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Type 2 Diabetes Mellitus and Metabolic Syndrome

Dhanya Hariharan* , Shibina Shan
1.Department Of Pharmacy Practice, Sreekrishna College Of Pharmacy and Research Center, Parassala, Trivandrum, India

ABSTRACT

Metabolic syndrome is a constellation of interrelated cardio-metabolic risk factors that include Central Obesity, Hyperglycemia, Hypertension and Dyslipidemia. It has been estimated that about 1 in 5 (20.4%) adults in the U.S. have high blood pressure, it is very crucial to evaluate the serious health problems, level of awareness and knowledge about conditions relevant to metabolic disorders. Metabolic syndrome is caused not by genetic defects alone; in most cases, genetic factors predispose a person to a disease, while lifestyle factors determine whether (and when) the disease will develop. Several studies have demonstrated clearly the importance of dietary factors and physical activity level in the development of the metabolic syndrome. Given the same dietary and lifestyle factors, some individuals may be more prone to type 2 diabetes than others because of different genetic backgrounds. At a public health level, more attention must be given to modification of lifestyles of the general public to reduce risk of obesity and T2DM and to increase physical activity. At a clinical level, individual patients with increased metabolic risk need to be identified so that their multiple risk factors can be reduced. Considering the long asymptomatic period often preceding the manifestation of T2DM and CVD, early diagnosis could enable earlier targeted interventions such as implementation of healthy lifestyle changes in nutritional behavior and exercise or pharmacotherapy, thus reducing disease development. A deeper understanding of the underlying gene- interactions In terms of both public health and for individuals and genetic subgroups is therefor needed.

Keywords: Metabolic Syndrome(MetS) ,Type II Diabetes Mellitus (T2DM),Impaired Fasting Glucose(Ifg), Maturity Onset Diabetes Of the Young(MODY)

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INTRODUCTION

Metabolic syndrome is a combination of medical-risk issues. People with metabolic syndrome (also called insulin resistance syndrome or syndrome X) are twice as likely to develop heart disease and five times more likely to develop type 2 diabetes mellitus. People also need to be aware of conditions that can be a precursor to diabetes, also known as pre-diabetes.

Metabolic syndrome is a combination of factors that multiply a person's risk for heart disease, diabetes and stroke and they are listed as:

- Overweight and Obesity – excess fat in and around the stomach (abdominal obesity)
- Raised Blood Pressure : ≥130/≥85 mm Hg
- High Blood Triglycerides : ≥ 150 mg/dl
- HDL-C : Men <40 mg/dl ,Women : <50 mg/dl
- Impaired Fasting Glucose (Ifg) Or Diabetes. Ifg Occurs When Blood Glucose Levels Are Higher Than Normal, But Not High Enough To Be Diagnosed As Type 2 Diabetes.

Metabolic syndrome is dangerous because when individual risk factors are seen together in a person, the likelihood increases for cardiovascular problems and Diabetes[1].

Diabetes

Diabetes is a serious medical problem related to how your body uses sugar. The worldwide estimation of people with diabetes is increasing day by day and it reaches to a peak value of approximately 347 million[2].

Primarily focusing on the adult-onset type, also called Type 2 diabetes. Type 2 diabetes results from cells in a person's body failing to use insulin properly. Insulin enables cells in the body to use glucose (a kind of sugar) to turn it into energy. In Type 2 diabetes, the rising glucose levels seen in the bloodstream are an indicator that the body is not using insulin well. The two main contributors to high blood sugar in Type 2 diabetes are insulin resistance and reduced production of insulin by the pancreas-beta Cell dysfunction[3].

Insulin resistance manifest by an increase in lipolysis and free fatty and production, increase in hepatic glucose production and decrease in skeletal muscle uptake of glucose. Free fatty and indirectly leads to the hyper glycemia by stimulating hepatic glucose production[4].

In type 2 patients the pancreatic β=-cell, are genetically vulnerable to injury, leading too accelerated cell tumor and premature aging, and ultimately to a modest reduction in β –cell mass. Chronic hyper glycemia may enhance the ability of β-cell to function as a consequence of persistent β-cell stimulation[5].

Epidemiology

T2D is the most common form of the disease, accounting for approximately 90% of all affected individuals. A diagnosis of T2DM is made if a fasting plasma glucose concentration is ≥ 7.0 mmol/L (≥ 126 mg/dl) or plasma glucose 2 hours after a standard glucose challenge is ≥ 11.1 mmol/L (≥ 200 mg/dl) (WHO, 1999) T2D is caused by relative impaired insulin secretion and peripheral insulin resistance. Typically, T2D is managed with diet, exercise, oral hypoglycemic agents and sometimes exogenous insulin. However, it is associated with the same long-term complications as T1DM[6].

