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BENEFITS AND RISKS OF ANTI-DIABETEIC MEDICATION

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ABSTRACT

Diabetes mellitus (DM) is a syndrome of chronically elevated glucose level in the blood either due to insulin resistance, insulin deficiency or both. In addition, it may occur due to defective metabolism of carbohydrates, fats and proteins. There are 3 main types of DM: Type 2 DM is more prevalent in adults and is typically due to relative insulin deficiency, deficiency of insulin in children leads to DM type 1; and lastly, gestational diabetes occurs during pregnancy resulting from an imbalance of placental hormones. Insulin, Biguanides and Sulfonylureas are some of the drug classes used to treat DM. However, their use is complicated by numerous side effects, such as; hypoglycemia & weight gain from insulin and sulfonylureas; lactic acidosis, vitamin B12 deficiency and gastrointestinal upset with metformin. Route of administration and cost are also important factors to consider when prescribing. It is for this reason the quest for newer, safer and easier to administer drugs is ongoing.

Keywords: diabetes, hypoglycemia, lactic acidosis, metformin

INTRODUCTION:

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, glycosuria, and hyperlipidemia. Diabetes is best regarded as a group of related condition in which blood glucose level tends to rise [1]. Prevalence of diabetes is increasing globally which may be linked to increasing level of other health Issues. Diabetes can lead to serious medical complication –blindness from retinopathy, renal failure, gangrene, and limb amputation, CVS diseases and premature death [2]. It represents a widespread pathological transformation which hardens your capillary basal layer and enhances the sequence of something like the vessel wall. And cellular proliferation resulting in vascular complication like lumen narrowing, early atherosclerosis [3]. Diabetes mellitus causes long-term harm to, dysfunction in, and failure of a number of organs. Metabolic disorder characterized by thirst, polyuria, vision problems, and weight loss. Ketoacidosis or a non-ketotic hyperosmolar condition may occur in its most severe stages, which might result in stupor or coma and death in the absence of adequate treatment [4]. Since symptoms are sometimes mild or even nonexistent, hyperglycemia that is adequate to produce pathological and functional abnormalities may exist for a considerable amount of time before the diagnosis is made [5]. Long term effects of Diabetes mellitus include the gradual emergence of the specific complications of retinopathy, which could result in blindness, nephropathy, which could cause renal failure, and/or neuropathy, which increases the risk of foot ulcers, amputation, Charcot joints, and characteristics of Charcot's diseases, sexual dysfunction and Cardiovascular, peripheral vascular, and cerebrovascular disorders are all more common in diabetes

TYPES OF DIABETES MELLITUS

Diabetes mellitus has been classified into two types on the basis of pathophysiology:

Insulin dependent (juvenile) diabetes type 1: In this types of diabetes beta cells of pancreatic islet do not secret that much level of insulin or little amount of insulin .this type of diabetes can occur at birth or below 20 years of age [6]. In all type I cases circulating insulin levels are low or very low, and patient are more intent to ketosis. This type is less common and has low degree of genetical predisposition.

SUBTYPES OF TYPE 1 DIABETES:

There are two type of type 1 diabetes which are as follow:

1) Type 1 A: An acute immune disorder occurs that damages the beta cells present in pancreatic islet. Like the autoimmune disease Type:1 Diabetes LADA occurs because your pancreas stops producing adequate insulin, most likely from some "insult" that slowly damage the insulin-producing cells in the pancreas.

2) Type 1B :Idiopathic : in this type of diabetes no beta cell antibody is found

Causes of type 1: major causes for this type of diabetes are Genetical and Autoimmune Reaction [7].

TYPE 2 Diabetes Mellitus:

Non insulin dependent diabetes mellitus: insulin secretes in normal rate but it does not absorb by cell & causes insulin and its receptor binding abnormality. It usually occur in older people who are typically (although not always) obese.

Type 2 diabetes is best thought of as a group of condition characterized by a variable combination of reduced insulin secretion and resistance to insulin blood glucose lowering action.[8]

Type:2 diabetes has a stronger like to family history and lineage than type 1. Moreover, twin studies have demonstrated that a significant amount of type 2 diabetes development is influenced by genetics. Race can also play a role. Yet is also depends on environment factors. [9]

Cause of type 2: Some of the prominent causes for this diabetes obesity, high blood pressure, Stress, Unhealthy food.

