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Review on Diabetics and Anti-Diabetic Drugs

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ABSTRACT

A very complex illness mainly caused by insulin deficit affecting world's most of the population is Diabetes.

The main types of the Diabetes are Insulin depended diabetes mellitus (IDDM)-Type 1 or Non-insulin depended diabetes mellitus (NIDDM)-Type 2. Also Gestational diabetes (GDM) is other type observed mainly in the women.

Type 1 diabetes mostly affects young people (known as juvenile-diabetes mellitus) and develops ketoacidosis where insulin therapy is needed but is not taken. Insensibility to insulin is Type 2 which could be the result of these factors: secretion of abnormal insulin, manifestation and activity of insulin antagonists or damage of aimed tissues. Gestational diabetes (GDM) is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy.

There are wide groups of drugs are available for the treatment of diabetes. The present review found 78.3% patient adherence to antidiabetic drug therapy. Although different prevalence of adherence were seen for each factor studied, the association was not statistically significant. For the specific treatment health providers assess adherence of patients to drug therapy in the event of poor glucose control and presumed failure of the prescribed therapeutic regimen. The review snapshots the type of diabetes and the treatment of therein.

Key-words: Diabetics, Insulin, Diabetes Mellitus

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INTRODUCTION:

The massive population of mankind lives with diagnosis of diabetes mellitus. It is a very complex illness mainly caused by insulin deficit and results many metabolic changes in metabolism of carbohydrates, lipids and proteins.

Deficit of insulin causes several pathological changes:

- Glucose can't reverse into glucose-5-phospha-stimulate glycogenolysis, inhibit glycogenesis
- Inhibits metabolism of glucose in pentose-phosphat cycle.
- Decrease glycolysis.
- Those changes increase blood sugar value and also:
- Inhibited lipogenesis, stimulated lipolysis, which produce more acetil-CoA and
- Inhibited Krebs cycle and proteins synthesis.

WHO classified diabetes mellitus as a:

- Insulin depended diabetes mellitus (IDDM)-Type 1 or
- Non-insulin depended diabetes mellitus (NIDDM)-Type 2.

Type 1 diabetes mostly affects young people (known as juvenile-diabetes mellitus) and develops ketoacidosis where insulin therapy is needed but is not taken.

Insulin deficit as a cause of hyperglycemia, relate to the disturb function of Langerhans islets (damaged synthesis, storage or secretion of insulin). The disturbed excretion of insulin could be the result of damaged gluco receptors, but usually is a result of multiple etiological factors (genetic factors, virus infections or autoimmune process). In type 1 patient there are two antibodies against 6-cells in circulation; one that attach to cytoplasm's compounds, other attaches to membrane.

Insensibility to insulin (type 2) could be the result of these factors: secretion of abnormal insulin, manifestation and activity of insulin antagonists or damage of aimed tissues. If the products of 8-cells are abnormal it is a consequence of inherited disturbance. The insulin antagonists are hormones with opposite activity than insulin. When they increase in circulation (hyper secretion) provoke hyperglycemia and then the higher insulin secretion. After some time, the B-cells are exhausted and result is their permanent damage.[1]

DIABETES MELLITUS:

Diabetes mellitus, often simply referred to as diabetes, is a group of metabolic diseases in which a person has high blood sugar either because the body does not produce enough insulin or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical

Symptoms of diabetes include:

- Excessive thirst (polydipsia)
- Excessive urination (polyurea)
- Unintentional weight loss
- Increase appetite (polyphagia)

Classification:

There are three main types of diabetes mellitus:

• **Type 1 diabetes(IDDM)**: results from the body's failure to produce insulin, and presently requires the person to inject insulin. (Also referred to as insulin-dependent diabetes mellitus, IDDM for short, and juvenile diabetes.)

• **Type 2 diabetes (NIDDM):** results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. (Formerly referred to as non-insulin-dependent diabetes mellitus, NIDDM for short, and adult-onset diabetes.)

• **Gestational diabetes(GDM):** is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. It may precede development of type 2 DM.

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes.

As of 2000 at least 171 million people worldwide have diabetes, or 2.8% of the population.[2] Type 2 diabetes is by far the most common, affecting 90 to 95% of the U.S. diabetes population.

Most cases of diabetes mellitus fall into three broad categories; **Type 1.Type 2 and GestationalDiabetes.**A few other types are described. The term diabetes, without qualification, usually refers to diabetes mellitus. The rare disease diabetes insipidus has similar symptoms as diabetes mellitus, but without disturbances in the sugar metabolism (insipidus*meaning* "without taste" in Latin).