A study of (Wild etal., 2004) indicated that the highest rates of Type 2 Diabetes Mellitus are found among Native Americans, particularly the Pima Indians who reside in Arizona in the US, and in natives of the South Pacific islands. Type 2 Diabetes Mellitus are also known to be more predominant in Hispanic and African American populations than in Caucasians. It is estimated that 171 million people (2.8% of the world's population) had diabetes in the year 2000 and that by 2030 this number will be 366 million (4.4% of the world's population). The vast majority of this increase will occur in men and women aged 45 to 64 years living in developing countries. According to Wild et al.(2004), the 'top' three countries in terms of the number of T2D individuals with diabetes are India (31.7 million in 2000; 79.4 million in 2030), China (20.8 million in 2000; 42.3 million in 2030) and the US (17.7 million in 2000; 30.3 million in 2030)[7]. Clearly, T2D has become an epidemic in the 21st century.

In addition to the burden of Type 2 Diabetes Mellitus there was an even larger number of people with raised levels of blood glucose but below the level for diabetes. The World Health Organization defines impaired fasting glucose as a fasting plasma glucose level of ≥ 6.1 $mmoll^{-1}$ and less than 7 $mmoll^{-1}$, and impaired glucose tolerance as 2 hour plasma glucose, post glucose challenge, of 7.8 to less than 11.1 $mmoll^{-1}$ (WHO, 1999)[6].

Prevalence

The prevalence of Type 2 Diabetes Mellitus increases with age of population. In developing countries, the largest number of people with diabetes are in the age group 45 to 64 years, while in developed the largest number is found in those aged 65 years and over. These differences largely reflected differences in population age structure between developed and developing countries. Worldwide rates are similar in men and women, although they are slightly higher in men < 60 years of age and in women > age 65 years[7].

Another matter of great concern is the recent increase in Type 2 Diabetes Mellitus in children by by a report from (Bloomgarden , 2004). A report based on the Pima Indians in Arizona noted that

between 1967-76 and 1987-96, the prevalence of Type 2 Diabetes Mellitus increased 6-fold in adolescents (Fagot-Campagna et al., 2000). The reported incidence of Type 2 Diabetes Mellitus in United States increased from 0.3-1.2/100,000/yr before 1992 to 2.4/100,000/yr in 1994 (Weill et al., 2004). Most T2D children diagnosed during this period were females from minority populations, with a mean age of onset at around puberty. They were also likely to have a positive family history of the disease, particularly maternal diabetes [8].

Impaired Glucose Tolerance (Pre-Diabetes)

Impaired fasting glucose and impaired glucose tolerance are sometimes referred to as 'pre-diabetes'. They occurs when your blood glucose level is higher than normal, but not high enough to be called diabetes. Prediabetic condition includes Impaired fasting glucose and impaired glucose tolerance. One third of people who have impaired glucose tolerance or impaired fasting glucose will develop diabetes unless lifestyle changes are made [9].

The metabolic syndrome quintuples the risk of type 2 diabetes mellitus. Type 2 diabetes is considered as an indicator for metabolic disorders. In people with impaired glucose tolerance or impaired fasting glucose, presence of metabolic syndrome doubles the risk of developing type 2 diabetes. It is likely that pre-diabetes and metabolic syndrome denote the same disorder, defining it by the different sets of biological markers. The presence of metabolic syndrome is associated with a higher prevalence of CVD than found in patients with type 2 diabetes or Impaired Glucose Tolerance (IGT) without the syndrome. Decreased levels of adiponectin has been shown to increase the resistance of insulin, and is considered to be a risk factor for developing metabolic syndrome. The relationship of Metabolic syndrome and insulin resistance proves that the body is not able to use insulin properly to remove blood sugar from your blood[10].

Recent evidence suggests that elevated liver enzymes, an indicator of non-alcoholic fatty liver disease, may comprise an additional component of the metabolic syndrome and may serve as a surrogate marker for type 2 diabetes, particularly if used in conjunction with C-reactive protein.

Diabetes mellitus and physiological effects of insulin.

Virtually all forms of DM are caused by a decrease in the circulating concentration of insulin (insulin deficiency) and a decrease in response of peripheral tissues to insulin (Insulin resistance). Insulin lowers the concentration of glucose in blood by inhibiting hepatic glucose production and by stimulating the uptake and metabolism of glucose by muscle and adipose tissue. Insulin inhibits the lipolysis, stimulate fatty and synthesis and also stimulate amino acid uptake and protein synthesis. In diabetic patients the insulin deficiency lead to enhanced rate of gluconeogenesis.