SYMPTOMS OF DIABETIES:

IN CHILDREN: Bed wetting, unexplained weight loss, and loss of appetite

IN ADULT: Frequent urination, excessive thirst, increased appetite, weight loss, genetical infection & slow healing

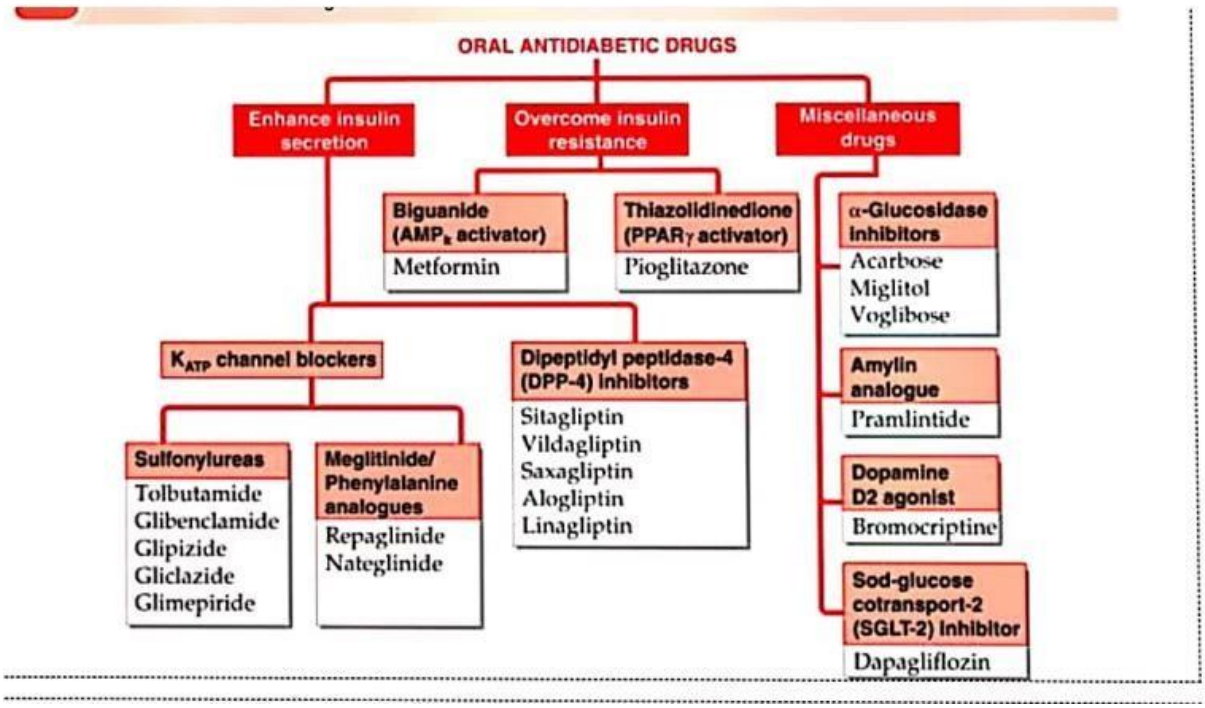
TEST OF DIABETES (10)

1) Fast & post – prandial blood sugar test (8hrs fasting)
2) HbA1c (hemoglobin A_1c) – average (3 months) , non – fasting 3) Oral glucose tolerance test.

Antidiabetic drug: The pancreatic islet cells naturally secrete the hormone insulin [10]. Patients with type 2 diabetes mellitus may also have diminished endogenous insulin synthesis, while those with type 1 diabetes mellitus have an absolute lack of insulin. All people with type 1 diabetes must take insulin as a lifelong treatment. When a type-2 diabetic patient's illness progresses, insulin is frequently administered as monotherapy or as adjunct therapy to oral antidiabetic medications. Numerous modifications and substitutions were made to the insulin molecule, which produced several forms of insulin. Based on their pharmacodynamic and pharmacokinetic features, such as onset, peak, and duration of action, they are described and delivered [11]. They are primarily categorized as rapid-acting, short-acting, intermediate-acting, or long-acting insulin kinds.

The type of drugs' mode of action Insulin decreases blood sugar by decreasing hepatic glucose synthesis and peripheral glucose uptake, specifically in skeletal muscle fat.

CLASSIFICATION :



KD Tripathi (12)

MECHANISM OF HYPOGLYCEMIC DRUGS:

Mechanism of action of various hypoglycemic drugs is as below:

SULFONYL UREAS: it is a type of Potassium Channel blocker. Sulphonyl ureas bind to a specific sulphonyl receptor located on the pancreatic beta cells which increases the release of insulin[13]. because when there is binding of sulfonyl urea with its receptor causes indirectly the blockage of K efflux which causes depolarization of the membrane and hence increase the influx of calcium ion into beta cells then this calcium causes the fusion of insulin stored vesicles which present inside the cytoplasm and releases into the blood stream[14].

