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AN OVERVIEW :TYPE 2 DIABETES MELLITUS AND FUTURE PROPECTS FOR THE TREATMENT

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ABSTRACT: Type-2 diabetes is a major, non-communicable disease with increasing prevalence at a global level. Type-2 diabetes results when the body does not make enough insulin or the body cannot use the insulin it produces. Type-2 diabetes is the leading cause of premature deaths. Improperly managed, it can lead to a number of health issues, including heart diseases, stroke, kidney disease, blindness, nerve damage, leg and foot amputations, and death. Type-2 diabetes or adult-onset diabetes is most common type of diabetes, usually begins when a person is in his or her mid-50s, but diabetes is not inevitable. Minor changes in your lifestyle can greatly reduce your chances of getting this disease. Therefore, in order to prevent this condition, action should be taken regarding the modifiable factors that influence its development-lifestyle and dietary habits. However, with proper testing, treatment and lifestyle changes, healthy eating as a strategy, promote walking, exercise, and other physical activities have beneficial effects on human health and prevention or treatment of diabetes, promoting adherence to this pattern is of considerable public health importance.

KEYWORDS: Type 2 Diabetes Mellitus, DPP4, GLP, SGLT2, Future Treatment.

INTRODUCTION:

More than 400 million people worldwide have type 2 diabetes mellitus (T2DM), a condition. More than 640 million people will have diabetes worldwide in 2040[1]. DM is brought on by either a lack of insulin secretion, injury to pancreatic cells, or insulin resistance brought on by inadequate insulin usage. The main factor contributing to the continued rise in the number of diabetic patients worldwide, which is predicted to reach 366 million in the elderly population (those over 65 years old) in 2030, may be a tendency toward sedentary living [2]. There are two different varieties of DM: type 1 and type 2. Type 1 diabetes is an autoimmune condition that damages pancreatic cells, reducing or impairing the production of insulin, whereas type 2 diabetes is caused by a malfunction of the pancreatic beta cells, which makes it difficult for the person to use insulin[3].

Good glycaemic control is essential for preventing the onset or progression of diabetes complications, according to treatment algorithms for the disease. There are now more hypo-glycaemic medications available for the treatment of T2DM than ever before. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recently released a policy statement on a patient-centred approach to the management of patients with type 2 diabetes (T2DM)[4]. TARGETS FOR GLYCEMIA The management of type 2 diabetic patients still places a lot of emphasis on glucose control. This should, however, always be done as part of a comprehensive programme to lower cardiovascular risk factors, which should also include quitting smoking and establishing other healthy lifestyle habits, managing blood pressure, managing lipids with statins as the first choice, and, in some cases, antiplatelet therapy.

PATHOPHYSIOLOGY OF DIABETES:

Several hormones work together to keep the body's level of glucose in equilibrium. However, the regulation of glucose homeostasis is mostly regulated by two hormones, glucagon and insulin[5]. When the level of glucose increases, cells secrete insulin. Insulin lowers blood sugar levels by either

A. by preventing the liver's glycogenolysis and gluconeogenesis processes from producing glucose or
B. by enhancing liver, muscle, and fat tissue glucose uptake[6].

Type 2 diabetes pathophysiology

Different ethnic groups suffer from type 2 diabetes with varying prevalence. Native Americans, especially Native Americans, Hispanics, and Asian Americans of the desert southwest are among the most affected groups in the United States[7]. The steady d ecline in β cell activity that occurs against the background of insulin resistance leads to changes in glucose metabolism.

β cell functions

An ongoing loss in β -cell function is one of the key causes of type 2 diabetes' protracted progression. According to a number of studies, the onset of diabetes and prediabetes occurs only when the β-cell is unable to adequately respond to the state of peripheral insulin resistance[8]. The mass and secretory capacity of the β -cell, which are regulated by genetic and environmental variables, are two elements that determine the β -cell's potential to release enough insulin to effectively respond to the peripheral insulin resistance condition[8].

Insulin resistance

The number of persons worldwide with type 2 diabetes mellitus is predicted to reach 250 million by the year 2020. Although the main causes of this illness are unknown, it is certain that insulin resistance plays a significant role in its progression[9]. Additionally, insulin resistance affects type 2 diabetes' gradual -cell failure by increasing the demand on the β -cell to produce excessive amounts of insulin[9].