Role of Genes In Type 2 Diabetes[11]

It has long been known that Type 2 Diabetes is an inherited form. Family studies have revealed that first degree relatives of individuals with type 2 diabetes are about 3 times more likely to develop this than individuals without a positive family history of the disease (Flores et al., 2003; Hansen 2003; Gloyn 2003). It has also been shown that concordance rates for monozygotic twins, which have ranged from 60-90%, are significantly higher than those for dizygotic twins. Thus, it is made clear that Type 2Diabetes had a strong genetic component. One approach to identify diseased genes is based on the identification of candidate genes (Barroso et al., 2003; Stumvoll, 2004). Candidate genes are selected because they are thought to be involved in pancreatic β cell function, insulin action / glucose metabolism, or other metabolic conditions that increase T2D risk (e.g., energy intake / expenditure, lipid metabolism). To date, more than 50 candidate genes for T2D have been studied in various populations worldwide. However, results for essentially all candidate genes have been conflicting. Possible explanations for the divergent findings include small sample sizes, differences in T2D susceptibility across ethnic groups, variation in environmental exposures, and gene-environmental interactions. Because of current controversy, this review will focus only on a few of the most promising candidate genes. These include **PPARγ, ABCC8, KCNJ11**, and **CALPN10**[11]

PPARy[12]

PPARγ (peroxisome proliferator-activated receptor-γ) This gene has been widely studied because it is important in adipocyte and lipid metabolism. In addition, it is a target for the hypoglycemic drugs known as thiazolidinediones. One form of the *PPARγ* gene (Pro) decreases insulin sensitivity and increases T2D risk by several fold. Perhaps more importantly is that this variant is very common in most populations[12].

Maturity-Onset Diabetes of the Young (MODY) [13]

An uncommon form of T2D (accounting for <5% of all T2D cases) that generally occurs before age 25 years is MODY. MODY is characterized by a slow onset of symptoms, the absence of obesity, no ketosis, and no evidence of beta cell autoimmunity. It is most often managed without the need for exogenous insulin. MODY displays an autosomal dominant pattern inheritance, generally spanning three generations (Stride and Hattersley, 2002). Because of advances in molecular genetics, it is now known that there are at least six forms of MODY, each of which caused by a mutation in a different gene that is directly involved with beta cell function (Winter, 2003). Because ~15% of MODY patients do not carry mutations in one of these genes, it is anticipated that other genes that cause MODY will be discovered in the near future [13].

Pathogenesis[14]

Insulin resistance is a major player in the pathogenesis of the metabolic syndrome and type 2 diabetes, and yet, the mechanisms responsible for it remain poorly understood. Magnetic resonance spectroscopy studies in humans suggest that a defect in insulin-stimulated glucose transport in skeletal muscle is the primary metabolic abnormality in insulin-resistant type 2 diabetics. Fatty acids appear to cause this defect in glucose transport by inhibiting insulin-stimulated tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) and IRS-1 associated phosphatidylinositol 3-kinase activity. A number of different metabolic abnormalities may increase intramyocellular/intrahepatic fatty acid metabolites; these include increased fat delivery to muscle/liver as a consequence of either excess energy intake or defects in adipocyte fat metabolism and acquired or inherited defects in mitochondrial fatty acid oxidation. Understanding the molecular/biochemical defects responsible for insulin resistance is beginning to unveil novel therapeutic targets for treatment of the metabolic syndrome and type 2 diabetes [14].

Insulin Resistance and Muscle Glucose Metabolism [15]

The magnetic resonance studies of glucose disposal in normal humans revealed that skeletal muscle accounts for the majority of insulin-stimulated glucose uptake and that >80% of this glucose is then stored as glycogen. The rate of glycogen synthesis in skeletal muscle was ≈50% lower in diabetic subjects than in normal volunteers. The only other organ capable of storing a significant amount of glycogen is the liver, and here again, glycogen stores were reduced in diabetics. Subsequent studies focused on the rate-controlling steps in this pathway as in Figure: 1.