Table 1: Comparison of Type 1 and 2 diabetes:

	Type 1	Type 2
Ketoacidosis	Common	Rare
Autoantibodies	Usually present	Absent
Endogenous insulin	Low or absent	Normal, decreased or increased [4]
Concordance in identical twins	50%	90%
Prevalence	Less prevalent	More prevalent -90 to 95% ofU.S diabetics [3]

The term "type 1 diabetes" has replaced several former terms, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes mellitus (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and non-insulin-dependent diabetes mellitus (NIDDM). Beyond these two types, there is no agreed-upon standard nomenclature. Various sources have defined "type 3 diabetes" as: gestational diabetes.[6]

Diabetes mellitus type 1

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to insulin deficiency. This type of diabetes can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune mediated nature, where beta cell loss is a T-cell mediated autoimmune attack.

There is no known preventive measure against type 1 diabetes, which causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Type 1 diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of the diabetes cases in children.

Common symptoms of type l diabetes include

- ✓ Increased urination (sometimes as often as every hour)
- ✓ Unusual weight loss or gain
- ✓ Fatigue or tiredness
- ✓ Nausea, perhaps vomiting
- ✓ Blurred vision
- ✓ In women, frequent vaginal infections
- ✓ In men and women, yeast infections (thrush) « Dry mouth
- ✓ Slow-healing sores or cuts
- ✓ Itching skin, especially in the groin or vaginal area.[5]

Diabetes mellitus type 2

Type 2 diabetes mellitus is characterized by insulin resistance which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor.In the early stage of type 2 diabetes, the predominant abnormality is reduced insulin sensitivity. At this stage hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver.

Causes of Type 2 Diabetes:

In type 2 diabetes, either the pancreas does not make enough insulin and/or the body does not use it properly. No one knows the exact cause of type 2 diabetes, but it's more likely to occur in people who:

- Are over 40 years of age
- Are overweight
- Have a family history of diabetes
- Developed gestational diabetes during a pregnancy
- Have given birth to a baby that is more than 4 kg (9 ibs)
- Have high blood pressure
- Have high cholesterol
- Have IGT or impaired fasting glucose
- Are of Aboriginal, Hispanic, Asian, South Asian, or South African descent

Symptoms and Complications of Type 2 Diabetes

People with type 2 diabetes may not have symptoms for years or decades, but as the disease progresses and blood sugar levels rise, symptoms develop. **People** with type 2 diabetes may have the following signs and symptoms:

- Blurred sight
- Decreased sensation or numbness in the hands and feet
- Dry, itchy skin
- Frequent bladder and vaginal infections » frequent need to urinate
- Increased thirst and hunger
- Male impotence (erectile dysfunction)
- Slow healing of cuts or sores
- tiredness

Unfortunately, many people with type 2 diabetes go undiagnosed for several years and are not diagnosed until they go to the doctor with symptoms or **complications** of diabetes.[5]

Common symptoms of type 2 diabetes

Type 2 diabetes - also known as type 2 diabetes mellitus - often doesn't cause symptoms and is identified on routine screening. When type 2 diabetes does cause symptoms these can include;

- Excessive thirst and appetite
- Increased urination (sometimes as often as every hour), especially at night
- Unusual weight loss or gain
- Fatigue or extreme tiredness

Other symptoms, not experienced by everyone, include:

- Blurred vision
- In women, frequent vaginal infections
- In men and women, yeast infections (thrush)
- Dry mouth
- Slow-healing sores or cuts
- Itching skin, especially in the groin or vaginal area.[5]

GESTATIONAL DIABETIS MELLITUS:

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2%-5% of all pregnancies and may improve or disappear after delivery. Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy. About 20%-50% of affected women develop type 2 diabetes later in life.A 2008 study completed in the U.S. found that the number of American women entering pregnancy with preexisting diabetes is increasing. In fact the rate of diabetes in expectant mothers has more than doubled in the past 6 years. This is particularly problematic as diabetes raises the risk of complications during pregnancy, as well as increasing the potential that the children of diabetic mothers will also become diabetic in the future.

Drugs used in diabetes and their basic pharmacology:

With the introduction of insulin, oral anti-diabetic drugs and antibiotics, diabetes is no longer a dreadful disease, and with proper management with diet, drug and exercise a diabetic can enjoy an almost normal life. The etiology of this condition however is still obscure although it definitely has a hereditary tendency[9].

Insulin Treatment:

Insulin is the mainstay for treatment of diabetes, virtually all type-I and many type-II diabetic patients. Its mode of action can be described as follows-

- Insulin decreases the intracellular concentration of cAMP by inhibiting enzyme adenylyl cyclase and stimulating phosphodiesterase. So protein kinase is not activated due to absence of cAMP and consequently break down of glycogen is inhibited.
- Insulin also reduces the sensitivity of protein kinase to cAMP and giycogen synthesis is enhanced.
- Insulin enhances facilitated diffusion of glucose and activates transport of amino acids to cells.
- Insulin promotes K^+ and Mg^{++} uptake into cells which may act as "second messenger" to mediate the actions of insulin.
- Insulin can be extInsulin can be extracted from porcine and bovine pancreases. Increasingly, 'human' insulin (Humulin) is used, usually made by recombinant DNA technology. It is destroyed in the gastrointestinal tract, and must be given parenterally, usually subscutaneously, but intravenously or occasionally, intramuscularly in emergencies[9].

