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OVERVIEW OF DISEASE DIABETES MELLITUS

Mr. Shinde Shubham Bhagunath*1, Mr. Gosavi Sarthak Abhay*2,
Miss. Bansode Bhakti Ravindra*3, Miss. Nehe Rutuja Balasaheb*4
*1,2,3,4Ashwin College Of Pharmacy, Manchi Hill, India.

ABSTRACT

Globally, the prevalence of type 2 diabetes mellitus (DM), a chronic metabolic condition, has been gradually rising. Due to this trend, the disease is quickly spreading to other parts of the world and is predicted to affect twice as many people in the next ten years as a result of an aging population. This will increase the burden already placed on healthcare providers, particularly in less developed nations. The Cochrane Database of Systemic Reviews, Medline, and citation lists of pertinent papers were searched in order to compile the basis for this review. Type 2 diabetes mellitus, prevalence, current diagnosis, and current therapy are included in the subject heading and key terms.

Criteria from the American Diabetes Association (ADA) and the World Health Organization (WHO) that take into account both laboratory and clinical data. Although there is currently no known cure for the condition, treatment options include changing one's lifestyle, managing obesity, taking oral hypoglycemic medications, and using insulin sensitizers like metformin, a biguanide that lowers insulin resistance. Metformin is still the first-line medication that is advised, particularly for patients who are obese. Other useful drugs include insulin, thiazolidinediones, alpha glucosidase inhibitors, and non-sulfonylurea secretagogues. New drugs such as glucagon-like peptide 1 analogs, dipeptidyl peptidase-IV inhibitors, insulin-releasing glucokinase activators, inhibitors of sodium-glucose cotransporter 2 and 11ß-hydroxysteroid dehydrogenase 1, pancreatic-G-protein-coupled fatty acid receptor agonists, glucagon-receptor antagonists, metabolic inhibitors of hepatic glucose output, and quick-release bromocriptine have been developed as a result of recent research into the pathophysiology of type 2 diabetes mellitus. Despite having a 2006 license to be used, inhaled insulin has been taken off the market due to minimal customer demand.

Keywords: Type 2 Diabetes Mellitus, Diagnosis, Management, Newer Drugs.

I. INTRODUCTION

Among the oldest diseases that humans have ever encountered is likely diabetes mellitus (DM). About 3000 years ago, it was first mentioned in an Egyptian manuscript[.1.] The distinction between type 1 and type 2 diabetes was established in 1936[2] In 1988, type 2 diabetes was initially identified as a part of the metabolic syndrome[3] The most prevalent kind of diabetes is type 2 DM, sometimes referred to as non-insulin dependent DM. It is characterized by hyperglycemia, insulin resistance, and relative insulin shortage[4]Interactions between genetic, environmental, and behavioral risk factors lead to type 2 diabetes.[5, 6]

Individuals with type 2 diabetes are more susceptible to a range of immediate and long-term consequences, many of which result in an early death. Patients with type 2 diabetes are more likely to have increased morbidity and mortality due to the type's prevalence, sneaky onset, and delayed diagnosis, particularly in underdeveloped nations with limited resources like Africa[7]

Epidemiology:

366 million people were expected to have had diabetes in 2011; by 2030, that number will have increased to 552 million.[8] Every country is seeing a rise in the number of persons with type 2 diabetes, with low- and middle-income nations housing 80% of those affected. In 2011, 4.6 million people died from DM.8 By 2030, 439 million individuals are predicted to develop type 2 diabetes.[9]. Type 2 diabetes is a condition where the incidence varies greatly between geographical regions due to lifestyle and environmental risk factors.[10] According to a literature search, there is a dearth of information on type 2 diabetes prevalence in Africa.