Fig. 1. Mechanism of Type 2 Diabetes

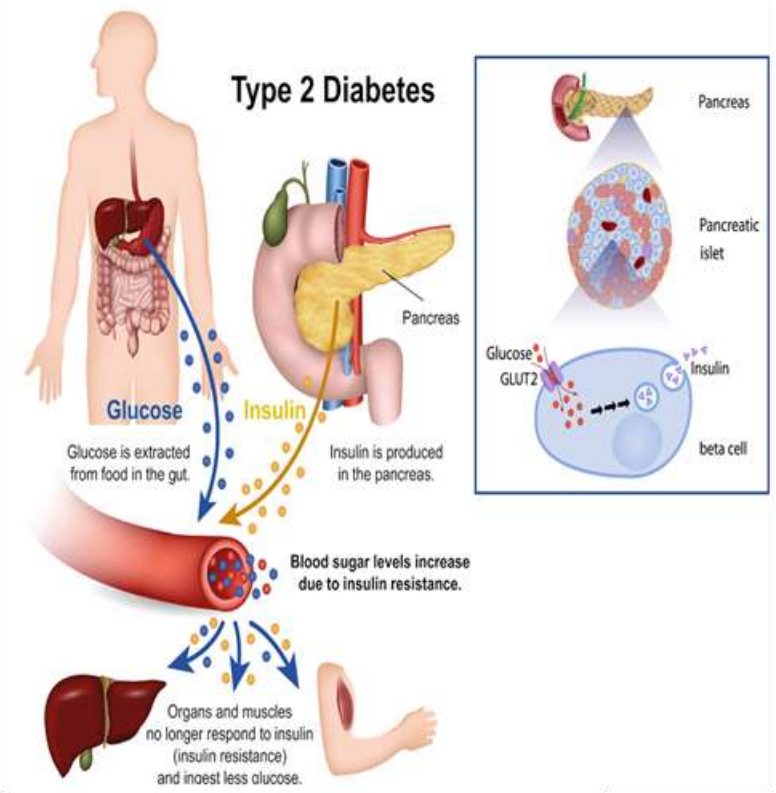
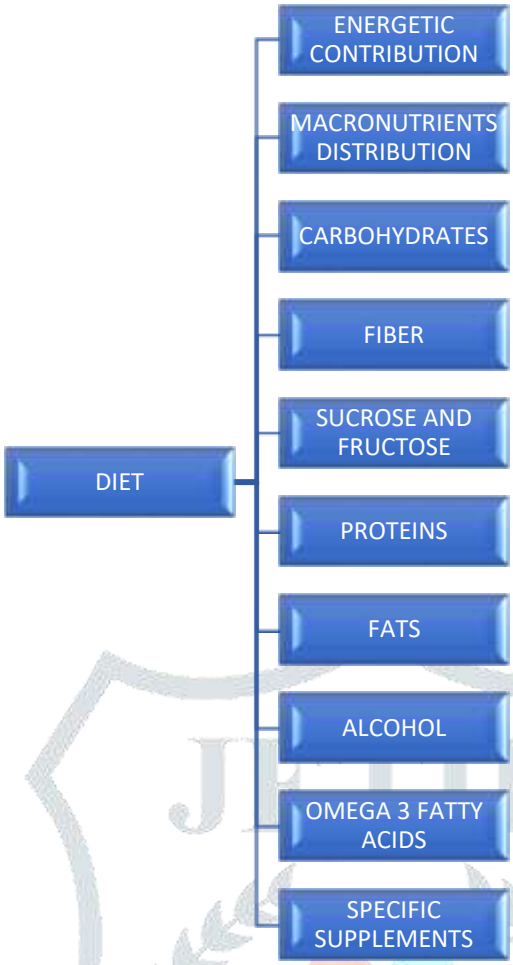


Fig. 1. Mechanism of Type 2 Diabetes

Lifestyle changes

Food intake and physical activity are the two main determinants of energy balance[10]. All patients should be advised to sleep around 7 hours a night, as adequate rest is essential for maintaining energy levels and general health[11]. Evidence suggests that sleeping 6-9 hours per night reduces the risk of cardiometabolic disease[12]. Sleep deprivation can worsen conditions like insulin resistance, high blood pressure, high blood sugar, and dyslipidemia[13]. Although drug options are expanding and providing additional treatment opportunities, particularly in T2D, lifestyle changes are central to the strategy for these patients and are necessary to achieve treatment goals[14].