Diagnosis

If diabetes is suspected it is important to see a doctor promptly so that an accurate diagnosis can be made and appropriate treatment given. Early diagnosis and treatment will help to prevent diabetes-related complications.

To assist with diagnosis, blood tests are used to measure the glucose levels in the blood. These include:

Fasting blood glucose test:

A sample of blood is taken to measure the blood glucose levels in the blood after the person has not eaten for several hours. This is usually performed in the morning, before breakfast. It is the most common blood test used to assist with diagnosis,

Random blood glucose-test:

A sample of blood is taken to measure the glucose levels in the blood - regardless of when the person last ate.

The acceptable range for glucose in the blood is 4.0 – 8.0A mmol/L (mmol of glucose per litre of blood) before a meal. A diagnosis of diabetes can usually be made if there are classical symptoms of the condition and blood glucose levels of greater than 11mmol/L for a random blood glucose test, or greater than 7mmol for a fasting blood glucose test.

Treatment:

While diabetes cannot be cured, it can be controlled. The aim of treatment is to maintain healthy blood glucose levels (ie: between 4.0 mmol/L and 8.0 mmoVL) and to prevent diabetic complications. This will normally involve balancing lifestyle factors (eg: diet and exercise) and medications.

In order for a person to effectively control the diabetes, it is important that they are treated and monitored by a doctor. Usually this is the person's GP, however other healthcare professionals will be included in a wider "diabetes management" team to assist with ongoing education, monitoring and treatment. This team may include a diabetes specialist (endocrinologist), diabetes nurse educator, dietitian, foot care specialist (podiatrist) and an eye specialist (ophthalmologist).

LIFESTYLE FACTORS:

Diet

Generally it is recommended that foods containing refined sugars be avoided. This includes foods such as chocolate, jam, soft drinks, sweet biscuits, cakes,, pastries and some fruit juices. Natural carbohydrates, which can be converted to energy, are recommended. This includes foods such as fruit, vegetables, whole meal bread and cereals.

The diet should also be low in fat and high in dietary fibre. Alcohol contains a lot of sugar so intake should be minimised. Having a regular eating pattern is also important as this helps to keep blood glucose levels balanced. In some cases, having snacks between meals may be recommended. Again this helps to balance blood glucose levels.

Exercise

Regular exercise is important in maintaining balanced blood glucose levels. Exercise also helps to maintain a healthy body weight and control blood pressure and blood cholesterol levels. This in turn helps to reduce the risk of related health conditions such as cardio-vascular disease (heart attacks and strokes).

It should be remembered however that excessive and/or prolonged exercise can cause the blood glucose levels to drop too low. It is therefore recommended that any exercise undertaken is regular and moderate.

MEDICATIONS:

Tablets

People with Type 2 diabetes may not be able to adequately control their blood glucose levels through diet, exercise and lifestyle changes alone. Therefore, in many cases diabetic tablets arerequired. There are a variety of tablets available, which work in different ways. These include:

Tablets to increase insulin output from the pancreas eg: Glipizide, Glibenclamide.

Insulin

In people with Type 1 diabetes and in some people with Type 2 diabetes, insulin injections are required. There are a number of different types of insulin available that vary in the duration of time they are effective. Some are short-acting; meaning they are absorbed quickly by the body and are effective for a short period of time. Others are long-acting; meaning they are absorbed more slowly by the body and are effective for a longer period of time. Often a combination of different types of insulin is required.

Blood Glucose Testing ("Blood Sugars")

To enable blood glucose levels to be tested, a droplet of blood is obtained from a small finger prick test and is measured on a special testing strip. The results will help to determine how much medication is required, how much exercise can be undertaken and what foods should be eaten. This simple home test needs to be performed regularly, in some cases up to several times per day. It is important to follow the guidelines given by the treating doctor as to how often they should be done.

ACUTE COMPLICATIONS:

Hypoglycaemia

This is a situation where there are abnormally low levels of glucose in the blood. It can occur when excessive amounts of diabetic medications have been given, when not enough food has been eaten, or when too much exercise has been undertaken.

Because cells rely on glucose for fuel in order to function, hypoglycaemia can affect the proper functioning of the cells - particularly the cells in the nervous system. This can lead to initial symptoms such as nervousness, dizziness, weakness, confusion, blurred vision and tremors.