Classification of sulfonyl urea [15]

1st gen Earlier :Tolbutamide , clopropamide

2nd gen now days: glimepride, gliclazide, glipizide, glibenclamide

USES: This type of drugs is only used for type 2 diabetes mellitus not for diabetes type.

ADVERSE EFFECTS: Hypoglycemia occurs in diabetic patient but also on normal patient cause serious adverse effects of hypoglycemia on normal patient [16].

INTERACTIONS: This class of drugs causes disulfiram like ractions in alcoholic persons [17].

MEGLITINIDE :

This is also an ATP sensitive potassium channel blocker. like sulfonyl ureas [18]. The only major difference is in the structure and also its duration of action because it is a short acting but sulfonyl ureas are long acting oral hypoglycemic drug which is an advantage over sulfonyl ureasbeacuase it is less prone to side effects [19].

DIPEPTIDYL PEPTIDASE-4: enzyme termed as DPP-4 have(20) a key role in the degradation of endogenous GLP -1, whereas GLP-1 enzyme is an incretin hormone which increases the release of insulin and also decrease the release of glucagon. But orally active inhibitor of DPP-4 causes the indirect release of insulin by inhibiting hat enzyme which is responsible for degradation of GLP 1 [20].

Drugs mainly that comes under this category are **Sitagliptin, Vildagliptin, Teneligliptin .**

Uses: This drug is used as adjuvant in the treatment of type 2 diabetes and also used in URTI upper respiratory cough tract infection [21].

CLASSIFICATION OF DRUGS THAT DECREAES INSULIN RESISTANCE:

BIGUANIDES: Also knows as adenosine mono phosphate phosphor kinase enzyme activator [22]. This type of drug work by reaching into target organ then converts from cAMP to AMP k leads to increase in the sensitivity of insulin in the pancreas [23]. This category of drug has advantage over Sulfonyl urea is that it cannot do hypoglycemia to normal patient. Make it same effective like sulfonyl ureas and tagged it as first choice of drug. Extra diabolical use of **Metformin** is that it used for poly cystic ovary cryst in females. It also decreases the glucose absorption from intestine[24]. This is contraindicated in the renal dysfunction and lactic acidosis [25].

ADVERSE EFFECT: It causes Vit B12 deficiency and lactic acidosis in alcoholic person.

THIAZOLIDINEDIONE (PPARγ activator): Drugs comes under this section is **Pioglitazoneit** is a selective agonist of the nuclear **Peroxisome** proliferator activated receptor[26]. Pioglitazone enhance the transcription of several insulinresponsive genes and tends to reverse inuslin resisitance by enhancement GLUT4 expression and translocation .the primary action is to increase the peripheral insulin sensitivity [27]. The magnitude of blood glucose reduction is some what less than metformin. Improved glycaemic control results in lowering of circulating HbA1c and insulin levels in type 2 DM patients [28]. Pioglitazone also lowers the level of trigyceride and raises good fat level in body. Pioglitazone, rosiglitazone, and thiazodinediones reduce insulin resistance by improving insulin-receptor sensitivity[29].

When a patient has type-2 diabetes mellitus, they are administered as supplements to diet or exercise. Thiazodinediones are occasionally used as monotherapy, although they are more usually used in individuals who do not meet their glycemic objectives in combination with other oral anti-diabetic medications and/or insulin [30]. Thiazodinediones should be used with caution in individuals with a history of prior myocardial infarction since recent clinical data indicate that they may put patients at an elevated risk of the condition and deathcardiac disease [31]. They are not recommended in patients with NYHA class III and IV heart failure. A structurally similar thiazodinedione, troglitazone, was removed from the market due to liver failure and death. In patients with hepatic impairment, it is advised abuse and misuse. HbAlc reduction is between 1 % - 1.5% [32].

ADVERSE EFFECT: plasma volume expansion, edema, weight gain, headache, myalgia and mild anaemia. Pioglitazone also increases risk of fractures [33].

CONTRAINDICATIONS : pioglitazone is restricted in liver and CHFs [34].

INSULIN

The pancreatic islet cells naturally secrete the hormone insulin [35]. Individuals with type 2 diabetes mellitus may also have diminished endogenous insulin synthesis, while those with type 1 diabetes mellitus have an absolute lack of insulin [36]. All people with type 1 diabetes must take insulin as a lifelong treatment. When a type-2 diabetic patient's illness progresses, insulin is frequently administered as monotherapy or as adjunct therapy to oral antidiabetic medications [37].