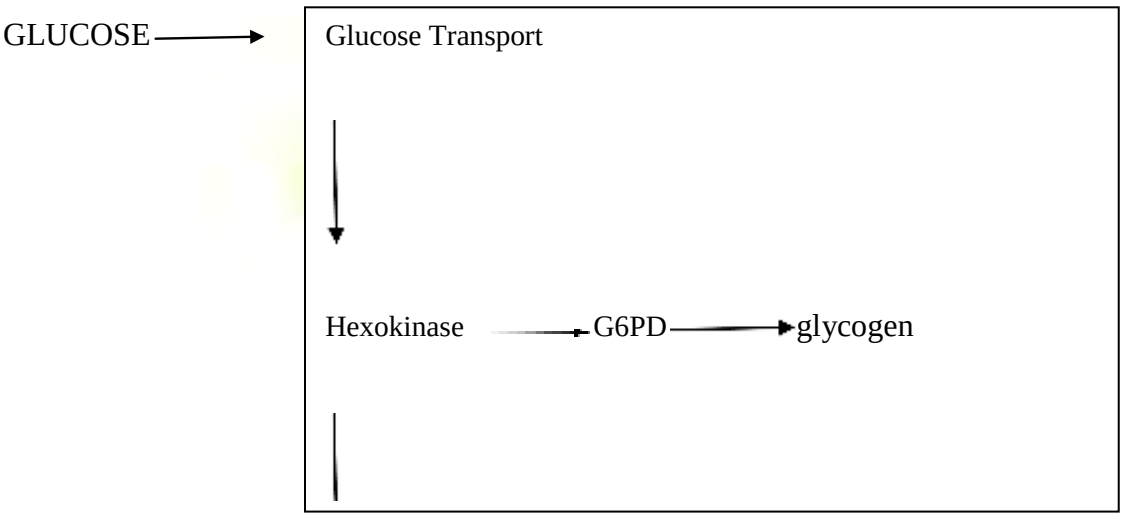

Figure: 1; Potential rate-controlling steps in insulin-stimulated glycogen synthesis in a myocyte.

Under the influence of insulin, glucose is transported into myocytes via GLUT4, where it is phosphorylated by hexokinase. Glucose 6-phosphate (G6P) is then either used in the glycolytic pathway or converted to glycogen by glycogen synthase.

Glucose-6-phosphate[16] is an intermediate between glucose transport into the cell and its subsequent phosphorylation by hexokinase and glycogen synthesis. The increment in glucose-6-phosphate concentration was significantly reduced in type 2 diabetics, suggesting that glucose transport or phosphorylation must be the rate-controlling step in insulin-stimulated glucose disposal in skeletal muscle rather than glycogen synthase. Similar observations were also made in insulin-resistant offspring of type 2 diabetes, suggesting that this defect precedes the development of type 2 diabetes. Glucose transport in skeletal muscle is largely mediated by a specific insulin-responsive transporter known as glucose transporter 4 (GLUT4).

Lipids /Fatty Acids Induced Insulin Resistance [17]

Insulin –stimulated glucose disposal in humans had been tremendously reduced by the specially designed Lipid infusions. Furthermore, fatty acid accumulation in skeletal muscle and liver is responsible for this reduction in insulin sensitivity during procedures. Randle et al originally showed that fatty acids compete with glucose for substrate oxidation in isolated rat heart muscle and rat diaphragm muscle. They speculated that an increase in fat oxidation might be responsible for insulin resistance in obese conditions. According to this proposal, increased fatty acid oxidation would cause an increase in the mitochondrial acetyl coenzyme A (Co A): Co A and NADH:NAD+ ratios with subsequent inactivation of pyruvate dehydrogenase. In turn, this would induce a rise in intracellular citrate levels, leading to inhibition of phospho fructokinase and glucose-6-phosphate accumulation. Because glucose-6-phosphate inhibits hexokinase activity, this would result in intracellular glucose accumulation and decreased glucose uptake. Maintaining high free fatty acid levels for 5 hours caused the expected reduction in insulin sensitivity, as assessed by glucose uptake, glucose oxidation, and glycogen synthesis in skeletal muscle, just as had been observed in type 2 diabetics and their insulin-resistant offspring. However, rather than increasing intracellular glucose-6-phosphate levels, as predicted by the Randle hypothesis, they found that elevating free fatty acid levels reduced intracellular glucose-6-phosphate levels. This was consistent with what had been repeatedly seen in type 2 diabetes [17].

