Review on: Safe Insulin Sanitizer And Their Use For Patients With Diabetes

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Abstract- *Diabetes is a chronic (long-lasting) health condition that affects how your body turns food into energy. Your body breaks down most of the food you eat into sugar (glucose) and releases it into your bloodstream.It acts as an insulin sensitizing agent , probably through activation of adenosine monophosphate dependent kinase in liver and muscle tissue.Thiazolidinediones are medications used to manage and treat type 2 diabetes mellitus. These medications may be acting as a nuclear transcription regulator and an insulin sensitizer.Before beginning TZD therapy and periodically during treatment, patients should have liver function tests (LFT) evaluated.The Diabetes Control and Complications Trial (DCCT) is a multicenter, randomized, clinical study designed to determine whether an intensive treatment regimen directed at maintaining blood glucose concentrations as close to normal as possible will affect the appearance or progression of early vascular complications in patients with insulin-dependent diabetes mellitus (IDDM). The United Kingdom Prospective Diabetes Study (UKPDS) was conceived to explore these uncertainties and provide clearer guidelines for the management of type 2 diabetes.The NIDDK-sponsored Diabetes Prevention Program (DPP) and ongoing DPP Outcomes Study (DPPOS) are major studies that changed the way people approach type 2 diabetes prevention worldwide. The DPP showed that people who are at high risk for type 2 diabetes can prevent or delay the disease by losing a modest amount of weight through lifestyle changes (dietary changes and increased physical activity). Taking metformin, a safe and effective generic medicine to treat diabetes, was also found to prevent the disease, though to a lesser degree.*

I. INTRODUCTION

Diabetes is a disease that occurs when your blood glucose, also called blood sugar,is too high. Blood glucose is your main source of energy and comes from the food you eat. Insulin, a hormone made by the pancreas, helps glucose from food get into your cells to be used for energy. Sometimes your body doesn't make enough—or any—insulin or doesn't use insulin well. Glucose then stays in your blood and doesn't reach your cells.

Types Of Diabetes:

1. **Type 1 Diabetes:**

when the body loses the ability to make insulin or can only make a very small amount of insulin. Type 1 diabetes is usually caused by an autoimmune process, and your body's immune system mistakenly destroys the insulin-producing cells. About 10% of individuals with diabetes have type 1 diabetes.

Diagnosis

Diagnostic tests include:

1. Glycated hemoglobin (A1C) test. This blood test indicates your average blood sugar level for the past two to three months. It measures the percentage of blood sugar attached to the oxygen-carrying protein in red blood cells (hemoglobin). The higher your blood sugar levels, the more hemoglobin you'll have with sugar attached. An A1C level of 6.5 percent or higher on two separate tests indicates diabetes.
2. Random blood sugar test A blood sample will be taken at a random time and may be confirmed by repeat testing. Blood sugar values are expressed in milligrams per deciliter (mg/dL) or millimoles per liter (mmol/L). Regardless of when you last ate, a random blood sugar level of 200 mg/dL (11.1 mmol/L) or higher suggests diabetes, especially when coupled with any of the signs and symptoms of diabetes, such as frequent urination and extreme thirst.
3. Fasting blood sugar test A blood sample will be taken after an overnight fast. A fasting blood sugar level less than 100 mg/dL (5.6 mmol/L) is normal. A fasting blood sugar level from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) is considered prediabetes. If it's 126 mg/dL (7 mmol/L) or higher on two separate tests, you have diabetes.

Treatment

Treatment for type 1 diabetes includes:

1. Taking insulin

2. Carbohydrate, fat and protein counting
3. Frequent blood sugar monitoring
4. Eating healthy foods
5. Exercising regularly and maintaining a healthy weight

Insulin and other medications

Type 1 diabetes needs lifelong insulin therapy.

Types of insulin are many and include:

- Short-acting (regular) insulin
- Rapid-acting insulin
- Intermediate-acting (NPH) insulin
- Long-acting insulin

2. **Type 2 Diabetes:**

caused by a dual defect of resistance to the action of insulin combined with an inability to make enough insulin to overcome the resistance. Type 2 diabetes is the most common form of diabetes and represents 80% to 90% of diabetes worldwide.