Diet



It is typically advised to follow a diabetic diet that restricts calories to encourage weight loss[15]. In addition, it is advised to emphasise the consumption of fruits, vegetables, low-fat dairy products, reduced saturated fat, and a macronutrient intake that is customised for each person in order to distribute calories and carbohydrates throughout the day[16]. Several diets may be effective such as the Dietary Approaches to Stop Hypertension (DASH), Mediterranean diet, low-fat diet, or monitored carbohydrate diets such as a low carbohydrate diet[17]. Viscous fibre supplements may be useful in those with diabetes[18].

Energetic contribution

The total amount of calories in the diet will depend on a number of variables, including whether or not there is overweight or obesity. The following equation can be used to determine the body mass index (BMI), a metric frequently used in clinical practise to categorise patients: Height (m2)/weight (kg)[19]

Classification of degree of obesity by body mass index

Body mass index (kg/m2)	
Normal weight	18.5-24.9
Overweight grade 1	25-26.9
Overweight grade 2	27-29.9
Obesity grade 1	30-34.9
Obesity grade 2	35-39.9
Obesity grade 3 (morbid)	40-49.9
Obesity grade 4 (extreme)	≥ 50

Adapted from World Health Organization (WHO) 1995, WHO 2000 and WHO 2004.

Macronutrients distribution

Due to the lack of evidence, an optimal distribution of proteins, fats and carbohydrates is not recommended. In addition to the many dietary patterns that have been studied, such as Mediterranean diets, vegetarian or vegan diets, antihypertensive diets (DASH), low-fat diets, and low-carb diets, several studies attempting to assign ratios macronutrients have failed. produce reliable results. However, these studies observed limited effectiveness of Mediterranean diets, vegetarian or vegan diets, low-fat diets, and low-carb diets for diabetes management. More research is needed, as benefits were only seen when weight loss was also included [20]. A low-fat diet limits fat and often cholesterol and saturated fat.

Low fat diet plans are designed to reduce the incidence of obesity and diseases such as heart disease. Since weight loss success is not influenced by macronutrient composition, they work similarly to low-carb diets in weight loss [21].

Carbohydrates

The amount and type of carbohydrates has been shown to be the most important variable in blood sugar management, although there is no general consensus on what percentage of carbohydrates people with diabetes should consume. According to research, all patients should count their carbohydrates. For people taking insulin, it may improve blood sugar regulation after meals. Using this method, patients consume known amounts of carbs, broken down into meals and calculated as grams of carbs per serving[22].

A low carbohydrate diet limits carbohydrate intake compared to a typical diet. Limit foods high in carbohydrates (such as sugar, bread and pasta) and replace them with foods high in fat and protein (such as meat, chicken, fish, shellfish, eggs, cheese , nuts, and seeds) and low-carb foods — Carbohydrate foods (such as spinach, kale, Swiss chard, kale, and other fibrous vegetables)[23].

Fig 2. An example of a low carbohydrate dish, cooked kale and poached eggs

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Fibres

Numerous dietitians concur that consuming 25 grammes of fibre daily is the recommended amount of fibre. In this regard, it is preferable to begin the first week with a dose of around 5 grammes per day. Next week, increase from 5 to 10. steadily up until you are consuming 25 grammes of fibre daily[24]. Consuming enough dietary fibre, particularly fibre that contains natural resources, has been demonstrated to help patients with diabetes manage their glycaemic and cardiovascular risk factors, which lowers their risk of cardiovascular mortality[25].

Sucrose and fructose

Consuming free fructose (naturally occurring from foods like fruit) did not impact glycaemic control more than other types of sugar, although it should be avoided beyond 12% of daily calories[26]. Fructose is absorbed from the small intestine into the bloodstream similarly to how glucose is. Compared to glucose, it elevates blood sugar levels more gradually, and it doesn't seem to quickly change insulin levels. Fructose may not immediately elevate blood sugar levels, but it may have more detrimental long-term effects[27]. Contrary to popular belief, when sucrose is replaced for isocaloric levels of starch, intakes of 10% to 35% of total energy do not negatively affect glycaemic or lipid responses[28].