Ketoacidosis

Some people with Type 1 diabetes can develop a complication called ketoacidosis, where the blood glucose levels become very high andassociated dehydration is severe. This cause substances called ketones to build up in the blood and make the blood acidic. This in turn can produce a headache and drowsiness and may cause the person to lapse into semi-consciousness. The person may also have an acetone smell on their breath - a sign that ketones are present in the blood. This situation requires urgent treatment in hospital.

CHRONIC COMPLICATIONS:

Chronic complications essentially occur as a result of damage to blood vessels. Diabetes can cause the small blood vessels to weaken and break, and the large blood vessels to harden, narrow and become blocked with fatty deposits (a process known as atheroscerlosis). The resultant poor circulation, compounded by the fact that people with diabetes are more prone to infections, can lead to various complication.

Circulatory problems

Atherosclerosis and damage to the large blood vessels can impede the circulation of blood around the body - particularly affecting to the heart, brain and lower limbs. This is compounded by the fact that people with diabetes are more prone to high blood pressure and high blood cholesterol levels.

When circulation to the heart is affected (cardiovascular disease) there is an increased risk of angina and heart attack.

When circulation to the brain is affected (cerebrovascular disease) there is an increased risk of stroke.

Nerves

Diabetes can damage the nerves - particularly the nerves of the lower legs and sometimes the hands. The nerve damage can cause symptoms such as decreased sensation, numbness, burning, tingling and pain in the affected area. When damage to the nerves is caused by diabetes it is referred to as diabetic neuropathy.

Medications to help relieve the pain caused by diabetic neuropathy may be given. Medications commonly used in the treatment of epilepsy and depression are sometimes used for this purpose.

Eyes

In people with diabetes, the many tiny blood vessels in the retina can weaken or break. This can affect the retina's ability to work properly and can cause blood to leak into the eyeball, clouding the vision. This process is known as diabetic retinopathy.

Diabetic retinopathy and cataracts do not tend to occur until diabetes has been present for many years. It is therefore recommended that people with diabetes are screened for these conditions by having their eyes checked every 1-2 years by an eye specialist (ophthalmologist). This allows for early detection and appropriate treatment.

Kidneys

The kidneys filter wastes from the blood and excrete them in the urine. When the delicate filtering structures and blood vessels within the kidneys are damaged, the kidneys are unable tofunction effectively and kidney failure can occur. When this is caused by diabetes it is referred to as diabetic nephropathy.

Diabetes is one of the leading causes of kidney failure in New Zealand. Approximately 40% of people with Type 1 and up to 10% of people with Type 2 will eventually develop kidney failure. Severe kidney failure may need to be treated with dialysis and in some cases a kidney transplant (sometimes combined with a pancreas transplant) may be required.

Teethandgum problems

People with diabetes are at greater risk of developing infections of the teeth and gums. It is therefore important that particular care is paid to the health of teeth and gums. It is also recommended that people with diabetes have regular checkups with their dentist.

Antidiabetic Drugs

Definition

Antidiabetic drugs are medicines that help control blood sugar levels in people with diabetes melHlus (sugar diabetes).

Purpose

Diabetes may be divided into type I and type II, formerly termed juvenile onset or insulin-dependent, and maturity onset or non-insulin-dependent. Type I is caused by a deficiency of insulin production, while type II is characterized by insulin resistance. Treatment of type I diabetes is limited to insulin replacement, while type II diabetes is treatable by a number of therapeutic approaches.

Description

Antidiabetic drugs may be subdivided into six groups: Insulin, Sulfonylureas, Alpha-Glucosidase Inhibitors, Biguanides, Metaglinides, and Thiazolidinedione:

Insulin (Humulin, Novolin) is the hormone responsible for glucose utilization. It is effective in both types of diabetes, since, even in insulin resistance, some sensitivity remains and thecondition can be treated with larger doses of insulin. Most insulins are now produced byrecombinant DNA techniques, and are chemically identical to natural human insulin. Isophane insulin suspension, insulin zinc suspension, and other formulations are intended to extend the duration of insulin action, and permit glucose control over longer periods of time. In 2003, research suggested that inhaled forms of insulin offered advantages to injected types, but further study was needed on its long-term effects on the lungs and cost-effectiveness.

Sulfonylureas (chlorpropamide [Diabinese], tolazamide [Tolinase], glipizide [Glucotrol] and others) act by increasing insulin release from the beta cells of the pancrease. Glimepiride (Amaryl), a member of this class, appears to have a useful secondary action in increasing insulin sensitivity in peripheral cells.

Metformin (Glucophage) is the only available member of the biguanide class. Metformin decreases hepatic (liver) glucose production, decreases intestinal absorption of glucose and increases peripheral glucose uptake and use. Metformin may be used as monotherapy (alone), or in combination therapy with a sulfonylurea.