Research looking at data trends in Africa provide evidence of a sharp rise in prevalence that affects both genders equally and occurs in both rural and urban settings.[11]

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Less than 10% of DM cases in Africa appear to be type 1 DM, with type 2 DM accounting for the bulk of DM cases.[11] According to a 2011 Centers for Disease Control and Prevention (CDC) report, type 2 diabetes affected 90–95% of the estimated 25.8 million Americans (7.8% of the population) with DM in 2010.[12]

According to predictions, within the next 20 years, there will be a significant increase in the prevalence of diabetes in adults, with type 2 DM becoming more common. Most of this growth is expected to occur in developing nations, where the majority of patients are between the ages of 45 and 64.[13] The present trend of diseases shifting from communicable to non-communicable would likely result in a twofold burden for emerging countries, as the latter is predicted to equal or even surpass the former.[14]

Lifestyle, Genetics, and Medical Conditions:

Genetics and lifestyle factors are the main causes of type 2 diabetes.[15] Type 2 diabetes is known to be influenced by a variety of lifestyle variables. These include a sedentary lifestyle, excessive alcohol intake, cigarette smoking, and physical inactivity.[16] It has been determined that about 55% of type 2 DM cases are influenced by obesity.[17] Type 2 diabetes in children and adolescents is thought to have increased as a result of the rise in juvenile obesity between the 1960s and 2000s.[18] Toxins found in the environment could be a factor in the recent rise in type 2 diabetes cases. Bisphenol A, a component of various plastics, has been discovered to have a weakly positive connection with the incidence of type 2 diabetes in urine.[19]

Type 2 diabetes is strongly inherited; having relatives with the disease, particularly first-degree relatives, significantly raises the risk of getting type 2 diabetes. Nearly all monozygotic twins show concordance, and approximately 25% of patients have a family history of diabetes mellitus.[20] Lately, it has been found that the genes TCF7L2, PPARG, FTO, KCNJ11, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1, and HHEX are strongly linked to the development of type 2 diabetes. The islet ATP-sensitive potassium channel Kir6.2 is encoded by KCNJ11 (potassium inwardly rectifying channel, subfamily J, member 11), and TCF7L2 (transcription factor 7-like 2) controls proglucagon gene expression, which in turn controls the synthesis of glucagon-like peptide-1.[21] Furthermore, a large genetic component contributes to obesity, an independent risk factor for type 2 diabetes.[22]

Up to 5% of cases are monogenic types, such as maturity-onset diabetes of the young (MODY).[23] Numerous medical disorders have the ability to cause type 2 diabetes or worsen existing cases. These include being obese, having high blood pressure, having raised cholesterol along with hyperlipidemia, and having what is commonly referred to as metabolic syndrome, also known as Syndrome X or Reaven's syndrome.[24] Acromegaly, Cushing's disease, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, malignancy, and medications are some more causes.[25] Age, high-fat diets, [26]and a less active lifestyle have also been linked to an increased risk of type 2 diabetes.[27]

Pathophysiology:

Insulin insensitivity, which results from insulin resistance, decreased insulin production, and ultimately pancreatic beta-cell loss, is a hallmark of type 2 diabetes.[28, 29] As a result, there is less glucose transported into the adipose, muscle, and liver tissues. Hyperglycemia causes an increase in the breakdown of fat. It has recently been established that altered alpha-cell function plays a role in the pathogenesis of type 2 diabetes.[30] This malfunction prevents the rise in hepatic glucose and glucagon levels that occur during fasting from being controlled by meals. Hyperglycemia is the outcome of low insulin levels and elevated insulin resistance. Important gastrointestinal mediators of insulin release and, in the case of GLP-1, glucagon suppression, are the incretins. Type 2 diabetes patients have reduced GIP activity, but their GLP-1 insulinotropic effects are maintained, making GLP-1 a potentially helpful treatment alternative.[30] Nevertheless, DPP-IV in vivo quickly inactivates GLP-1, much like it does GIP.To address this issue, two novel therapeutic strategies have been developed: GLP-1 analogues with longer half-lives and DPP-IV inhibitors, which stop endogenous GLP-1 and GIP from breaking down.[30] These types of drugs have demonstrated promise in improving beta-cell mass and functionality as well as normalizing postprandial glucose levels and fasting. Research on the connection between mitochondrial dysfunction and the genesis of type 2 diabetes and the emergence of insulin resistance is still underway.[31] Adipose tissue is also crucial, according to the endocrine organ theory (secretion of different adipocytokines, such as resistin, adiponectin, and TNF-alpha, implicated in insulin resistance and possibly beta-cell dysfunction).[30]