Fatty acid infusion could conceivably have direct effects on GLUT4 activity, or it could alter insulin-regulated GLUT4 trafficking between intracellular compartments and the cell membrane. To explore the latter possibility, we examined insulin-signaling intermediates in skeletal muscle biopsies from subjects exposed to high fatty acid levels for 5 hours before and during

hyperinsulinemic-euglycemic clamps. Glucose oxidation and glycogen synthesis were 50% to 60% lower after the lipid infusion than with the glycerol (control) infusion and were associated with an ≈90% decrease in the increment in intramuscular glucose-6-phosphate concentration, implying diminished glucose transport or phosphorylation activity. The rate limiting step was that the intracellular glucose concentrations were significantly lower in the lipid infusion with those during glycerol infusion . Insulin receptor substrate-1 (IRS-1)–associated phosphoinositol 3-kinase (PI 3-kinase) activity was significantly reduced under these conditions. Subsequent rodent and human studies suggested that this might be a consequence of serine phosphorylation of IRS-1. An unanswered element in this proposed mechanism for insulin resistance is the precise nature of the lipid moiety responsible for fatty acid induced-insulin resistance. Triglycerides are generally perceived to be metabolically inert associates of more candidates, which include long-chain acyl-CoAs and diacylglycerol. If this hypothesis is true, any perturbation that results in accumulation of fatty acyl-CoA or other fatty acid derivative within muscle and liver, either through increased delivery or decreased metabolism, ought to induce insulin resistance.

Mechanism of fatty acid-induced insulin resisance . Fatty acid metabolites (long-chain acyl-CoA [LCCoA] and diacylglycerol [DAG]), which may accumulate within myocytes because of increased fatty acid delivery or decreased mitochondrial oxidation, trigger a serine/threonine kinase cascade (possibly involving novel protein kinase C, IKK-β, or JNK1). This ultimately induces serine/threonine phosphorylation of critical IRS-1 sites, thereby inhibiting IRS-1 binding and activation of PI 3-kinase, resulting in reduced insulin-stimulated glucose transport.

Risk Factors and Symptoms[18]

The risk factors for prediabetes and those for type 2 diabetes are more or less the same.

- Overweight/ Obese state.
- Sedentary lifestyle
- Previous diagnosis of gestational diabetes (diabetes during pregnancy)
- Age over 45
- Family history of type 2 diabetes.

SIGNS[19]

- Acanthosis Nigricans (Which Is A Darkening Of The Skin In Places Such As The Neck, Armpits, Elbows, Knees, And Knuckles).
- Dry and Itchy Skin
- Blurred Vision

- Slow healing Wounds
- Urinating more often than normal (Polyuria)
- Brain Fog-Inability to Focus Properly
- Increased Hunger

Clinical Manifestations [20]

The most common clinical manifestation is chronic skin infections. In women, pruritis and symptoms of vaginitis are common. Retinopathy or the combination of neuropathy, peripheral vascular disease and infections may manifest as foot ulceration or gangrene.

Complications[20]

Persistent hyper glycemia and hyper tension are the two major controllable factors that influence the development of diabetic complication. These can be divided into those caused by micro vascular disease and those secondary to macro vascular disease.

Renal failure due to severe micro vascular nephropathy is the major cause of death in Type1, where as macrovascular disease is the leading cause Type 2. blindness may occur in both type 1 and type 2.

Although neuropathy is common in both types, severe autonomic neuropathy is much more common type 1. Peripheral vascular disease causing ulceration or gangrene in the lower limbs is the major cause of hospital bed occupancy by patients with diabetes. Some of these chronic complications are discussed below.

Eye disease:

Blurring of vision is usually a benign occurrence associated with rapid changes in blood control. Open – angle glaucoma is more common in patients with diabetes. Cataracts are also common in patients with diabetes, past middle age.

In any population of adults with diabetes, retinopathy will be present in between 10% and 50%. In the early stages retinopathy may not interfere with the patient's vision.

Diseases of the Urinary Tract

Nephropathy is one of the potentially life-threatening complications of diabetes. Poor control of diabetes is associated with enlargement of kidney and in high glomerular filtration rate. Patients who go on to develop micro albuminuria are at risk of developing frank albuminuria and renal failure in later years.

Nerve damage:

Neuropathy can affect patients with diabetes in many different ways. Peripheral neuropathy is the

most common complication seen in type 2 DM patients. Paresthesias, numbness or pain may be predominant symptom. The feet are involved for more often than hands. It is most prevalent in elderly patients with type2, but may be found with any type of diabetes, at any age beyond childhood. Painful diabetic neuropathy is a cause of considerable morbidity.

Autonomic neuropathy may affect any part of the sympathetic or Para-sympathetic nervous system. The commonest manifestation is diabetic impotence bladder dysfunction usually takes the form of loss of Bladder tone with a large increase in volume. Diabetic diarrhoea may occur at night. Gastro paresis may cause delayed gastrointestinal transit and variable food absorption causing difficulty in the insulin – treated patients, or it may cause vomiting. Postural hypotension may also occur.

Cardio vascular disease:

Myocardial infarction is the major cause of death in diabetes. Peripheral vascular disease is associated with foot problems. Cerebrovascular events may also occur.