Insulin:

The greatest short term risk of insulin is hypoglycemia, which may be the result of either a direct overdose or an imbalance between insulin injection and level of exercise and diet. This also may occur in the presence of other conditions which reduce the glucose load, such as illness with vomiting and diarrhea. Treatment is with glucose in the form of glucose tablets or liquid, although severe cases may require intravenous therapy. Allergic reactions and skin reactions also may occur. Insulin is classified as category B in pregnancy and is considered the drug of choice for glucose control during pregnancy. Insulin glargine (Lantus), an insulin analog which is suitable for once-daily dosing, is classified as category C, because there have been reported changes in the hearts of newborns in animal studies of this drug.

Sulonylureas:

AH sulfonylurea drugs may cause hypoglycemia. Most patients become resistant to these drugs over time, and may require either dose adjustments or a switch to insulin. The list of adverse reactions is extensive, and includes central nervous system problems and skin reactions, among others. Hematologic reactions, although rare, may be severe and include aplastic anemia and hemolytic anemia.The administration of oral hypoglycemic drugs has been associated with increased cardiovascular mortality as compared with treatment with diet alone or diet plus insulin.

Alpha-glucosidase:

Alpha-glucosidase inhibitors are generally well tolerated, and do not cause hypoglycemia. The most common adverse effects are gastrointestinal problems, including flatulence, diarrhea, and abdominalpain. These drugs are classified as category B in pregnancy. Although there is no evidence that the drugs are harmful to the fetus, it is important that rigid blood glucose control be maintained during pregnancy, and pregnant women should be switched to insulin. Alpha-glucosidase inhibitors may be excreted in small amounts in breast milk, and it is recommended that the drugs not be administered to nursing mothers.

Metformin:

Metformin causes gastrointestinal (stomach and digestive) reactions in about a third of patients. A rare, but very serious, reaction to metformin is lactic acidosis, which is fatal in about 50% of cases. Lactic acidosis occurs in patients with multiple medical problems, including renal (kidney-related) insufficiency. The risk may be reduced with careful renal monitoring, and careful dose adjustments to metformin. Metformin is category B during pregnancy. There have been no carefully controlled studies of the drug during pregnancy, but there is no evidence of fetal harm from animal studies. It is important that rigid blood glucose control be maintained during pregnancy, and pregnant women should be switched to

insulin. Animal studies show that metformin is excreted in milk. It is recommended that metformin not be administered to nursing mothers.

Meglitinides:

These drugs are generally well tolerated, with an adverse event profile similar to placebo. The drugs are classified as category C during pregnancy, based on fetal abnormalities in rabbits given about 40 times the normal human dose.

Thiazolidinedione:

These drugs were generally well tolerated in early trials, but they are structurally related to an earlier drug, troglitazone, which was associated with liver function problems. However, in 2003, researchers reported that these drugs, which are used by more than 6 million Americans, may lead to serious side effects. Research showed that after one to 16 months of therapy with pioglitazone or rosiglitazone, some patients developed serious edema and signs of congestive heart failure. Additional studies were underway in late 2003 to determine how these drugs caused fluid build-up and if the symptoms occurred more frequently in certain age groups. The mean age of patients in the 2003 study was 69 years.[15]

COMPARISON:

The following table compares some common anti-diabetic agents, generalizing classes although there may be substantial variation in individual drugs of each class;

Table2:Comparison of Anti-Diabetic Agents

Agent	Mechanism	Site of action	Main advantages	Main side effects
Sulfonylureas	Stimulating insulin production byinhibitingthe KATP channel	Pancreatic betacells	EffectiveInexpensive	Hypoglycemia, Weight gain
Metformin	Decreases insulinresistance	Liver	May resultin mild weight lossDoes notcausehypoglycemia	GL symptoms, including diarrhea, nausea, abdominal pain, Lactic acidosis, Vitamin B12Deficiency, Metallic taste.
Acarbose	Reduces intestinal glucose absorption	GI tract	Low risk	Gl symptoms,including diarrhea,abdominal cramping, flatulence
Thiazolidinediones	Reduce insulinresistance byactivating PPAR-Y	Fat, muscle		Hepatoxicity

Absolute contraindication to liver transplantation:

1. Diabetes mellitus is common in patients with cirrhosis; patients with DM undergoing liver transplantation often have many other co-morbid illnesses including obesity, coronary artery disease (CAD), autonomic neuropathy, gastro paresis, and nephropathy.

2. Long-term survival of patients with diabetes mellitus (DM) is significantly lower and morbidity higher when compared to non-diabetics mainly because of cardiovascular complications, infections, and renal failure.

3. Obesity, CAD, and renal failure are confounding factors that result hi poor patient survival.

4. Patients with DM should undergo carefiil cardiovascular diagnostic work up, including routine coronary arteriogram, and necessary interventions before liver transplantation. This is especially important in those over 50 years old, and in those with retinopathy, nephropathy, and neuropathy.