Diagnosis

Type 2 diabetes is usually diagnosed using the glycated hemoglobin (A1C) test. This blood test indicates your average blood sugar level for the past two to three months. Results are interpreted as follows:

- Below 5.7% is normal.
- 5.7% to 6.4% is diagnosed as prediabetes.
- 6.5% or higher on two separate tests indicates diabetes.

Random blood sugar test. Blood sugar values are expressed in milligrams of sugar per deciliter (mg/dL) or millimoles of sugar per liter (mmol/L) of blood. Regardless of when you last ate, a level of 200 mg/dL (11.1 mmol/L) or higher suggests diabetes, especially if you also have signs and symptoms of diabetes, such as frequent urination and extreme thirst.

Fasting blood sugar test. A blood sample is taken after an overnight fast. Results are interpreted as follows:

- Less than 100 mg/dL (5.6 mmol/L) is normal.
- 100 to 125 mg/dL (5.6 to 6.9 mmol/L) is diagnosed as prediabetes.
- 126 mg/dL (7 mmol/L) or higher on two separate tests is diagnosed as diabetes.

Oral glucose tolerance test. This test is less commonly used than the others, except during pregnancy. You'll need to fast overnight and then drink a sugary liquid at the doctor's office. Blood sugar levels are tested periodically for the next two hours. Results are interpreted as follows:

- Less than 140 mg/dL (7.8 mmol/L) is normal.
- 140 to 199 mg/dL (7.8 mmol/L and 11.0 mmol/L) is diagnosed as prediabetes.
- 200 mg/dL (11.1 mmol/L) or higher after two hours suggests diabetes.

Screening. The American Diabetes Association recommends routine screening with diagnostic tests for type 2 diabetes in all adults age 45 or older and in the following groups:

- People younger than 45 who are overweight or obese and have one or more risk factors associated with diabetes
- Women who have had gestational diabetes
- People who have been diagnosed with prediabetes
- Children who are overweight or obese and who have a family history of type 2 diabetes or other risk factors

Treatment

Management of type 2 diabetes includes:

- Healthy eating
- Regular exercise
- Weight loss
- Possibly, diabetes medication or insulin therapy
- Blood sugar monitoring

These are pills and non-insulin medicines routinely used to treat type 2 diabetes:

1. Metformin:
   Pills that reduce sugar production from the liver
2. Thiazolidinediones (glitazones):
   Pills that enhance sugar removal from the blood stream
3. Insulin releasing pills (secretagogues):
   Pills that increase insulin release from the pancreas
4. Starch blockers:
   Pills that slow starch (sugar) absorption from the gut
5. Incretin based therapies:
   Pills and injections that reduce sugar production in the liver and slow the absorption of food
6. Non-insulin Treatment for Type 2 Diabetes – Amylin analogs:
   Injections that reduce sugar production in the liver and slow the absorption of food

Medication and therapies : Insulin replacement is known as insulin therapy.

Type 2 diabetes is caused by two problems:

1. Resistance to the action of insulin
2. An inability to make enough insulin to overcome that resistance

So, type 2 diabetes treatment focuses on ways to control the blood sugar, lower the insulin resistance, and increase insulin levels. Every treatment plan usually starts with a healthy diet, losing extra weight and staying active. If this doesn't keep the blood sugar on target, then your provider will prescribe medicine.

Type 2 Non insulin dependent therapy :

Pramlintide is an injected medicine for people with diabetes.

In type 1 diabetes, Pramlintide can be taken in addition to insulin to help control mealtime blood sugars.

3. **Other Types of Diabetes:**

a miscellaneous category that includes unusual or rare inherited or acquired causes of diabetes. This represents the minority of people with diabetes. Other is a "catch all" category that refers to other specific and unusual forms of diabetes. Traditional examples are single genetic defects (also known as Maturity Onset Diabetes Of the Young or MODY), cystic fibrosis, hemochromatosis, surgical causes and drug causes.Currently, MODY accounts for less than 5% of individuals diagnosed with diabetes. If you have MODY, characteristically three or more generations and multiple family members have diabetes. Also the diabetes is diagnosed early in life and has no autoimmune basis. Some forms of MODY can be treated with diet alone, while other forms of MODY require pills or insulin therapy. With increased research into the genetic causes of diabetes, and the availability of the diagnostic tests, the diagnosis of families' who have a single genetic defect or MODY will increase