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Most people with type 2 diabetes are obese and have central visceral adiposity. As a result, adipose tissue is essential to the pathophysiology of type 2 diabetes. The ectopic fat storage syndrome (triglyceride deposition in muscle, liver, and pancreatic cells) and the portal/visceral hypothesis, which plays a major role in high non-esterified fatty acid concentrations, are two new emerging theories that are being used to explain this link. These two theories provide the platform for future research on the relationship between our obesogenic environment and the risk of type 2 diabetes, as well as the interaction between insulin resistance and beta-cell malfunction in that condition.[30]

Screening and Diagnosis:

There are many easily accessible tests for DM diagnosis and screening. A positive screen is the same as a diagnosis of pre-diabetes or diabetes mellitus because the tests used for screening and diagnosis are the same.[32] Approximately 25% of those diagnosed with type 2 diabetes already have microvascular problems, indicating that they have had the condition for more than five years.[33]The World Health Organization's (WHO) National Diabetic Group Criteria for 2006 and the American Diabetic Association's (ADA) 1997 guidelines are still used. These criteria call for two raised readings of either fasting plasma glucose (FPG) 37.0 mmol/L (126 mg/dL) or, in the case of an oral glucose tolerance test (OGTT), a plasma glucose ^{3}11.1 mmol/L (200 mg/dL) two hours after the oral dose.[32]

Whereas the WHO emphasizes the OGTT, the 1997 ADA criteria for DM diagnosis place more emphasis on the FPG.[32] Fructosamine and glycated hemoglobin (HbA1c) are still helpful markers of blood sugar control over time. Still, practical doctors often take additional precautions on top of the suggested ones. The International Expert Committee (IEC) suggested in July 2009 that DM patients should have an extra diagnostic criterion of a HbA1c value ±6.5%. This committee defined the range of HbA1c levels ^{3}6.0% and <6.5% to identify persons at high risk of developing diabetes mellitus, but they also indicated that the term pre-diabetes may be phased out.[34]

Similar to glucose-based testing, there is no precise HbA1c cutoff point between normalcy and diabetes.[32] The IEC decided to suggest a cut-off point for the diagnosis of diabetes mellitus that prioritizes specificity. They noted that this struck a balance between the minimal clinical consequences of delaying the diagnosis in a patient with a HbA1c level <6.5% and the stigma and expense of incorrectly diagnosing someone as having diabetes.[34]

Management:

Through dietary and lifestyle adjustments. Research has indicated that a combination of maintaining a body mass index of 25 kg/m2, eating a diet high in fiber and unsaturated fat and low in saturated and trans fats and glycemic index, regular exercise, quitting smoking, and moderate alcohol consumption can significantly reduce the incidence of type 2 diabetes.[5, 16, 35–37] implying that changing one's lifestyle can prevent the bulk of type 2 diabetes. A medical nutrition assessment should be given to patients with type 2 diabetes; lifestyle suggestions should be customized based on the patient's functional and physical abilities.[38]