Proteins

Differentiating diabetic people with renal disease from those who do not is an interesting concept. Although evaluating scientific studies, it was not possible to draw a solid judgement regarding this matter. In adults without kidney disease, the typical recommended protein intake ranges from 15% to 20%. Various randomised clinical trials with this topic have been conducted and the results are available in the literature. On the one hand, studies show that the levels of HbA1c, triglycerides, total cholesterol, and/or LDL cholesterol can be improved by including 28% to 40% of the diet's energy as proteins[29].

Fats

Fats and the risk of developing obesity and cardiovascular disease have been linked in epidemiological research[30]. There is no ideal fat proportion, as there is with the other immediate principles, and diabetic patients typically follow the recommendations for the general population (between 20% and 35%), paying particular attention if the patient is overweight, in which case the percentage should be at the lower limits. In spite of these recommendations, diabetic patients frequently consume more fat than is advised[31]. Few research have been conducted on the consumption of saturated fatty acids or cholesterol in diabetic patients; however, the general public's guidelines apply to diabetic patients as well: A minimum trans fatty acid intake, a contribution of cholesterol of 300 mg/dL, and a contribution of saturated fat of no more than 10%[32].Since about 20 years ago, most people are aware of how a high-fat diet might cause insulin resistance and T2D. Obesity is brought on by a high-fat diet that boosts cellular lipid build up. Increased levels of pro-inflammatory cytokines and other hormones or substances linked to insulin resistance are brought on by excess body fat[33].

Alcohols

Alcohol should be consumed in moderation and shouldn't be consumed in amounts greater than one serving per day for women or two servings per day for males. This contribution must be traded for other items in order to prevent an excess of energy when

they are consumed. In several research, it has been discovered that moderate consumption improves glycaemic control and lowers the risk of cardiovascular events rather than harming glycaemic control[34].

Omega 3 fatty acid

Although there have been some discrepancies, over all we cannot state that omega-3 supplements have clearly benefited cardiovascular health[35]. However, consumption of products high in omega-3 can be positive in preventing cardiovascular disease[36].

Specific supplement

Trials have been conducted to determine the possible advantages of dietary supplements containing certain particular nutrients for diabetic patients. Despite this, there is no solid evidence to support the benefits of supplementing the diet with antioxidants such vitamins and carotenes, micronutrients like chromium, or other herbs in order to improve glycaemic control. The recommended intakes of vitamins and minerals are the same as for the general population, and they are met through a diversified diet[30].

Exercise

The foundations of diabetic management are an appropriate diet and regular exercise[37]. with one study showing that more exercise led to better results[38]. Regular exercise has been shown to lower blood lipid levels, reduce body fat, and enhance blood sugar control[39]. In general, there are numerous advantages to encouraging exercise within a certain strategy. improved glycaemic management and increased insulin sensitivity in tissues[40].

Benefits of glycaemic control

In several trials, patients with T2DM who exercise have shown to have a considerable reduction in HbA1c. The features of the patient and the type of training will determine the difference in the degree of progress seen in the various studies, thus it is more beneficial when training programmes are based on aerobic exercises than programmes based on muscle strength in isolation[41].

Other benefits

Other metabolic markers also improve as a result of physical activity. Dyslipidaemia, hypertension, weight maintenance, psychological advantages, decreased mortality, enhanced cardiorespiratory fitness, and peripheral neuropathy are some of the cardiovascular risk factors it helps manage[32,41].

Types of exercise:

Both aerobic and resistance exercises have demonstrated benefits in people with diabetes through increased glucose uptake and decreased insulin resistance[1].

Aerobic exercise

Walking, jogging, and cycling are examples of activities that use large muscle groups continuously and rhythmically for aerobic exercise. According to the most recent ADA standards, individual sessions of aerobic exercise should ideally last at least 30 minutes per day and be undertaken three to seven days a week[42]. Cardiovascular output (VO2max) is improved by moderate to intense aerobic exercise training (65%–90% of maximum heart and rate), which is linked to significantly lower cardiovascular and overall mortality risk in type 2 diabetic individuals[44]. Significantly, there is considerable evidence to support the benefits of aerobic exercise on weight loss and the improved control of lipid and lipoprotein metabolism, and it is a well-established method to lower HbA1c[44].

Resistance training

Resistance training has become widely recognised over the past 20 years as a suitable kind of exercise for those with type 2 diabetes. Resistance exercise, often known as strength training, involves motions performed with the use of free weights, weight machines, body weight exercises, or elastic resistance bands[45].

