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Review Article

Role of Lifestyle Interventions in Diabetes Prevention and Management

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ABSTRACT

Type 2 diabetes mellitus (DM) is a persistent metabolic condition that is increasingly prevalent worldwide, posing an emerging epidemic, particularly in certain nations, with anticipated doubling of affected individuals in the next decade due to population aging. This review draws from searches in Medline, the Cochrane Database of Systemic Reviews, and relevant publication citations, focusing on type 2 diabetes mellitus prevalence, diagnosis, and treatment. Diagnosis still relies on World Health Organization (WHO) and American Diabetes Association (ADA) criteria encompassing clinical and laboratory parameters, with treatment primarily centered on lifestyle modifications, obesity management, and medications such as metformin, particularly for obese patients. Other effective medications include non-sulfonylurea secretagogues, thiazolidinediones, alpha-glucosidase inhibitors, and insulin. Recent advancements in understanding type 2 DM pathophysiology have introduced new medications like glucagon-like peptide 1 analogs, dipeptidyl peptidase-IV inhibitors, and inhibitors of the sodium-glucose cotransporter 2, among others. Inhaled insulin, licensed in 2006, has been withdrawn from the market due to low demand.

INTRODUCTION

Diabetes mellitus (DM) is likely one of the oldest diseases documented in human history, with its first report found in an Egyptian manuscript dating back about 3000 years ago. In 1936, a clear distinction between type 1 and type 2 DM was established. Type 2 DM was identified as a component of metabolic syndrome in 1988. Formerly known as non-insulin dependent DM, type 2 DM is the most prevalent form characterized by hyperglycemia, insulin resistance, and relative insulin deficiency. The development of type 2 DM involves a complex interplay of genetic, environmental, and behavioral factors. Individuals with type 2 DM face increased vulnerability to various short- and long-term complications, often leading to premature mortality. This elevated risk stems from

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the common occurrence of type 2 DM, its insidious onset, and delayed recognition, particularly prevalent in resource-poor regions like Africa.

Epidemiology

In 2011, an estimated 366 million people were living with DM, a number projected to rise to 552 million by 2030. The prevalence of type 2 DM is on the rise globally, with 80% of affected individuals residing in low- and middle-income countries. DM accounted for 4.6 million deaths in 2011 alone, and it is predicted that 439 million people will have type 2 DM by 2030.

Geographical variations in type 2 DM incidence stem from diverse environmental and lifestyle risk factors. Literature reveals limited data on type 2 DM prevalence across Africa, but studies suggest a significant increase in both rural and urban settings, impacting genders equally.

The predominant form of diabetes mellitus (DM) burden in Africa seems to be type 2 DM, with less than 10% of DM cases being type 1 DM. According to a 2011 report from the Centers for Disease Control and Prevention (CDC), DM affected approximately 25.8 million people in the US in 2010, constituting 7.8% of the population, with 90% to 95% of cases being type 2 DM.

Projections suggest that the prevalence of DM in adults, particularly type 2 DM, will escalate in the next two decades, with a significant portion of this increase occurring in developing countries where the majority of patients are aged between 45 and 64 years.

In developing nations, it's anticipated that the prevalence of non-communicable diseases will match or surpass that of communicable diseases, Resulting in a double burden as the transition progresses.

Lifestyle, Genetics, and Medical Conditions

Type 2 DM is due primarily to lifestyle factors and genetics.15 A number of lifestyle factors are known to be important to the development of type 2 DM. These are physical inactivity, sedentary lifestyle, cigarette smoking and generous consumption of alcohol. 16 Obesity has been found to contribute to approximately 55% of cases of type 2 DM. The increased rate of childhood obesity between the 1960s and 2000s is believed to have led to the increase in type 2 DM in children and adolescents.18 Environmental toxins may contribute to the recent increases in the rate of type 2 DM. A weak positive correlation has been found between the concentration in the urine of bisphenol A, a constituent of some plastics, and the incidence of type 2 DM.