4. Gestational Diabetes:

diabetes diagnosed during pregnancy. The Center for Disease control estimates that up to 9.2% of pregnant women will develop gestational diabetes. Pregnancy hormones can interfere with the way insulin works in the mother's body which can lead to elevated blood glucose levels during pregnancy. Women are typically screened for gestational diabetes at 24-28 weeks of pregnancy, however women who have risk factors may be screened earlier. Risk factors for developing gestational diabetes include having a family history of diabetes, being overweight, or over 25 years old. Women who are black, Hispanic, American Indian or Asian

are more likely to develop gestational diabetes. Blood glucose control during pregnancy is critical as elevated maternal glucose levels can lead to pregnancy complications and poses risks to the health of the baby. Gestational diabetes is likely to recur during subsequent pregnancies.

Gestational diabetes requires specialized treatment for the rest of the pregnancy. After the pregnancy is over, most women will have normal blood sugars again; however, up to 20-50 % will develop type 2 diabetes within 10 years. Regular screening is recommended. The best prevention strategy is to eat healthy, control weight, and stay active.

Insulin Sensitizers:

Thiazolidinediones decrease resistance to insulin.

TZDs work to lower your blood sugar by increasing the muscle, fat and liver's sensitivity to insulin.

Thiazolidinediones (glitazones: rosiglitazone and pioglitazone)

Thiazolidinediones (TZDs) work to lower your blood sugar by increasing the muscle, fat and liver's sensitivity to insulin. TZDs are referred to as "insulin sensitizers" and also are blood sugar normalizing or euglycemics, (drugs that help return the blood sugar to the normal range without the risk of low blood sugars.) TZDs take a while to begin working (several weeks); so don't stop the pill if you don't notice your blood sugar responding right away.The main side effects are weight gain and fluid retention (you may notice your ankles swelling) and anemia. Fluid retention is most common in individuals who are also taking insulin secretagogues and insulin, and has been linked with an increased rate of congestive heart failure. Thiazolidinediones increase the amount of certain fat particles, called LDL. Women taking these medications have a greater chance of bone fractures.

One of the thiazolidinediones, rosiglitazone, Avandia®, is reported to increase heart disease. The United States FDA has limited the use of this medication to those individuals already using it, and to those who have failed therapy with other medications, or who decline to take pioglitazone. Some European countries (Germany and France) have withdrawn pioglitizone, Actos®, because of concern about an increased risk of bladder cancer.You shouldn't take a thizolidinedione if you have congestive heart failure, or significant liver or kidney problems. If you are female or have an increased risk of heart disease, discuss with you provider whether these are appropriate medications for youIn short, thiazolidinediones decrease insulin resistance.

Indication : The use of thiazolidinediones, also called "glitazones," in managing type 2 diabetes can help with glycemic control and insulin resistance. There are two thiazolidinediones, rosiglitazone, and pioglitazone, currently approved by the FDA as monotherapy or combined with metformin or sulfonylureas to manage type 2 diabetes mellitus. These medications should be in conjunction with lifestyle modifications such as diet, exercise, and weight reduction. Thiazolidinediones may also be used to treat polycystic ovarian syndrome, as these may lead to improved endothelial function, improved ovulation, and reduction of insulin resistance. Pioglitazone specifically reduces hepatic fat and may improve liver fibrosis in patients with nonalcoholic steatohepatitis (NASH); however, additional variables and risks require assessment in NASH patients.The most significant advantage of TZDs is that they do not cause hypoglycemia as monotherapy and are not contraindicated in patients with renal disease.[7,8,9]

Mechanism :

Thiazolidinediones (TZDs) are insulin sensitizers that act on intracellular metabolic pathways to enhance insulin action and increase insulin sensitivity in critical tissues. TZDs also increase adiponectin levels, decrease hepatic gluconeogenesis, and increase insulin-dependent glucose uptake in muscle and fat. Adiponectin, a cytokine secreted by fat tissue, increases insulin sensitivity, and fatty acid oxidation increases with TZD therapy.[7]