Increases in strength, bone mineral density, blood pressure, lipid profiles, cardiovascular health, insulin sensitivity, and muscle mass have been observed in studies investigating the effects of resistance training in type 2 diabetes. These improvements vary from 10% to 15%. Furthermore, because of the increased prevalence of type 2 diabetes with aging, coupled with age-related decline in muscle mass, known as sarcopenia, resistance training can provide additional health benefits in older adults[47].

American Diabetes Association recommendations for exercise in type 2 diabetes
Aerobic exercise: At least 150 minutes/week of moderate to vigorous exercise • **spread over 3 to 7 days/week, with no more than 2 consecutive days between exercise bouts** • **Daily exercise is suggested to maximize insulin action** • **Shorter durations (at least 75 minutes/week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit patients** • **May be performed continuously, or as high-intensity interval training**
Resistance exercise: Progressive moderate to vigorous resistance training should be completed 2 to 3 times/week on non-consecutive days • **At least 8 to 10 exercises, with completion of 1 to 3 sets of 10 to 15 repetitions**

Table 1: American Diabetes Association recommendation for exercise in type 2 diabetes

Unstructured physical activity

Additionally, it is advised to encourage patients to use more energy during normal everyday activities. It calls for greater unstructured physical activity (walking more in the day, climb the stairs)[48].

TREATMENT:

It is important to promote a diet rich in fibre and monounsaturated fats, low in processed carbs, high fructose corn syrup, and saturated fat. 90 to 150 minutes per week of aerobic exercise is also useful. Weight loss is the main goal for obese T2DM patients[49].

Table 2: Treatment of type 2 diabetes

Oral antidiabetics	Mechanism of action	Side effects
Sulfonylureas		
Glimiperide (Amaryl) Glipiside (Glucotrol) Glipiside-gits (Glucotrol-XL) Glyburide (Diabeta, Micronase) Glyburide micronized (Glynase) Tolbutamide (Orinase) Chlorpropamide (Diabinese) Tolazamide (Tolinase) Acetoheximide (Dymelor)	Stimulate first-phase insulin secretion by blocking K^+ channel in β-cells	Late hyperinsulinemia and hypoglycaemia Weight gain
Meglitinides		
Repaglinide (Prandin) Nateglinide (Starlix)	Stimulate first-phase insulin secretion by blocking K^+ channel in β-cells	Hypoglycaemia Weight gain
Biguanides		
Meformin (Glucophage, Riomet) Metformin-XR (Glucophage-XR)	Decrease hepatic glucose production Increase muscle glucose uptake and utilization	Nausea, Diarrhea Anorexia, Lactic acidosis
Thiazolidinediones		
Rosiglitazone (Avandia) Pioglitazone (Actos)	Increase insulin sensitivity via activation of PPAR-γ receptors	Fluid retention and weight gain
α-Glucoside Inhibitors		
Acarbose (Precose) Miglitol (Glyset)	Decrease hepatic glucose production Delay glucose absorption	Flatulence Abdominal bloating

Table 2: Treatment of type 2 diabetes

Sulfonylureas and Meglitinides-

Sulfonylureas and meglitinides or glinides (insulin secretagogues), two distinct groups of oral hypoglycaemic medications, share a similar mode of action in that they both encourage the release of insulin from pancreatic beta cells. From its debut to clinical practise in the 1950s, sulfonylureas have been widely used as a first- or second-line therapy for patients with T2DM[50].

Mechanism of action

Sulfonylureas and glinides both work by boosting insulin secretion, which is controlled by potassium channels that are sensitive to ATP (KATP potassium channels), which are found in the membrane of beta cells in the pancreas. Sulfonylureas and glinides both cause channel closure and cell depolarization, which in turn raises cytoplasmic calcium levels and, as a result, insulin production, even though the receptor's binding site is distinct for each[51].

Pharmacokinetics

The distinct reactions that each medication produces are a result of variations in the pharmacokinetic and binding characteristics of insulin secretagogues. One can distinguish between first- and second-generation sulfonylureas. Second-generation sulfonylureas include glimepiride, glipizide, gliclazide, and glyburide (also known as glibenclamide in Europe). Agents of the new generation are more powerful and cause fewer side effects. Even though second-generation sulfonylureas are equally effective, there are differences in how they are absorbed, how they are metabolised, how long they last, and how much of them to take. For instance, glyburide has active metabolites that can extend how long they take effect[51].