Type 2 DM has a strong hereditary genetic component; having relatives, especially first degree, with the condition substantially increases the risk of developing it. Concordance among monozygotic twins approaches 100%, with about a quarter of individuals with the disease having a family history of DM. Recently, various genes, such as TCF7L2, PPARG, FTO, KCNJ11, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1, and HHEX, have been discovered to be significantly associated with type 2 DM development. KCNJ11, for instance, encodes the islet ATP-sensitive potassium channel Kir6.2, while TCF7L2 regulates proglucagon gene expression, affecting the production of glucagon-like peptide-1. Furthermore, obesity, which is an independent risk factor for type 2 DM, is strongly inherited. Monogenic forms like Maturity-onset diabetes of the young (MODY) constitute up to 5% of cases. Additionally, numerous medical conditions, including obesity, hypertension, and elevated cholesterol, can potentially give rise to or exacerbate type 2 DM. These conditions are often associated with metabolic syndrome, also known as Syndrome X or Reaven's syndrome. Other causes encompass acromegaly, Cushing's syndrome, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, cancer, and certain medications. Furthermore, additional factors such

as aging, high-fat diets, and a sedentary lifestyle have been found to increase the risk of type 2 DM.

Pathophysiology

Type 2 DM is distinguished by insulin insensitivity stemming from insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure. This cascade leads to diminished glucose transport into liver, muscle, and fat cells, coupled with heightened fat breakdown and hyperglycemia. Recently, impaired alpha-cell function has emerged as a recognized factor in the pathophysiology of type 2 DM.

Consequently, glucagon and hepatic glucose levels, which typically rise during fasting, remain unimpeded by meal consumption.

Certainly, here's the revised version with replaced sentences:

Given insufficient insulin levels and heightened insulin resistance, hyperglycemia ensues in type 2 DM. The incretins play a crucial role as gut mediators of insulin release, with GLP-1 also suppressing glucagon. While GIP activity is impaired in type 2 DM, GLP-1's insulinotropic effects remain intact, making GLP-1 a potential therapeutic avenue. However, both GIP and GLP-1 are swiftly deactivated by DPP-IV in vivo.

To address this challenge, two therapeutic strategies have emerged: GLP-1 analogues with prolonged half-lives and DPP-IV inhibitors, which preserve endogenous GLP-1 and GIP by inhibiting their breakdown. Both classes of agents show promise, not only in normalizing fasting and postprandial glucose levels but also in enhancing beta-cell function and mass. Ongoing research investigates the role of mitochondrial dysfunction in insulin resistance development and type 2 DM etiology. Additionally, adipose tissue's role as an endocrine organ is crucial, with the adipocytokines leptin, TNF-alpha, resisting, and adiponectin implicated in insulin resistance and potentially beta-cell dysfunction.

A majority of individuals with type 2 DM are obese, particularly with central visceral adiposity, underscoring the pivotal role of adipose tissue in the development of the condition. While the primary theory, the portal/visceral hypothesis, highlights the significance of elevated non-esterified fatty acid concentrations, two emerging theories are gaining traction: the ectopic fat storage syndrome, characterized by triglyceride deposition in muscle, liver, and pancreatic cells. These alternative hypotheses form the foundation for investigating the interaction between insulin resistance and beta-cell dysfunction in type 2 DM, as well as the correlation between our obesogenic environment and the risk of developing DM in the forthcoming decade.

Screening and diagnosis

Screening and diagnosis of DM are facilitated by readily available tests. The recommended test for screening is the same as that for making a diagnosis, whereby a positive screen equates to a diagnosis of pre-diabetes or DM. Approximately 25% of patients with type 2 DM already exhibit microvascular complications at the time of diagnosis, indicating a duration of the disease exceeding 5 years.

Diagnosis is typically based on either the American Diabetic Association (ADA) guidelines of 1997 or the World Health Organization (WHO) National diabetic group criteria of 2006. These criteria include a single elevated glucose reading with symptoms (polyuria, polydipsia, polyphagia, and weight loss), or elevated values on two occasions: fasting plasma glucose (FPG) $\geq$ 7.0 mmol/L (126 mg/dL) or a plasma glucose $\geq$ 11.1 mmol/L (200 mg/dL) two hours after an oral glucose tolerance test (OGTT).

The 1997 ADA recommendations emphasize FPG, while WHO focuses on OGTT. Additionally, glycated hemoglobin (HbA1c) and fructosamine are useful for assessing blood sugar control over time. However, practicing physicians often utilize

other measures beyond those recommended. In July 2009, the International Expert Committee introduced (IEC) proposed a new diagnostic criterion for diabetes mellitus (DM), suggesting an HbA1c level of 6.5% or higher. The term "pre-diabetes" may be phased out, with HbA1c levels between 6.0% and 6.5% identifying those at high risk of DM.