Many modifications and substitutions were made to the insulin molecule, which produced several forms of insulin.[38] Based on their pharmacodynamic and pharmacokinetic features, such as onset, peak, and duration of action, they are described and delivered [39]. The most important distinction is whether they are rapid-acting, short-acting, intermediate-acting, or long-acting insulin kinds.

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Many modifications and substitutions were made to the insulin molecule, which produced several forms of insulin [49]. Based on their pharmacodynamic and pharmacokinetic features, such as onset, peak, and duration of action, they are described and delivered [36]. Most importantly, they are divided into categories that act quickly, quickly, quickly, slowly, or slowly [5].

MECHANISM OF ACTION:

By increasing peripheral glucose uptake, insulin decreases blood sugar, notably in skeletal muscles, muscular fat and by preventing the liver from producing glucose [40]. Lipohypertrophy or lipoatrophy at the injection location. Acetazolamide, Diuretic, Oral Contraceptives, Albuterol, Epinephrine, Phenothiazine, Asparginase, Tolbutaline, Corticosteroids, HIV antiviral, Diltiazem, Lithium, Thyroid hormones are the main drugs that interact with each other to decrease hypoglycemic effect. Alcohol, Fluoxitine, Sulphonamides,

Anabolic Steroids, H-Blockers, and Clonidine are all drugs that affect insulin and increase hypoglycemic effect [41].

TOXICITY AND SIDE EFFECT MANAGEMENT

Hypoglycemia is one of the most common adverse effects of insulin. Gastrointestinal upset is the most common side effect of many of the T2DM medications [42]. Sulfonylureas can lead to hypoglycemia and may promote cardiovascular death in patients with diabetes. Thiazolidinediones have fallen out of favor in clinical practice due to their adverse effects, specifically resulting in fluid retention, worsening heart failure, and fractures. Compared to other treatments such metformin, DPP-4 may generate less nausea and constipation but may raise the risk for upper respiratory tract infections. SGLT-2 inhibitors can lead to increased urinary tract infections due to increased urinary glucose excretion. Both SGLT2 inhibitors and GLP-1 Receptor agonists reduce ASCVD events and are now considered the second line to metformin in such patients [43].

PROGNOSIS

The Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study found that individuals with T1DM and T2DM respectively had increased micro vascular complications with chronic hyperglycemia. Patients who can revert to normal glucose during the progression from pre-diabetes to frank DM had a good prognosis and may be able to slow disease progression [45].

COMPLICATIONS

No matter what type of diabetes a person has, consequences might include neuropathy, microvascular, and macrovascular problems [45]. Nephropathy, retinopathy, neuropathy, and ASCVD events are all examples of microvascular and macrovascular effects that vary depending on the severity and length of poorly controlled diabetes, especially if it also coexists with accompanying comorbidities like dyslipidemia and hypertension. One of the most devastating consequences of DM is its effect on cardiovascular disease (ASCVD) [47]. Approximately two-thirds of those with DM will die from a myocardial infarction or stroke. Fasting glucose levels of more than 100 mg/dL in individuals who have T2DM substantially improve their probability of developing ASCVD, and cardiovascular risk can arise before blatant hyperglycemia. Fasting glucose levels of more than 100 mg/dL in individuals who have T2DM substantially improve their probability of developing ASCVD, and cardiovascular risk

can arise before blatant hyperglycemia. It is the leading contributor to end-stage renal disease (ESRD) in the United States, and many patients with ESRD will need to start dialysis or receive a kidney transplant [50]. If the albuminuria persists in the range of 30 to 300 mg/day (microalbuminuria), it seems to be a predictable earliest marker for the onset of diabetic neuropathy. The progression to ESRD quickens after macroalbuminuria (greater than 300 mg/24 hr) develops. The most popular and preferred way to detect microalbuminuria is the random spot urine samples for testing of the albumin-to-creatinine ratio. This method is quick, simple, and predictable. The diagnostic of microalbuminuria is confirmed by two out of three experiments taken over a six-month duration that reveal a continuous level more than 30 mcg/mg creatinine.

Moreover, type 2 diabetes (DM) is the most common reason for loss of limbs in the United States, mostly because of the vasculopathy and neuropathy it causes. Regular foot inspections are necessary for many people who acquire neuropathy in order to stop infections from undetected sores [46].