II. PHARMACOLOGICAL AGENTS

- **Biguanides:**

Biguanides suppress hepatic glucose production, increase insulin sensitivity, enhance glucose uptake by phosphorylating GLUT-enhancer factor, increase fatty acid oxidation, and decrease the absorption of glucose from the gastrointestinal tract. Metformin is the most widely used biguanide in patients who are overweight or obese.[39] A 2008 study demonstrates that metformin also acts by activating AMP-activated protein kinase, an enzyme involved in the production of hepatic gluconeogenic genes.Forty Metformin usage in senior diabetes patients with renal impairment should be cautious due to the possibility of developing lactic acidosis. Comparing it to sulfonylureas, the incidence of hypoglycemia is lower.[39]

- **Sulfonylureas :**

These are usually well tolerated, although there is a chance of hypoglycemia because they increase the body's natural production of insulin.[38] Compared to younger individuals, elderly DM patients receiving sulfonylurea treatment have a 36% higher incidence of hypoglycemia.[41] When glipizide is used instead of glycoride, hypoglycemia rates are greater with glycoride.[42] Age-related reduced renal function, using insulin or insulin sensitizers concurrently, being older than 60, having recently been released from the hospital, abusing alcohol,

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restricting calories, taking several drugs, or using medications that intensify the effects of sulfonylureas are some risk factors for hypoglycemia.[43] In older patients with diabetes mellitus, short-acting glipizide should be used instead of long-acting sulfonylureas like glyburide.[38]

- **Meglitinides :**

Similar to sulfonylurea, but with a different binding site, repaglinide and nateglinide are non-sulfonylurea secretagogues that stimulate the release of insulin from the pancreatic beta cells by acting on the ATP-dependent K-channel.[44] Meglitinides reduce the risk of hypoglycemia because of their quick onset and brief (4-6 hours) duration of action. Before meals, meglitinides are administered to manage blood glucose levels after a meal. Pre-prandial medication gives you flexibility if you miss a meal without running the danger of hypoglycemia.[45] Patients with renal insufficiency do not require dose adjustments for repaglinide, with the exception of those with end-stage renal disease, as the drug is mostly processed in the liver and excreted in very small amounts through the kidneys.[44]

- **Thiazolidinediones :**

Insulin sensitizer thiazolidinedione selectively binds to the transcription factor peroxisomes proliferator-activated gamma. These medications are the first to target the fundamental issue of insulin resistance in patients with type 2 diabetes.[46] The class of these medications currently consists primarily of pioglitazone, as the Food and Drug Administration (FDA) recently advised against the restricted use of rosiglitazone due to an increase in cardiovascular events associated with the medication.[36] Because pioglitazone is well tolerated by older persons and can be administered in cases of renal impairment, it is not linked to hypoglycemia. However, its use in older persons with DM may be restricted due to worries about peripheral edema, fluid retention, and fracture risk in women. Pioglitazone is contraindicated in people with congestive heart failure and should be avoided in older patients with class III-IV heart failure.[47]

- **Alpha-Glucosidase Inhibitors :**

Although they haven't been used much, miglitol, acarbose, and voglibose have all been shown to be safe and effective in treating type 2 diabetes. These medications should not be used in patients who have severe renal impairment because they are most beneficial for treating postprandial hyperglycemia. Because of the high frequency of adverse effects such diarrhea and flatulence, their use is typically restricted.[38] In a recent research, the newest medication, vosibose, shown a significant improvement in glucose tolerance as measured by a delayed rate of disease development and a higher proportion of patients achieving normoglycemia[48]

- **Incretin-Based Therapies :**

The basis of incretin-based therapy is the use of glucagon-like peptide 1 (GLP-1) analogues, which are intended to target this until unidentified aspect of the pathophysiology of diabetes mellitus and produce long-lasting improvements in body weight control and glycemic control.[49] For individuals with type 2 diabetes, they can be used as monotherapy, in addition to diet and exercise, or in conjunction with oral hypoglycemic medications. Liraglutide and the incretin mimic exenatide are two examples.[38]

Unless used in conjunction with insulin secretagogues, GLP-1 therapies do not carry the risk of hypoglycemia. Furthermore, new research indicates that incretin-based treatments may benefit the central nervous system, inflammation, hepatic and cardiovascular health, and sleep.[49]