Hypotension occurs in association with both macrovascular and microvascular disease. A further risk factor for cardio vascular disease is dyslipidaemia.

Diabetic foot:

Foot problems in diabetes cause more inpatient bed occupancy. Foor ulcer can be divided in to 3 categories. Classical neuropathic ulceration occurs on the sole of the foot. The values can be deep but are usually painless.

Ischaemic ulcers are classically painful, usually occur on the distal end of the toes, and are associated with signs of peripheral vascular disease and ischaemia. The most common lessons are infected foot ulcers.

Diagnosis[18-20]

To diagnose diabetes, either fasting plasma glucose, random glucose or a post 75g glucose challenge glucose level can be used. Currently, there is international consensus that a fasting blood glucose level of ≥12mg/dl or a random or post meal glucose tolerance level of ≥200mg/dl in the presence of symptoms of hyperglycemia confers a diagnosis of diabetes.

THERAPY

Dietary therapy:

Diet and excurse are the first treatment of choice for patients with type 2 DM. 'Diabetic foods' are not recommended as they are often expensive and their nutritional content is not always compatable with healthy eating advice.

Dietary advice for people with diabetes is given below:

- Use high fat dietary foods eg:- skimmed milk, low fat yoghurt etc.
- Use grill, steam or oven bake foods
- Eat at least 5 portions of fruits and vegetables.
- Mono unnatural fats such as olive Oil are preferred.

When the diet and exercise do not achieve adequate blood glucose control, initiation with oral anti-diabetic is advocated.

Type 2 diabetes is a progressive metabolic disorder characterized by increasing b-cell failure with time. Treatment regimens that depend on some quantity of endogenous insulin secretion become less effective as the duration of type 2 diabetes increases. Treatment for hyperglycemia in type 2 diabetic patients usually progresses from lifestyle intervention, which ranges from dietary management and increased physical activity to addition of a single oral antihyperglycemic agent (monotherapy) to combinations of oral antihyperglycemic

agents and, finally, to combinations of oral antihyperglycemic agents with insulin.

Insulin therapy:

Insulin is the mainstay of treatment for patients with type1 diabetes, insulin is also important in type 2 diabetes when blood glucose levels can not be controlled by diet, weight loss, exercise and oral medications.

The common used insulin types are,

- Humlog and novolog / very short acting
- Regular / short acting
- NPH / Inter mediate acting
- Lente / Inter mediate acting.
- Ultrot Lente / Long acting
- Lanctus
- Combinations – 75 / 25, 70/30, 50/50.

Different methods of insulin delivery are,

- Prefilled insulin pens
- Insulin pump
- Intranasal, Transdermal, or inhalation.

Pharmacotherapy:

Type 2 diabetes is a common fast growing disease that affects about 5% of the population world wide. This disease is complicated by specific cardiovascular events and mortality rate. Pharmacological treatment is needed in greater than 80% of type 2 diabetes subjects.

There have been a tradition for many years to use only one antibiotic drug at a time and most patients are still treated with either insulin secretagogues or insulin alone. Both these have only a minor effect on cardio vascular events and mortality rate. Normalization of HbA1C results in declination of complication and mortality rate.

The three pathophysiological components which leads to development of hyper glycemia in obese adults are peripheral insulin resistant (reduced insulin mediated glucose uptake in skeletal muscle) insulin resistance in the liver (Resulting in inappropriate glucose production) and impared of insulin response to glucose.

Oral Hypoglycemic Agents

I. **Sulfonyl ureas**

(a) I Generation

Tolbutamide

Chlorpropamide

(b**)** **II Generation**

Glibenclamide

Glipizide

Gliquidone

Gliclazide

Glimepiride

II Biguanides

Metformin

III Non Sulfonyl urea insulinotropic

Repaglinide

Netaglinide

IV Thiazolidine diones

Rosiglitazone

Pioglitazone

I SULFONYL UREAS

Sulfonyl urea derivatives are a class of antidiabetic drugs that are used in the management of DM type 2. They act by increasing insulin release from the beta cells in the pancreas.

MODE OF ACTION

Sulfonyl ureas bind to an ATP – dependent K+ channel on the cell membrane of pancreatic beta cells. This inhibits a tonic, hyperpolarizing out flux of potassium (K+), which causes the electric potential over the membrane to become more positive. This depolarization opens voltage – gated Ca++ channels. The rise in intracellular Ca++ leads to increased fusion of insulin granula with the cell membrane, and therefore increased secretion of insulin.

There is some evidence that Sulfonyl urea also sensitise beta cells to glucose, that they limit glucose production in the liver, that they decrease lipolysis (break down and release of fatty acids by adipose tissue) and decrease clearance of insulin by the liver.