5. Patients with coronary artery disease that is not amenable to surgery or stents, and those with impaired left ventricular function, should not be considered for liver transplantation. Other relative or absolute contraindications are those with proteinura and renal failure who are not candidates for combined liver/kidney transplantation, those with severe gastroparesis, especially when it is associated with diabetic autonomic neuropathy, and those with two or more risk factors such as CAD, morbid obesity, and renal failure.

Classification of oral Antidiabetic medication:

Sulfonylureas:

1 Generation I:Tolbutamide, Chlorpropamide, Tolazamide.

2. Generation II:Glibenclamide, Glipizide, Gliclazide, Gliquidone.

3- Generation III: Glimepiride.

- **Biguaoides:**Metformin, Buformin.
- **Thiazolidinediones:**Pioglitazone, Rosiglitazone.
- **Meglitinides:**Repaglinide, Nateglinide.
- **Alpha giucosidase inhibitors:**Acarbose, Miglitol, Voglibose.
- **New antidiabetic drugs:**Exenatide (Byetta), Sitagliptin (Januvia).
- **Combinations:**Glibomet (metformin + glibenclamide), Avandamet (rosiglitazone + metformin), Competact (pioglitazone + metformin), Janumet (sitagliptin + metformin).

Thiazolidinediones:

Thiazolidinediones have been introduced in the treatment of type 2 diabetes in 1999.

Mechanism of action.Thiazolidinediones lower blood glucose levels by reducing insulinresistance in adipose tissue, in the muscle and in the liver, thus increasing insulin sensitivity, in this way it favors the hypoglycemic action of insulin.

Adverse effects. Before and during treatment with thiazolidinediones, is necessary to control liver enzymes (AST, ALT in particular). This class of oral antidiabetic medication is well tolerated in general, however, sometimes may occur mild edema of the lower limbs, through the loss of elimination of salt and water, which, on the one hand, may decrease hemoglobin, with the appearance of anemia, and on the other hand, requires to be administered with caution to patients with type 2 diabetes and heart failure.

Meglitinides:

After oral administration, meglitinides are absorbed at intestinal level, are metabolized in the liver and will result inactive byproducts, which are excreted into the bile.

Mechanism of action.This drugs are fixing on specific sites of potassium channels and increase insulin secretion stimulated by glucose level if there is a residual function of pancreatic beta cells.

Adverse effects.Rarely can cause hypoglycemia.

Considering that this class of oral antidiabetic medication has a short half-life, meglitinides are useful in correcting postprandial hyperglycemia. The tablets of this class are given after every meal ("one meal-one dose").

DRUG-DISEASE INTERACTIONS:

Many comorbid diseases can affect metabolism in people with diabetes. Patients with diabetes have higher rates of cardiovascular, renal, gastrointestinal, neurological, and thyroid diseases and ophthalmological complications compared with individuals without diabetes.

Sulfonylurea drugs:

Several drug-drug interactions occur with sulfonyiureas. First-generation sulfonylureas, especially chlorpropramide, may cause a facial flushing reaction when alcohol is ingested. This may be similar to that caused by disulfiram, which blocks aldehyde dehydrogenase, resulting in increased levels of acetaldehyde. Acetaldehyde can result in flushing and possibly nausea or vomiting at higher levels. Switch to a second-generation sulfonylurea would be advised (Table 2).

Sulfonylureas are commonly listed as having protein-binding drug interactions, and the first-generation sulfonylureas (acetohexamide, chlorpropamide, tolazamide, and tolbutamide), which bond ionically to plasma proteins, are thought to have a higher risk of protein-binding drug interactions, If they do occur, they should occur shortly after the second medication is added to the sulfonylurea by displacing the sulfonylurea and increasing the active drug available. This would result in a reduction of plasma glucose and possibly hypoglyceima, if the plasma glucose was near normal. As stated previously, most of these have now been restated as interactions resulting from the CYP450 isoenzyme system.

Table 3: Anti Diabetic Agents Mechanism, Site of action, Advantages & side effects

Agent	Mechanism	Site of action	Main advantages	Main side effects
Sulfonylurease	Stimulatingproductio ninhibiting the KATP channel	Pancreatic betacells	Effective, Inexpensive	Hypoglycemia, Weight gain
Metformin	Decreases insulin resistance	Liver	May result in mild weight loss, Does not cause hypoglycemia	Gl symptoms, including diarrhea, nausea, abdominal pain, Lactic acidosis,Metallic taste
Acarbose	Reduces intestinal glucose absorption	GI tract	Low risk	GI symptoms,including diarrhea,abdominal cramping, flatulence

Although not because of a drug interaction, metformin should be taken with a meal to limit gastrointestinal side effects. Metformin may cause malabsorption of vitamin B12, which may result in B12 deficiency and subsequent anemia. The mechanism by which metformin causes malabsorption of B12 is not clearly defined, although oral or injected B12 (cyanocobalamin) or calcium supplementation may be effective for correction(Table 2).[10]

Metformin does not undergo metabolism and is eliminated renally by tubular secretion and glomerular filtration. Metformin is a cationic (positively chained) molecule and may compete with other cationic drugs for renal secretion through organic cation transporters in the kidneys.Procainamide, digoxin, quinidine, trimethoprim, and vancomycin are all cationicdrugs that have the potential to interact with metformin, but **only** cimetidine. which is available over the counter for heart-burn, has been implicated in one case of metformin-associated lactic acidosis (Table 2).