The most important risk factor for the emergence of diabetic retinopathy is the length of diabetes. It usually appears in persons with type 1 diabetes approximately 5 years after the disease first manifests. Thus, it is advised that these individuals start yearly retinal exams approximately five years after diagnosis [54]. Countless individuals suffering from type 2 diabetes might already possess retinal damage when they are diagnosed. Nonproliferative retinal disease will affect 10% of people at ten years, 40% of people at fifteen years, and 60% of people at twenty years. The guideline for these people is to begin yearly retinal screening at the time of diagnosis. Countless studies have demonstrated that good blood glucose management has a positive impact on the development and progression of diabetic retinopathy. An additional risk factor for macular is uncontrolled blood pressure [47].Thus, lowering blood pressure in people with diabetes also increases their risk of retinopathy progression. In conditions of eye disease, injections of anti-vascular endothelial growth factor (anti-VEGF) treatments are commonly used as the initial therapy. Pan-retinal photocoagulation is performed in nonproliferative diabetic retinopathy conditions. Patients with diabetes mellitus sometimes suffer sudden loss of blindness for a number of reasons, the most prevalent of which is vitreous bleeding. Vascular occlusion (involving the macula and involving the central retinal vein or a branch vein), loss of vision, end-stage hypertension, and inflammatory optic neuropathy are less uncommon reasons that should be taken into account [48].

Evidence also suggests to a possible connection between T2DM and cancer, notably bladder cancer, in people on pioglitazone. After taking metformin, patients with prostate, pancreatic, breast, and colorectal cancers showed better cancer-specific survival. The exact mechanism by which metformin affects diabetic patients' cancer is unknown [49].

Chronic hypertension and vaginal pregnancies are so much more likely in those with gestational diabetes. With exception of to those with T1DM, pregnant people with T2DM typically have a better prognosis in terms of pregnancy and neonatal difficulties. Commonly, hypoglycemia and macrosomia will be present in newborns of DM mothers [50].

Diabetic ketoacidosis (DKA), which generally shows in T1DM, is the most acute DM condition. Usually, poor medication, missed doses, or a continuing infection are to blame for this disease. The absence of insulin in this situation prevents tissues from absorbing glucose from the bloodstream. In order to make up for this, lipids are converted into ketones and used as a source of energy instead, which results in systemic acidity and can be measured as a high anion-gap metabolic acidosis [51]. The interaction of hyperglycemia with ketosis results in diuresis, acidemia, and vomiting, which can constitute life-threatening electrolyte imbalances and dehydration. Hyperosmolar hyperglycemic syndrome (HHS) is a rapidly developing issue in T2DM. It presents signs which are comparable to those associated with DKA, including excessive urination, high blood sugar, dry mouth, polyuria, tachypnea, and tachycardia. Although insulin is still produced by pancreatic beta cells, HHS normally does not display urine ketones, in contrast to DKA. Insulin delivery and intensive intravenous hydration are part of the treatment for DKA or HHS. In the treatment of these urgent situations, careful electrolyte management, particularly potassium management, is essential [52].

CONCLUSION:

Insulin is good for controlling acute hyperglycemic states in DM but it causes acute hypoglycemia and lipodystrophy. Metformin is good hypoglycemic and easily available but causes hypoglycemia, metallic taste, Lactic acidosis and B12 deficiency. Sulfonylureas are good hypoglycemic but causes severe hypoglycemia acutely and weight gain so contraindicated for obese or hypertensive patients. While newer antidiabetics such as GLP 1 agonists increases secretions has very low risk of hypoglycemia, causes weight loss as compared to insulin and decreases risk of cardiovascular side effects but still cannot be used in renally impaired patients, causes pancreatitis and cannot be given in gastroparesis patients, similarly a newer drug of this

class known as LY2189265 has long half-life of 90 hours, better efficacy, but causes pancreatitis and increase diastolic BP in high doses, pancreatitis is not associated with lixisenatide (GLP 1 agonist), while DPP4 inhibitors which increases GLP 1 in body has less risk of hypoglycemia, GI side effects, are weight neutral can be used in CKD but causes headaches and Nasopharyngitis. Bromocriptine or pegvisomant are used in patients of growth hormones adenoma induced DM as a medical therapy but are associated with psychosis and hallucinations. Meglitinides increases insulin secretion and has minuscule risk of hypoglycemia but cannot be used in CKD patients. Otelixizumab and Teplizumab decrease T cell functions and save beta cells from immune reactions used in DM 1 but cause immune suppression and is an orphan drug. Recombinant GAD used in vaccines decreased antibody mediated beta cell damage but is still under studies.

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