USES

Among 10% of patients, Sulfonyl urea used alone are ineffective in controlling blood glucose levels. Therefore an addition of metformin or a thiazolidine- dione may be necessary, or (ultimately) insulin.

II BIGUANIDES

MODE OF ACTION

The mechanism of action of biguanides are poorly been understood. They reduces gastro intestinal absorption of Carbohydrate; inhibition of hepatic gluconeogenesis; stimulation of tissue uptake of glucose; and increased insulin receptor binding. Of these the most important is the effect on hepatic gluconegenesis.

The major advantage of metformin over Sulfonyl urea is that it does not cause either hypoglycaemia or weight gain. Metformin is used in the obese patients with diabetes as it does not cause weight gain.

III REPAGLINIDE

MODE OF ACTION

Repaglinide acts by mediating the closure of ATP – sensitive K+ channels in the pancreatic beta cells, which causes subsequent depolarization, thereby stimulating the release of insulin from beta cells.

USE

Repaglinide is an effective first line therapy in type 2 diabetes and may be used in combination with metformin to produce a synergistic effect. It is indicated in type 2 patients who are not controlled on diet alone or on metformin alone. Repaglinide lowers fasting and post – prandial blood glucose by approximately 4 m mol/l and 7m mol/l respectively.

IV THIAZOLIDINE DIONES

MODE OF ACTION

They acts by enhancing insulin action and promoting glucose utilization in peripheral tissues, possibly by stimulating non – oxidative glucose metabolism in muscle and suppressing gluconeogenesis in liver. They also have an effect on reducing insulin resistance.They act most effectively in combination with other oral antidiabetic agents including Sulfonyl urea and metformin.

USE

Thiazolidine - diones improves glycaemic control in patients with insulin resistance by reducing HbA1C levels to 1.5%. The combination of Thiazolidine diones with metformin is preferred to combination with Sulfonyl urea, especially in overweight patients.

GLYCEMIC CONTROL WITH MONOTHERAPY[7]

First line mono therapy typically begins with (an insulin secretagogue) or metformin (which inhibit hepatic gluconeogenesis).

Metformin is after used in overweight or obese subject, unless contra indicated or not tolerated and Sulfonyl ureas (SUS) are prescribed in leaner subjects and those who can't receive or tolerate metformin.

Studies have reported decrease in basal and post prandial plasma glucose (PPPG) levels of ~ 3 to 5 m mol/l following 3 to 6 months of treatment Sulfonyl ureas. Glycated haemoglobin has also been demonstrated to decrease by 20%. Clinical studies have reported significant reduction in fasting plasma glucose concentration (FPG) (22 to 26% of pre treatment levels) and glycated haemoglobin levels (12 to 17% of pre treatment levels) with metformin monotherapy.

For patients with type 2 diabetes, oral mono therapy may be initially effective for controlling blood glucose. But it is associated with a high secondary failure rate.(Primary failure is frequent only in patients with high base line blood glucose at the time of beginning mono therapy, where as secondary failure is to be expected in the course of disease).

GLYCEMIC CONTROL WITH COMBINATION THERAPY [20]

A major problem in the management of type 2 diabetes is that glycemic control with diet and / or drug treatment declines as the disease progresses. Various anti diabetic combination therapies have been established to overcome this and should be introduced as soon as diet or drug mono therapy fail.

The combination therapy can improve insulin insensitivity β-cell function or both. The different classes of oral agents used to treat type 2 diabetes have complementary mechanism of action, and their use in combination often results in blood glucose reduction. Once "Secondary failure" to

monotherapy occurs combinations therapy is introduced, usually metformin and sulfonyl urea; or a Thaizolodene dione + sulfonyl urea or metformin. Thaizolidine diones stimulate increased peripheral in the muscle, liver and adipose tissue. Metformin inhibits glucose genesis.

Combination therapy with Thiazolidine dione and a biguanide (Metformin) offers the additional benefit of complementary mechanism of action without increasing the risk of hypoglycemia. Thiazolidine diones and metformin lower cardiac rule factors, as well as lowering serum glucose are there for the best choice, for the initial therapy of type 2 Diabetes Mellitus.

COMBINATION THERAPY[7-8]

The basic principal of combination therapy is that small doses of 2 drugs, there is greater efficiency and fever side effects than with a large dose of either drug used as mono therapy.