Metformin:

Metformin (BP, pronounced, sold as Glucophage) is an oral antidiafaetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obesepeople and those with normal kidney function.Its use in gestational diabetes has been limited by safety concerns. It is also used in the treatment ofpolycystic ovary syndrome, and has been investigated for other diseases where insulin resistance may be an important factor. Metformin works by suppressing glucose production by the liver.Metformin is the only antidiabetic drug that has been conclusively shown to prevent the cardiovascular complications of diabetes. It helps reduce LDL cholesterol and triglvceride levels, and is not associated with weight gain. As of 2010, metformin is one of only two oral antidiabetics in the World Health Organization Model List of Essential Medicines (the other being glibenciamide).[4]

When prescribed appropriately, metformin causes few adverse effects—the most common is gastrointestinal upset—and is associated with a low risk of hypoglvcemia. Lactic acidosis (a buildup of lactate in the blood) can be a serious concern inoverdose and when it is prescribed to people with contraindications, but otherwise, there is no significant risk.

Metformin is primarily used for type 2 diabetes however is increasingly being used in polvcystic ovary syndrome (PCOS) non-alcoholic fatty liver disease (NAFLD) and premature puberty,three other diseases that feature insulin resistance: these indications are still considered experimental. The benefit of metformin in NAFLD has not been extensively studied and may be only temporary;[10] although some randomized controlled trials have found significant improvement with its use, the evidence is still insufficient.[11,12]

Type 2 diabetes

The main use for metformin is in the treatment of diabetes melletus (Type 3), especially in overweight people. In this group, over 10 years of treatment, metformin reduced diabetes complications and overall mortality by about 30% when compared withinsulin and suifonylureas (glibenclamide and chlorpropamide) and by about 40% when compared with the group only given dietary advice[11].This difference held in people who were followed up for five to 10 years after the study.[14]Since intensive glucose control withmetformin appears to decrease the risk of diabetes-related endpoints in overweight people with diabetes, and is associated with less weight gain and fewer hypoglycaemic attacks than are insulin and sulphonylureas, it may be the first-line pharmacological therapy of choice in this group. In addition, metformin had no effect on body weight: Over the 10-year treatment period, the metformin group gained about 1 kg, the same as the dietary advice group, while the sulfonylureas group gained 3 kg, and the insulin group, 6 kg.As metformin affords a similar level of blood sugar control to insulin and sulfonylureas, it appears to decrease mortality primarily through decreasing heart attacks, strokes and other cardiovascular complications.Metformin has a lower risk of hypoglycemia than the sulfonylureas,although it has uncommonly occurred during intense exercise, calorie deficit, or when used with other agents to lower blood glucose. Metformin is also not associated with weight gain, and modestly reduces LDL and triglyceride levels.[16]

Thiazolidinedione:

Thiazolidinediones (TZDsX also known as "glitazones," bind to PPAR-y. a type of nuclear regulatory protein involved in transcription of genes regulating glucose and fat metabolism. These PPARs act on peroxysome proliferator responsive elements (PPREJJJ). The PPREs influence insulin sensitive genes, which enhance production of mRNAs of insulin-dependent enzymes. The final result is better use of glucose by the cells.

Typical reductions in glycated hemoglobin (A1C) values are 1.5-2.0%. Some examples are:

- ✓ Rosiglitazone (Avandia): the European Medicines Agency recommended in September 2010 that it be suspended from the EU market due to elevated cardiovascular risks. pioglitazone (Actos)
- ✓ Troglitazone (Rezulin): used in 1990s, withdrawn due to hepatitis and liver damage risk[4]

ACE inhibitors and ARBs

Drug-food interactions are important for two ACE inhibitors, rnoexipril and captopril, which should be administered 1 hour before or at least 2 hours after a meal.7 A 40=50% decrease in systemic levels may be seen when valsartan, an ARE, is taken with food. Because both classes may increase serum potassium levels, caution should be taken when potassium supplements or a high-potassium diet are consumed with either class (Table 2).