Side effects

The three main side effects of using these medications are efficacy loss, hypo glycaemia, and weight gain. As beta cell failure and islet dysfunction worsen over time, insulin secretagogues lose their ability to operate (secondary failure). As a result, the proportion of patients who consistently maintain acceptable glycaemic control gradually declines. Although this impact might also be linked to the development of the disease, it has demonstrated a higher rate of secondary failure than other medications[52].

Biguanides-

Metformin is considered the agent of first line for treatment of T2DM, in the absence of contraindications.

Mechanism of action

The intestinal barrier's integrity is maintained by mucosal AMP-activated protein kinase (AMPK), which is triggered by metformin and can alter the composition of the gut microbiota. These outcomes appear to represent the method by which metformin reduces lipopolysaccharide (LPS) levels in the blood and the liver, in conjunction with the activation of AMPK in hepatocytes[54].

Side effects

The most common ones, which are typically minor and temporary, are gastrointestinal, including anorexia, nausea, abdominal pain, and diarrhoea. Metformin also reduces vitamin B12 absorption through the digestive tract. Lactic acidosis is far less typical. There were no instances of lactic acidosis in a review of 347 randomised trials and prospective cohort studies. Nonetheless, due to the high case-fatality rate, is crucial. Predisposing circumstances include all circumstances that increase the risk of hypoperfusion and hypoxemia (sepsis, heart failure, dehydration, acute or progressive renal impairment[55].

Thiazolidinediones-

Mechanism of action

Through affecting muscle, adipose tissue, and the liver to improve glucose utilisation and decrease glucose synthesis, TZD increases insulin sensitivity. TZD bind to receptors that are triggered by peroxisome proliferator (PPARs). The central nervous system, macrophages, vascular endothelium, adipose tissue, and pancreatic beta-cells are the main locations of PPAR-. Those who are obese or diabetic have higher levels of PPAR gamma in their skeletal muscle. Weight gain related with TZD is partially caused by the stimulation of PPAR-gamma in the central nervous system, which promotes greater feeding[56].

Side effects

Heart Failure- When PPAR-gamma is stimulated by TZD treatment, sodium reabsorption is activated in the luminal membrane of the collecting tubule cells, causing fluid retention that may precipitate heart failure or exacerbate it. PPAR- is more prevalent in the collecting tubules of the nephron. In individuals on TZD treatment, peripheral oedema develops in 4%–6% of cases; patients with a history of heart failure are more likely to experience this condition.

Weight gain - Fluid retention, the activation of PPAR- in the central nervous system (which increases feeding), and the upregulation of genes that facilitate adipocyte lipid storage are just a few of the diverse mechanisms that contribute to weight gain. In part, weight gain may also be a result of the proliferation of new adipocytes. It depends on both time and dose[1].

α Glucoside Inhibitors –

There are now three agents on the market: acarbose, miglitol, and voglibose. They have distinct features compared to other antidiabetics because of how they work. For more than 20 years, acarbose has been used to treat hyper glycemia[57].

Mechanism of action

Alpha-glucosidases are enzyme complexes that hydrolyse oligosaccharides into monosaccharides and are found in the brush border membrane of the small intestine. They produce a reversible suppression of membrane-bound intestinal alpha-glucoside hydrolase enzymes and are structurally related to natural oligosaccharides with increased affinity for alpha-glucosidases. This delays the digestion and absorption of carbohydrates and lowers postprandial hyper glycemia. Plasma RA-GLP1 levels are raised by the

unprocessed carbohydrates in the small intestine's lower portion. Alpha-glucosidase inhibitors do not increase insulin secretion because of lower blood glucose levels[58].

Side Effects

The gastrointestinal side effects, which primarily include flatulence, diarrhoea, and stomach pain. Although they are typically not severe, these symptoms are the most frequent cause of treatment termination and may hinder compliance. These signs appear when undigested carbohydrates enter the colon, which causes fermentation by bacteria in the large intestine and the formation of intestinal gas[59].

THE FUTURE TREATMET FOR DIABETES:

All anti-diabetic medications, sadly, have side effects and are expensive. Thus, one of the biggest challenges for researchers is to look into novel anti-diabetic regimens that are less expensive and have negative side effects.

The ability to self-renew and differentiate into every type of body cell exists in embryonic stem cells (ESCs) and induced pluripotent stem (iPS) cells. They guarantee an almost limitless supply of particular cell types for fundamental study, pharmacological testing, and perhaps future transplant therapy[59].