The choice of addition on Thiazolidine dione or insulin therapy when 2 oral agents are sufficient to control glycemia in patients with type 2 diabetes. Because the addition of a third oral agent is unlikely to decrease HbA1C levels by >1.5-1.7%, insulin is often the only means of lowering HbA1C to target levels when the base line is >8.5-9.0% the introduction of triple agent combination at lower base line HbA1C levels, (ie, earlier in the disease course) could potentially increase the percentage of patients attending HbA1C -7%. In addition longer term studies beyond 24 weeks may demonstrate that more patients can attain and sustain these glycemic targets.

A higher incidence of confirmed overall and nocturnal hypoglygcemic events occurred in the insulin glargine group. However, compared with rosiglitazone, insuline glargine was associated with fever adverse effects, less weight gain, and no odema, where as 12.5% of patients receiving rosigliitazone reported odema, a common side effects associated with these agents. Although insulin therapy produce modest weight gain, rosiglitazone led to twice as much weight gain (3kg) as insulin glargine (1.6). Thus patients treated with insulin glargine resulted in a significantly improved serum lipid profile compared with those treated with rosiglitazone.

In summary, both low dose insulin glargine and maximam dose rosiglitazone effectively. Lowered HbA1C levels in triple therapy regimens, with glargine conferring lower FPG levels over all and greater improvements in patients with higher baseline HbA1C levels.

COMBINATION THERAPY WITH ORAL AGENTS [20]

When a maximal dose of metformin or sulfonyl urea is used as mono therapy, about 25% of patients with type 2 diabetes with a starting fasting plasma glucose level of 12.2 -13.3 mm/l will achieve an acceptable level of glycemic control accordingly to American diabetes association guidelines (Fasting plasma glucose level < 7.8 mmo/l and HbA1C values < 8.0%, however because the hypoglycemic effect of troglitazone can anticipate that a smaller percentage of patients

will reach the desired therapeutic goal. An even smaller percentage of patients with type 2 diabetes will achieve acceptable glycemic control with acarbose therapy. There for most patients with type 2 diabetes will require combination therapy to reach an acceptable level of glycemic control. Moreover, because type 2 diabetes mellitus is a progressive disease, even patients with a good initial response to oral agents eventually will require a second (or third) medication.

The most commonly used combination therapy is metformin + a sulfonyl urea. Addition of met forming to sulfonyl urea therapy gives an additive glucose- lowering effect. It also gives an additive response both with respect to glucose lowering and lipid lowering effects. Numerous studied have shown that addition of acarbose to sulfonyl urea or to met forming therapy provides an addictive effect.

When insulin is used as mono therapy large dosages (>80 to 100 v/d) are required to achieve normoglycemia, and significant weight gain commonly occurs. Because combination therapy with bed tine insulin and oral agents effectively reduces elevated plasma glucose levels, requires considerably less insulin (Therapy minimizing, weight gain) and often allows for fewer insulin injections per day.

COMBINATION THERAPY WITH BEDTIME INSULIN PLUS ORAL AGENTS [20]

The effectiveness of bedtime insulin therapy in patients with type 2 diabetes in acceptable glycemic control does not occur with oral agents alone or in combination and is well documented. In such patients, the elevated fasting plasma glucose level is caused by incomplete suppression of basal hepatic glucose production by sulfonyl urea or metformin. Low doses of insulin effectively suppress hepatic glucose production and have a much smaller effect on stimulating muscle glucose uptake. By giving a modest dose of intermediate – acting insulin(such as NPH insulin) at bed time, the elevated basal rate of hepatic glucose production can be reduced to normal, and the likelihood of hypoglycaemia will decrease. A meta- analysis of 16 randomized, place bed controlled trials comparing sulfonyl urea plus insulin with place plus insulin showed significantly lower fasting plasma glucose and HbA1C values.

In diabetic patients receiving sulfonyl urea plus metformin in whom the desired therapeutic goal in not reached, option include addition of a third oral agent (acarbose), addition of bed time NPH insulin or switching to a multiple insulin injection regimen.

TRIPLE DRUG ORAL ANTI DIABETIC THERAPY [8]

Triple drug oral anti diabetic therapy is an effective long term treatment for a substantial proportion of patients with type 2 diabetes. This stepwise, progressive, combination therapy is essential if the target glycemic goal of a HbA1c 7% is to be achieved and maintained.

CONCLUSION

Diabetes is a global epidemic that will continue to affect the lives of millions of people, their families and health care systems. The evidence was overwhelming that diabetes can be prevented through life style changes and medications. In addition, aggressive risk factors management with particular focus on blood glucose lipid and blood pressure control can mitigate the complications associated with diabetes. By promoting prevention , early treatment and risk reduction of diabetes linked metabolic syndrome ,health care professionals can improved diabetes outcome in their own backyard globally.

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