TZDs function by regulating gene expression through binding to peroxisome proliferator-activated receptor-gamma (PPAR-gamma), a nuclear transcription regulator. Peroxisome proliferator-activated receptors (PPARs) are a family of ligand-activated transcription factors of nuclear hormone receptors that regulate energy homeostasis. The genes activated by the PPAR-gamma subtype are present in muscle, fat, and liver, regulating glucose metabolism, fatty acid storage, and adipocyte differentiation.[12] The binding of TZD will induce a conformational change to alter gene expression of numerous pathways involved in metabolism regulation, including lipoprotein lipase, glucokinase, fatty acyl-CoA synthase, and others.[11] PPAR-gamma agonists improve insulin resistance by increasing adiponectin, GLUT4 expression, and opposing the effect of TNF-alpha in adipocytes. Increased GLUT 4 expression will increase glucose uptake in adipocytes and skeletal muscle cells in response to insulin.[12]

In addition to their function in glycemic control and improvement of insulin resistance, TZDs potentially have anti-inflammatory and anti-cancer properties. There is evidence that TZDs may slow the progression of medial intimal thickening and decrease coronary intimal hyperplasia. Research has shown additional beneficial effects on endothelial function, atherogenesis, fibrinolysis, and ovarian steroidogenesis. Some studies demonstrated that activation of PPAR-gamma receptors could induce cancer cell apoptosis. However, these mechanisms are still under investigation due to conflicting studies and possible confounders.[7]

The most common side effects are:

1) Fluid retention
2) Weight gain
3) Anemia
4) Increased LDL
5) Congestive heart failure
6) Increase risk of heart disease (Avandia®)
7) Increased bone fractures in women

Diabetes Control and Complications Trial (DCCT):

This landmark trial showed the superiority of intensive blood glucose management in controlling blood glucose and reducing the incidence of complications in type 1 diabetes.

The DCCT demonstrated that intensive therapy was better than the conventional therapy used at that time. Conventional therapy relied on one or two fixed doses of insulin that did not vary with meals.

DCCT also demonstrated that maintaining an HbA1c value of around 7% reduced the risk of long-term eye, kidney and nerve complications by approximately 60%. The Diabetes Control and Complications Trial (DCCT) is a multicenter, randomized, clinical study designed to determine whether an intensive treatment regimen directed at maintaining blood glucose concentrations as close to normal as possible will affect the appearance or progression of early vascular complications in patients with insulin-dependent diabetes mellitus (IDDM). We present the baseline characteristics and 1-yr results of the initial cohort of 278 subjects randomized in phase II of the trial, a phase designed to answer several feasibility questions before initiating a full-scale trial. During phase II, recruitment was completed on schedule. The 191 adults and 87 adolescents were randomized either to standard treatment (90 adults and 42 adolescents), designed to approximate conventional diabetes treatment, or to experimental treatment (101 adults and 45 adolescents), designed to achieve near-normal blood glucose and HbA1c concentrations. With few exceptions, baseline demographic, ophthalmologic, renal, and other medical characteristics were evenly distributed by randomization between the two treatment groups in both age strata. Glycemic control at baseline, as assessed by HbA1c concentrations and by blood glucose profiles, was comparable between the treatment groups in both age strata. The treatment strategies employed produced statistically significant and clinically meaningful differences in HbA1c concentrations and blood glucose profiles between the experimental- and standard-group subjects for both adults and adolescents. These differences were maintained throughout the feasibility phase. Except for an increased incidence of hypoglycemia in the experimental group, the two treatment regimens maintained or improved the clinical well-being of subjects in both groups. Adherence and completeness of follow-up were excellent (greater than 95%), and the methods employed to measure biochemical and pathologic characteristics of IDDM proved to be reliable, reproducible, and precise. The feasibility phase of the DCCT demonstrated that a complex multicenter, randomized study of the relationship between diabetes control and complications can be performed. The full-scale, long-term trial therefore has been initiated.

II. DISCUSSION

Review the importance of collaboration and coordination among the interprofessional team and how it can enhance patient care with thiazolidinedione therapy to improve patient outcomes for patients who have diabetes.The DCCT showed that people with type 1 diabetes who kept their blood glucose levels as close to normal as safely possible with intensive diabetes treatment as early as possible .

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