- **Dipeptidyl-Peptidase IV Inhibitors :**

Dipeptidyl-peptidase (DPP) IV inhibitors raise the amounts of both hormones that are active and, as a result, improve islet function and glycemic control in type 2 diabetes by inhibiting dipeptidyl peptidase-4 (DPP-4), a ubiquitous enzyme that quickly inactivates both GLP-1 and GIP.50 DPP-4 inhibitors are a novel class of anti-diabetogenic medications with efficacy comparable to existing therapies. When combined with metformin, thiazolidinediones, and insulin, they are useful as add-on therapy and as monotherapy for individuals whose diet and exercise regimens are insufficiently controlling their condition. The DPP-4 inhibitors are weight neutral, well tolerated, and have a minimal chance of causing hypoglycemia. They are somewhat pricey, though.[50] It is yet unknown how long-lasting the impact will be on beta-cell morphology and function, as well as glycemic control.[50, 51]

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- **Insulin :**

Insulin can be taken on its own or in conjunction with oral hypoglycemic medications. If some beta cell function is still present, basal insulin augmentation therapy can be helpful. In the event of beta cell exhaustion, basal-bolus insulin replacement is required. In cases of glucose poisoning, rescue therapy utilizing replacement is required, and it should resemble the regular release of insulin by the pancreatic beta cells.[52] There are four injectable kinds of insulin available: long acting, short acting, intermediate acting, and rapid acting. Compared to the short acting variants, the long acting forms have a lower risk of causing hypoglycemia.

- **Insulin analogues:**

The capacity of insulin therapy to imitate typical physiological insulin production was found to be restricted. The peaks of action and uneven absorption of traditional intermediate- and long-acting insulins (NPH insulin, lente insulin, and ultralente insulin) might cause hypoglycemia.[53,54] The novel insulin analogues have different pharmacokinetic profiles from normal insulins, and they have varying rates of onset and duration of action (from quick to protracted). There is now one long-acting insulin analog, insulin glargine, and two rapid-acting insulin analogs, insulin lispro and insulin aspart.[53, 54]

- **Future in Drug Therapy Inhaled Insulin:**

The FDA and European Medicines Evaluation Agency both authorized the inhaled version of quickly acting insulin in 2006,[55] making it available for the treatment of type 1 and type 2 diabetes in people.[55–57] It is a fast-acting type of insulin having the benefit of being delivered straight to the lungs; it was recommended for use in persons with both type 1 and type 2 diabetes. However, research indicates that inhaled insulin is just as effective as short-acting insulin, if not more so.[55] The manufacturer pulled it off the market in October 2007 because of low sales.

- **Bromocriptine:**

Rapid-release Recently, bromocriptine has been created to treat type 2 diabetes. The exact mode of action is unclear, though. After 24 weeks of treatment, studies have indicated that they lower the mean HbA1c levels by 0.0% to 0.2%.[58]

- **Others:**

Glucocorticoid effects in fat and liver are lessened by inhibitors of 11ß-hydroxysteroid dehydrogenase 1, while inhibitors of sodium-glucose cotransporter 2 improve renal glucose elimination. In order to create innovative medication therapy for individuals with type 2 diabetes, insulin-releasing glucokinase activators, pancreatic-G-protein-coupled fatty acid receptor agonists, glucagon-receptor antagonists, and metabolic inhibitors of hepatic glucose output are being evaluated.[59]

III. CONCLUSION

Type 2 diabetes is a metabolic illness that can be avoided by controlling nutrition, weight, and lifestyle factors that contribute to overweight and obesity. Public education continues to be essential to controlling this new epidemic. Despite the development of novel medications and increased understanding of the disease's pathogenesis, there is still no known cure for the illness. The goal of management should be to enhance the quality of life for those who have type 2 diabetes.

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