Similar to glucose-based tests, there isn't a definitive HbA1c threshold for distinguishing normality from DM. The IEC recommends a cut-off emphasizing specificity, considering the stigma and cost of misdiagnosis against the minimal clinical impact of delayed diagnosis with an HbA1c level below 6.5%.

Treatment

Lifestyle and dietary changes play a crucial role in preventing type 2 diabetes mellitus (DM). Studies indicate that maintaining a body mass index (BMI) of 25 kg/m², consuming a diet rich in high fiber and unsaturated fats while low in saturated and trans-fats and glycemic index, engaging in regular exercise, refraining from smoking, and moderating alcohol intake can significantly reduce the incidence of type 2 DM. These findings suggest that the majority of type 2 DM cases can be prevented through lifestyle modifications. Patients diagnosed with type 2 DM should undergo a medical nutrition evaluation, and lifestyle recommendations should be personalized based on their physical and functional capabilities.

DRUG THERAPIES

Insulin

Insulin is administered either alone or in conjunction with oral hypoglycemic agents. Basal insulin augmentation is beneficial when residual beta cell function exists, while basal-bolus insulin replacement is required in cases of beta cell exhaustion. In instances of glucose toxicity, which necessitates normal insulin release akin to pancreatic beta cells, rescue therapy with insulin replacement is necessary. Injectable insulin is available in various forms, including rapid-acting, short-acting, intermediate-acting, and long-acting formulations. Long-acting insulin formulations pose a lower risk of hypoglycemia compared to short-acting counterparts.

Biguanides.

Biguanides, with metformin being the most commonly prescribed for overweight and obese patients, work by inhibiting hepatic glucose production, improving insulin sensitivity, promoting glucose uptake via GLUT-enhancer factor phosphorylation, increasing fatty acid oxidation, and reducing glucose absorption from the gastrointestinal tract. Recent research from 2008 reveals another mechanism of action for metformin: activation of AMP-activated protein kinase, which influences the expression of hepatic gluconeogenic genes. Despite its efficacy, metformin should be used cautiously in elderly diabetic patients with renal impairment due to the risk of lactic acidosis. Notably, it has a lower risk of hypoglycemia compared to sulfonylureas.

Sulfonylureas.

While generally well tolerated, sulfonylureas pose a risk of hypoglycemia due to their stimulation of endogenous insulin secretion. Elderly patients with diabetes mellitus (DM) receiving sulfonylureas have a 36% higher risk of hypoglycemia compared to younger patients. Glyburide carries a higher risk of hypoglycemia compared to glipizide. Risk factors for hypoglycemia include age-related impaired renal function, concurrent use of insulin or insulin sensitizers, age over 60 years, recent hospital discharge, alcohol abuse, caloric restriction, multiple medications, or drugs that enhance sulfonylurea effects. Long-acting sulfonylureas like glyburide should be avoided in elderly DM patients, with short-acting glipizide preferred instead.

Meglitinides

Repaglinide and Nate glinide are non-sulfonylurea secretagogues that target the ATP-dependent K-channel in pancreatic beta cells, stimulating insulin release similarly to sulfonylureas, albeit with a different binding site. Meglitinides have a rapid onset and short duration of action (4-6 hours), resulting in a lower risk of hypoglycemia. They are typically administered before meals to control postprandial blood glucose levels. This pre-prandial dosing provides flexibility if a meal is missed without increasing the risk of hypoglycemia. Repaglinide is primarily metabolized in the liver, with minimal renal excretion, hence dose adjustment is generally unnecessary in patients with renal insufficiency, except for those with end-stage renal disease.

Thiazolidinediones.

Thiazolidinediones act as insulin sensitizers by selectively binding to the transcription factor peroxisome proliferator-activated gamma. They are the first drugs to target insulin resistance in type 2 diabetes mellitus (DM) patients. Currently, the class mainly includes pioglitazone, following the restricted use of rosiglitazone due to increased cardiovascular events reported by the Food and Drug Administration (FDA). Pioglitazone use is not linked to hypoglycemia and can be utilized in cases of renal impairment, making it well tolerated in older adults. However, concerns regarding peripheral edema, fluid retention, and fracture risk in women may limit its use in older adults with DM. Pioglitazone should be avoided in elderly patients with congestive heart failure and is contraindicated in those with class III-IV heart failure.

