ejpmr, 2016,3(9), 189-192.

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 3294-3211

EJPMR

A REVIEW ON CARDIOVASCULAR RISK OF SULFONYL UREAS IN DIABETIC PATIENTS

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Article Received on 05/07/2016 **Article Revised on 25/07/2016** **Article Accepted on 15/08/2016**

ABSTRACT

Diabetes is a chronic metabolic disorder. Untreated diabetes mellitus may cause many microvascular complications. Better control of diabetes mellitus reduces microvascular complications, but has limited effect on macrovascular complications including cardiovascular mortality. A spite of controversial reports has shown that some new oral antidiabetic drugs may paradoxically increase cardiovascular and mortality. Some sulfonyl ureas increase cardiovascular risks presumably by preventing protective ischemic cardiac preconditioning. We review here publish data on cardiac safety of currently available oral antidiabetic drugs.

KEYWORDS: sulfonyl ureas, cardiovascular risk, metabolic disorder, oral antidiabetic drugs.

1. INTRODUCTION

Diabetes commonly referred to as group of metabolic diseases in which there are high blood sugar levels over a prolonged period.[1] Diabetes is due to either pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. If left untreated, diabetes can be cause many complications. Acute complications can include diabetic keto acidosis, non ketotic hyperosmolar coma, or death.

TYPES OF DIABETES

Diabetes mellitus is mainly divided into three types:

1. Type I Diabetes Mellitus,
2. Type II Diabetes Mellitus,
3. Gestational Diabetes.

TYPE I DIABETES MELLITUS

Diabetes mellitus results from the pancreas failure to produce enough insulin. This form was previously referred to as Insulin Dependent Diabetes Mellitus (IDDM) or juvenile diabetes. This type is unknown.

TYPE II DIABETES MELLITUS

Diabetes mellitus begins with the insulin resistance a condition in which cells fail to respond to insulin to insulin properly as the disease progress a lack of insulin may also develop. This form was previously referred to as Non- Insulin Dependent Diabetes Mellitus (NIDDM) or adult onset diabetes mellitus. The primary causes are excessive body weight and not enough exercise.

GESTATIONAL DIABETES

It is the third main form and occurs when pregnant women without previous history of diabetes develop high blood sugar levels.

2. EPEDEMIOLOGY

Globally as of 2010, an estimated 285 million people had diabetes, with type II making up about 90% of the cases.[2] In 2013 according to International Diabetes Foundation, 381 million people had diabetes. Its prevalence is increasing rapidly and by 2030 its number is almost double. Diabetes mellitus occurs throughout the world but it is more common in the more developed countries.

3. ETIOLOGY[3]

Type I diabetes is caused by,

- Genetic susceptibility,
- Auto immune destruction of beta cells,
- Environmental factors.

Type II diabetes

The most common form of diabetes-is caused by a combination of factors including insulin resistance, a

condition in which the body cells, muscle, fat and liver cells don't use insulin effectively.

- Obesity and physical inactivity
- Insulin resistance
- Abnormal glucose production
- Beta cell dysfunction
- Cell signaling and regulation
- Metabolic syndrome
- The roles of insulin and glucagon in normal blood glucose regulation.

The following is a comprehensive list of other causes of diabetes:

- Genetic defects of β cell function
- Genetic defects in insulin processing or insulin action
- Exocrine pancreatic defects
- Infections.

4. SIGNS AND SYMPTOMS[4]

1. CLASIC SYMPTOMS OF UNTREATED DIABETES

- weight loss.
- Polyuria (increased urination).
- Polydipsia (increased thirst).
- Polyphagia (increased hunger).

Symptoms may develop rapidly in type I diabetes mellitus, while they usually develop much more slowly and absent in type II diabetes mellitus.

2. OTHER SYMPTOMS

Other signs and symptoms can also mark for the onset of diabetes although they are not specific to the disease. They include:

- Blurry vision
- Fatigue
- Headache
- Slow healing of cuts
- Itchy skin
- Diabetic dermadromes.