ACE inhibitors and ARBs have several interactions of importance. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may blunt the antihypertensive effect of an ACE inhibitor, presumably through inhibition of ACE inhibitor-induced prostaglandin synthesis. Clinically, the interaction does not appear to affect the ACE inhibitor's ability to prevent adverse cardiovascular or renal outcomes .41 ACE inhibitors may increase hypersensitivity reactions, such as flulike symptoms and skin rash, with allopurinol, although the exact mechanism is not known.[7] ACE inhibitors and ARBs may increase lithium levels, and concurrent use warrants close monitoring of lithium levels.Captopril, a CYP2D6 substrate, and enalapril, a CYP3A4 substrate, may be affected by strong inhibitors or inducers of these pathways? (Table 2). Concentration changes resulting from these interactions should be monitored by following the ambulatory blood pressure. Losartan is the only ARB with significant interactions with CYP3A4, although losartan and irbesartan are substrates of CYP2C9. Strong inhibitors or inducers of these pathways would likely increase or decrease the antihypertensive effectiveness of losartan (Table 3).Despite potential interactions, very few clinically significant drug interactions have been documented with ARBs. Caution should be taken when either class is started in renal insufficiency because both can worsen renal function or even cause acute renal failure in patients with renal artery stenosis. Neither class is recommended in pregnancy because severe birth defects to neonatal kidneys can occur.Calcium channel blockers. Most CCBs are metabolized by CYP3A4 and will be affected by strong inhibitors and inducers of CYP3A4 (Table 3). Grapefruit juice in sufficient quantities can block intestinal CYP3A4, which can lead to an enhancement of the effects of CCBs. This could affect the blood pressure response for all CCBs and further lower the pulse rate when diltiazem and verapamil are used. Studies that have explored the effect of grapefruit juice on diltiazem and verapamil have not reported changes in blood pressure or heart rate, despite increases in systemic drug concentrations. Alcohol ingestion appears to have variable effects on the antihypertensive effects of CCBs, and intake should be limited. In addition, diltiazem and verapamil are weak inhibitors of CYP3A4, and drug interactions with HMG-CoA inhibitors, which will be discussed later, have been documented.The risk of cardiac conduction abnormalities with diltiazem or verapamil is the main drug-disease interaction to monitor. Diltiazem or verapamil given in combination with a p-blocker can further lower the pulse rate, increasing the risk for heart block. Dihydropyridine CCBs do not cause heart conduction drug-disease interactions, but they may cause peripheral edema, which may worsen preexisting edema present from heart failure, venous insufficiency, or other causes.

Nicardipine is an inhibitor of CYP3D6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4, and alcohol ingestion may enhance its antihypertensive effects.45 Nicardipine is not recommended because other medications within the class have fewer drug-drug interactions(Tables 2 and 3).

Fibric acid derivatives:

Both gemfibrozil and fenofibrate should be taken with food to reduce gastrointesinal upset. Bile acid sequestrants may interfere with absorption of fibric acid derivatives and should be separated from each other by at least 2 hours.Gemfibrozil can significantly block CYP2C8/9/19, glucuronidation, and possibly human organic anion transporting polypeptide-2 (OATP2).Several medications commonly used in the

treatment of patients with diabetes are metabolized by these pathways, including sulfonylureas, repaglinide, sertraline, fluoxetine, and carvedilol. These medications may need dose reductions or close monitoring when combined with gemfibroz.

The interaction of gemfibrozil with statins may be caused by a glucuronidated metabolite of gemfibrozil competing for metabolism after the OATP2 allows it into hepatocytes. Details can be further explored in a recent review article. Further information on this important interaction can be found in the statins section.Whengemfibrozil is added to ezetitnibe (Zetia), it likely blocks glucuronidation of ezetimibe, increasing systemic levels, but the clinical relevance of this interaction has yet to be documented. Fenofibrate, which appears to have less potential to interact with the aforementioned drugs, also has a questionable ability to lower cardiovascular events in people with type 2 diabetes.Drug interactions that inhibit metabolism of statins increase systemic exposure, which may predispose to a greater risk of myopathy.[7][8]

Medication documentation/drug-drug interaction tool for diabetes educators:

Caution should be taken when strong inhibitors of CYP3A4 are given with lovastatin, simvastatin, or atorvastatin. Strong inhibitors of CYP2C9 may increase fluvastatin and rosuvastatin levels (Table 3). Common classes of drugs that are strong inhibitors of CYP3A4 include azole antifungals, macrolide antibiotics (except azithromycin), protease inhibitors used for HIV, amiodarone, diltiazem, and verapamil (Table 3).Gemfibrozil and the immunosuppressant cyclosporine appear to increase the risk of myopathy with all statins/

CONCLUSIONS:

The present review found 78.3% patient adherence to antidiabetic drug therapy. Although different prevalence of adherence were seen for each factor studied, the association was not statistically significant. It can be concluded that, since the prevalence of adherence found in the present study is below that recommended in the literature, it is crucial that health providers assess adherence of patients to drug therapy in the event of poor glucose control and presumed failure of the prescribed therapeutic regimen.

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