Alpha-glucosidase inhibitors

such as acarbose, voglibose, and miglitol are less commonly used in treating type 2 diabetes mellitus (DM) but are considered safe and effective. They are particularly effective for postprandial hyperglycemia but should be avoided in patients with significant renal impairment due to potential complications. However, their use is often limited due to high rates of side effects such as diarrhea and flatulence. Voglibose, the newest among these drugs, has shown significant improvement in glucose tolerance, delaying disease progression, and increasing the number of patients achieving normoglycemia.

Incretin-based therapies

particularly glucagon-like peptide 1 (GLP-1) analogues, target a previously unrecognized feature of DM pathophysiology, leading to sustained improvements in glycemic and body weight control. These therapies can be used alone, as an adjunct to diet and exercise, or in combination with oral hypoglycemic agents in adults with type 2 DM. Examples include Exenatide, an incretin mimetic, and Liraglutide.

The use of GLP-1 therapies does not carry a risk of hypoglycemia unless combined with insulin secretagogues. Additionally, emerging evidence suggests the efficacy and safety of incretin-based therapies. May have a positive impact on inflammation, cardiovascular and hepatic health, sleep and the central nervous system.

Dipeptidyl-peptidase (DPP) IV inhibitors

Dipeptidyl-peptidase (DPP) IV inhibitors inhibit dipeptidyl peptidase-4 (DPP-4), an enzyme that quickly deactivates both GLP-1 and GIP hormones. By increasing active hormone levels, they enhance islet function and improve glycemic control in type 2 diabetes mellitus (DM). DPP-4 inhibitors represent a novel class of anti-diabetic drugs with efficacy comparable to current treatments. They can be used as monotherapy in patients inadequately controlled with diet and exercise, or as add-on therapy in combination with metformin, thiazolidinediones, and insulin. These inhibitors are generally well tolerated, carry a low risk of hypoglycemia, and do not lead to weight gain. However, they are relatively expensive. The long-term durability of their effects on glycemic

control and beta-cell morphology and function is still being studied.

Insulin analogues

Insulin therapy has historically struggled to replicate normal physiological insulin secretion. Traditional intermediate- and long-acting insulins, such as NPH insulin, lente insulin, and ultra-Lente insulin, are hindered by inconsistent absorption and peaks of action that can lead to hypoglycemia. The pharmacokinetic profiles of newer insulin analogues differ significantly from those of regular insulins, with onset and durations of action ranging from rapid to prolonged. Currently, there are two rapid-acting insulin analogues available, insulin lispro and insulin as part, as well as one long-acting insulin analogue, insulin glargine.

Future in drug therapy inhaled insulin

The inhaled form of rapid-acting insulin became available in 2006, following approval by both the European Medicines Evaluation Agency and FDA for treating type 1 and type 2 diabetes mellitus (DM) in adults. It offers a rapid-acting insulin delivery method directly into the lungs. However, studies have indicated that while inhaled insulin is as effective as short-acting insulin, it does not offer superior efficacy. Despite initial approval, the manufacturer withdrew it from the market in October 2007 due to poor sales.

Bromocriptine

Quick-release bromocriptine has been developed for the treatment of type 2 diabetes mellitus (DM), although its mechanism of action remains unclear. Studies have demonstrated a reduction in mean levels by 0.0% to 0.2% after 24 weeks of therapy.

Others

Inhibitors of the sodium-glucose cotransporter 2 (SGLT2), which enhance renal glucose elimination, and inhibitors of 11β-hydroxysteroid dehydrogenase 1, which reduce glucocorticoid effects in the liver and fat, are being explored for the development of new drug therapies for type 2 diabetes mellitus (DM). Additionally, insulin-releasing glucokinase activators, pancreatic G-protein-coupled fatty-acid-receptor agonists, glucagon-receptor antagonists, and metabolic inhibitors of hepatic glucose output are under assessment for potential therapeutic use in type 2 diabetic patients.

CONCLUSION

Type 2 diabetes mellitus (DM) is a metabolic condition that can be prevented through lifestyle changes, dietary adjustments, and the management of excess weight and obesity. Educating the population remains crucial in combating this emerging health crisis. Despite advances in understanding the disease's underlying mechanisms, a cure for type 2 DM is not yet within reach. Treatment should be customized to enhance the quality of life for those with type 2 DM.

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