DIAGNOSIS

Diabetes mellitus is characterized by reccurent or persistent high blood sugar and it is diagnosed by demonstrating any one of the following;

- Fasting plasma glucose levels ≥ 7.0mmol/lit(126mg/dl)
- Plasma glucose ≥ 11.1mmol/lit (200mg/dl) two hours after a 75g oral glucose load as in a glucose tolerance test.
- Symptoms of high blood sugar and casual plasma glucose ≥ 11.1mmol/lit(200mg/dl)
- Glycated haemoglobin(HbA_{1c}) ≥ 48mmol/mol(≥ 6.5 DCCT %).[16]

Table 1: WHO diabetes diagnostic criteria[6,7]

Condition	2 hour glucose	Fasting glucose	HbA_{1C}	
Unit	**mmol/l (mg/dl)**	**mmol/l (mg/dl)**	**mmol/mol**	**DCCT %**
Normal	< 7.8 (< 140)	<6.1 (<110)	<42	<6.0
Impaired fasting glycaemia	<7.8(<140)	≥ 6.1(≥ 110) & < 7 (<126)	42-46	6.0-6.4
Impaired glucose tolerance	≥7.8 (≥ 140)	<7.0 (<120)	42-46	6.0-6.4
Diabetes mellitus	≥11.1(≥ 200)	≥ 7.0 (≥ 126)	≥48	≥6.5

MANAGEMENT

Diabetes mellitus is a chronic disease, for which there is no known cure except in very specific situations. Management concentrates on keeping blood sugar levels as close to normal, without causing low blood sugar. This can usually being accomplished with a healthy diet, exercise, weight loss and use of appropriate medications.

The goal of treatment is HbA1c level of 6.5%, but should not be lower than that and may be set higher.[8] Attention is also paid to other health problems that may accelerate the negative effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure and lack of regular exercise.[8] Specialized foot ware is widely used to reduce the risk of ulceration, or re-ulceration, in at risk diabetic feet. Evidence for the efficacy of the risk remains equivocal, however.

Life style

People with diabetes can benefit from education about the disease and treatment, good nutrition to achieve a normal body weight and exercise, with the goal of keeping both the short term and long term blood glucose levels within acceptable bounds. In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications are recommended to control blood pressure.

Medications

Medications used to treat diabetes do so by lowering blood sugar levels. There are a number of classes of anti-diabetic medications. Some are available by mouth, such as metformin, while others are only available by injection such as GLP-1 agonists. Type-1 diabetes can only be treated with insulin, typically with a combination of regular and NPH insulin or synthetic insulin analogs.

Metformin is generally recommended as first line treatment for type-2 diabetes, as there is good evidence that it decreases mortality. It works by decreasing the liver products of glucose. Several other groups of drugs, mostly given by mouth, may also decrease blood sugar in

type-2 diabetes mellitus. These include agents that increase insulin release, agents that increase absorption of sugar from the intestines and agents that make the body more sensitive to insulin. When insulin is used in type-2 diabetes, a long acting formulation is usually adding initially, while continuing oral medications. Doses of insulin are then increase to effect. Since Cardiovascular disease is a serious complications associated with diabetes, some have recommended blood pressure levels below 130/80mmHg. A 2016 review found potential harm to treating lower than 140mmHg. Among medications that lower blood pressure, angiotensin converting enzyme inhibitors (ACEIs). Improve outcomes in those with diabetes mellitus. While the similar medications angiotensin receptor blockers (ARBs) don't. Aspirin is also recommended for people with cardiovascular complications, however routine use of aspirin has not been found to improve outcomes in uncomplicated diabetes.

COMPLICATIONS[9]

Long term complications of diabetes developed gradually. The longer you have diabetes and the less controlled your blood sugars and higher the risk of complications. Eventually, diabetes complications may be disabling are even life-threatening. possible complications include.

Cardiovascular complications

Diabetes dramatically increases the risk of cardiovascular problems including coronary artery disease with chest pain (angina), heart attack, stroke and atherosclerosis. if you have diabetes you are more likely to have heart disease or stroke.

Neuropathic complications

Excess sugar can include injure the walls of tiny blood vessels that nourish your nerves especially in your legs. this can cause tingling, numbness, burning or pain that usually begins at the tip of toes or fingers and gradually spreads upwards. Left untreated, you could lose all sense of feeling and the affected limbs.