Smart Insulin Patch-

A novel intelligent insulin patch has been developed. There are more than 100 tiny needles covering the thin square. The biocompatible patch is simple to apply and works quickly. Little, painless needles packed with insulin and glucose-sensitive enzymes in minuscule storage units make up the patch. These enzymes are released by the patch when blood glucose levels rise. Patch treatment resulted in lower glucose levels in a mouse model for up to 9 hours. As humans are more sensitive to insulin than mice, it is hypothesised that the patch may work longer on diabetic people[60].

Dual Acting Peptide-

The two principal incretin hormones that are released from the intestine in response to meal intake are GLP1 and GIP. Both hormones increase the release of insulin that is dependent on blood sugar. GLP1 co-administration with the incretin hormone GIP may increase its anti-obesity efficacy, according to evidence from animal research. According to research by Finan et al., an acylated form of the GLP1 and GIP dual agonist decreased weight (-18.8% vs -8.8%, P 0.001), food consumption (P 0.05), fat mass (P 0.001), and blood sugar (P 0.05) when compared to liraglutide. revealed that liraglutide did not have any effect on increases in plasma insulin or C-peptide (P 0.001 for both)[61].

G protein coupled receptor-

Agonists for G protein-coupled receptor 119 (GPR119) are G protein-coupled receptors that are mostly expressed in the pancreas, gastrointestinal system, and brain of rats, humans, and other mammals. Rats with the receptor activated consumed less food and gained less weight. It has been demonstrated that GPR119 controls the release of incretin and insulin. Novel therapies for diabetes and obesity have been proposed using new drugs that operate on this receptor[1].

Oral Insulin –

An innovative method of treating patients with T2DM is by giving them insulin orally. Parenteral insulin acts more physiologically than oral insulin. In comparison to parenteral insulin, it decreases glycogenolysis, hepatic glucose synthesis, and the risk of hypo-glycaemia because it first passes via the liver. Presently available evidence from human trials indicate that could be a cutting-edge method for treating diabetes[62].

GLP- 1Ras-

GLP-1RAs were first launched in 2005; they are either exendin-like peptides (exenatide and lixisenatide) or more homologous GLP-1 analogues that have been structurally modified and designed to lessen breakdown by DPP-4. Present-day GLP-1RAs are injected subcutaneously and work by activating the GLP-1 receptor to increase the incretin action. Its glucose-lowering action, which bears a minimal risk of hypo- glycemia, is connected to the administration schedule (once or twice daily or once weekly), so that short-acting medicines can target prandial glucose excursions and longer-acting drugs can give a delayed incretin effect[63].

SGLT 2 Inhibitors-

After their release in 2012, SGLT-2 inhibitors have gained popularity as second- and third-line glucose-lowering medications with little risk of hypo-glycemia as well as effects on weight and blood pressure. With acceptable renal function, their insulin-independent glucosuric activity distinguishes them from other glucose-lowering drugs and enables administration in combination with any other drug class at any point in type 2 diabetes' natural course[64].

CONCLUSION:

By shifting from a broad algorithm to one that is stratified by group and then adjusted to provide a more personalised approach, the evolution of treatment advice for type 2 diabetes has aimed to improve the individual's choice of medication. In particular, cardio-renal illnesses and other ailments that frequently accompany diabetes are among the co-morbidities and problems that prescribers are increasingly searching for features that will also address. If regulators mandate that large prospective outcome trials like the CVOTs continue in their current format, this may discourage pharmaceutical companies from investing in wholly novel high-risk agents. Large prospective outcome trials like the CVOTs are very expensive (likely costing in the range of 200-500 million US dollars).

T2DM can currently be treated using a variety of medication families that come in both oral and injectable forms. Sulfonylureas, meglitinides, insulin, TZD, and alpha-glucosidase inhibitors are a few of these. More recently, RA-GLP1 receptor agonists iDPP4 and iSGLT2 have also been included. Moreover, insulin analogues have been created that more accurately mimic endogenous insulin production. Most patients still choose metformin as their first-line therapy. Other alternative or second-line treatment options should be tailored to the specific patient, taking into account their co-morbidities, level of hyper-glycemia, preferences for and

access to treatments, as well as the treatment's efficacy and durability in lowering blood sugar, risk of hypo-glycaemia, and effectiveness in reducing complications related to diabetes.

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