superfamily and there are three subtypes currently identified, PPAR γ, PPAR α and PPAR δ, which play a significant role in lipid metabolism. Various fatty acids and natural eicosanoids serve as endogenous ligands for PPARs, whereas fibrates and thiazolidinediones are potent synthetic ligands affecting lipid and glucose metabolism. After ligand binding, PPARs undergo specific conformational changes that allow recruitment of one coactivator protein or more. Once activated, the PPARs form heterodimers with another nuclear receptor, the 9-cis-retinoic acid receptor (RXR). These heterodimers PPAR/ RXR bind to specific DNA sequences (PPAR response elements: PPRE). Furthermore, PPARs can interact with other transcription factors in a DNA binding-independent manner and exhibit anti-inflammatory properties by repressing gene expression for some cytokines (interleukins IL-2, IL-6, IL-8, tumour necrosis factor TNF- α, and metalloproteases). There is probably a repression of nuclear factor- IB and activator protein-1 (AP-1) transcription pathways. PPARα are expressed predominantly in the heart, liver, kidneys and skeletal muscle and are the main target for fibrates (fenofibrate, ciprofibrate, and gemfibrozil), which have hypolipidaemic and anti-inflammatory effects. PPAR δ are expressed primarily in the adipose tissue and are involved in lipid metabolism, body weight reduction and modulation of skeletal muscle to training or fasting. PPARγ are expressed more abundantly in adipose tissue but are also found in vascular endothelium, monocytes, macrophages, pancreatic beta cells and atherosclerotic lesions in vivo. Their expression is low in tissues that express predominantly PPARα, such as the liver, the heart, and skeletal muscles. Thus, it is clear that adipose tissue, in addition to other sites, is the main target for glitazones, which increase insulin sensitivity, reducing plasma concentrations of free fatty acids (**Figure 3**).

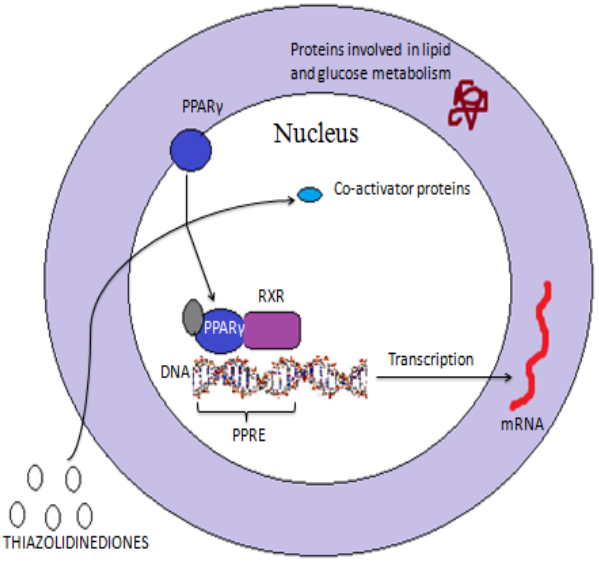

Figure 3 Action of thiazolidine-2,4-dione.

Thiazolidinediones lower fasting and postprandial insulin and glucose plasma concentrations, increase glucose uptake in peripheral tissues and reduce free fatty acid levels. In skeletal muscles, insulin resistance is greater compared to other tissues; thiazolidinediones activate two proteins, phosphatidylinositol3- kinase and Akt, which are inactivated in patients with type 2 diabetes. Another important effect of thiazolidinediones is the proliferation of

small adipocytes in comparison to larger ones, a process that promotes glucose uptake from adipose tissue. In this way, the use of glitazones leads to weight gain, as they increase subcutaneous adipose tissue mass (a more insulin-sensitive type of fat tissue) and cause redistribution of fat between visceral (decrease) and subcutaneous (increase) body compartments. In addition, by reducing plasma concentrations of free fatty acids, thiazolidinediones decrease their toxic effects upon the pancreatic beta cells. Furthermore, various inflammatory mediators, such as adiponectin, TNF- α and resistin, are regulated by PPARγ agonists in a manner which results in improved adipose tissue function. Adiponectin's plasma concentration is low in patients with type 2 diabetes, especially in obese patients, and thiazolidinediones have been shown to increase it in vivo. In animals this process can ameliorate insulin resistance, but this does not occur in humans. Several clinical studies indicate that rosiglitazone has a greater PPARγ binding affinity than does pioglitazone, which translates to a clinical dose that is about 1/6 that of pioglitazone.[5-11, 45-54, 67-72]

4 Conclusion

Glitazones are potent antidiabetic agents with good euglycemic and hypolipidemic activity. Modifications of thiazolidinediones have proven highly effective and do not exhaust the possible changes that can be made to improve potency, safety and efficacy of these thiazolidinedione derivatives. TZDs have been approved for type 2 diabetes mellitus, particularly for overweight patients who are inadequately controlled by diet and exercise alone, for which metformin and sulphonylurea are inappropriate because of contraindications or intolerance.

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