Nephropathic complications

The kidneys contain millions of tiny blood vessel clusters (glomeruli) that filter waste from blood. Severe damage can lead to kidney failure or irreversible end stage kidney disease, which may require dialysis or kidney transplantation.

Retinopathic complications

Diabetes can damage the blood vessels of retina, potentially leading to blindness. Diabetes also increases the risk of glaucoma and cataracts.

Foot damage

Nerve damage to the feet or poor blood flow to the feet increases the risk of various foot complications. Left untreated, cuts and blisters can develop serious infections which often heal poorly.

Skin conditions

Diabetes may leave you more susceptible to skin problems including bacterial fungal infections.

CARDIOVASCULAR COMPLICATIONS BY USING SULFONYL UREAS

- **Congestive heart failure**

Second generation drugs in that class are associated with 18% higher risk of developing congestive heart failure. Diabetes is a strong predictor of incident heart failure almost 40% of patients hospitalized for acute decompensated heart failure have diabetes. In the context of T2DM, once heart failure is present the patients prognosis is poor. The risk of heart failure associated with blood glucose lowering medications may arise as an undesired effect of drugs or as a consequence or lack of effectiveness. For example, glitazones are associated with weight gain and fluid retention leading to edema, which might trigger the development of congestive heart failure in predisposing patients. Glitazones are contraindicated in patients with heart failure due to an increased risk of exacerbations. Another systemic review evaluated the risk of heart failure associated with other drug comparisons, but did not numerically summarizes the findings. The effects of blood glucose lowering drugs on the risk of heart failure in routine clinical practice, other than the risk observed for glitazones, has not been systematically reviewed and integrated.

- **Ischemic complications**

Cardiac myocytes have ATP-sensitive potassium channels associated with different forms of sulphonyl urea receptor, which have differing affinities for sulphonyl urea drugs (SUR1 on beta cells and SUR2A on cardiac muscle cells). This is relevant when considering possible detrimental effects of sulphonyl urea during myocardial ischemia.

As outlined, sulphonyl urea effect in pancreatic beta cells is closure of ATP-sensitive potassium channels. In myocardial cells, opening ATP-sensitive potassium channels helps protect the heart during myocardial ischemia. The reduction in voltage dependent calcium influx reduces myocardial contractility and oxygen demand. This mechanism is believed to be important in ischemic preconditioning which is the phenomenon of protection of myocardium from brief periods of ischemia before a prolonged infarction. Therefore, there is a theoretical risk of sulphonyl ureas with affinity for myocardial cell receptors inhibiting this process.

Evidence in humans

Speechly-Dick *et al*. looked for evidence of ischemic preconditioning and ATP-sensitive potassium channel involvement in human tissue in 1995. They prepared right atrial samples via 9 different protocols to compare the effects of a variety of factors including ATP-sensitive potassium channels and the effect of glibenclamide. They simulated ischemia and measured percentage recovery of contractile function. The effect of

preconditioning was significantly impaired by glibenclamide; 63.5% reduced to 24.8% recovery of contractile function.

- **Myocardial infarction complications**

Sulphonyl urea therapy appears to attenuate the magnitude of ST-segment elevation during an AMI, resulting in failure to meet criteria for thrombolytic therapy and a consequence leading to inappropriate withholding therapy, in this subset of diabetic patients.

Sulphonyl urea block adenosine triphosphate-sensitive potassium channels found in the pancreas and heart. Animal studies have demonstrated that the opening of these cardiac channels results in ST-segment elevation during AMI, and pretreatment with sulphonyl ureas blunts these ST-segment changes.

CONCLUSION

The present review study concludes that, sulfonyl urea increase the risk of cardiovascular events. Sulfonyl drugs must be included in treatment regimen as 3rd line agents for managing type-2 diabetes and euglycemia, traditional agents should be avoided in fact a no of oral anti diabetic drugs may actually increase the risk of myocardial infraction and cardiovascular mortality. Physicians should therefore weigh the cardiovascular risk against potential benefits when prescribing anti-diabetic medications.

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