



REVIEW ON DIABETES MELLITUS 2

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Abstract

Type 2 diabetes mellitus (DM) is a chronic metabolic disorder in which prevalence has been increasing steadily all over the world. As a result of this trend, it is fast becoming an epidemic in some countries of the world with the number of people affected expected to double in the next decade due to increase in ageing population, thereby adding to the already existing burden for healthcare providers, especially in poorly developed countries. This review is based on a search of Medline, the Cochrane Database of Systemic Reviews, and citation lists of relevant publications. Subject heading and key words used include type 2 diabetes mellitus, prevalence, current diagnosis, and current treatment. Only articles in English were included. Screening and diagnosis is still based on World Health Organization (WHO) and American Diabetes Association (ADA) criteria which include both clinical and laboratory parameters. No cure has yet been found for the disease; however, treatment modalities include lifestyle modifications, treatment of obesity, oral hypoglycemic agents, and insulin sensitizers like metformin, a biguanide that reduces insulin resistance, is still the recommended first line medication especially for obese patients.

Keywords: Type 2 diabetes mellitus, Diagnosis, Management, Newer drugs



Introduction

Diabetes mellitus (DM) is probably one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago.¹ In 1936, the distinction between type 1 and type 2 DM was clearly made.² Type 2 DM was first described as a component of metabolic syndrome in 1988.³ Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency.⁴ Type 2 DM results from interaction between genetic, environmental and behavioral risk factors.^{5,6}

People living with type 2 DM are more vulnerable to various forms of both short- and long-term complications, which often lead to their premature death. This tendency of increased morbidity and mortality is seen in patients with type 2 DM because of the commonness of this type of DM, its insidious onset and late recognition, especially in resource-poor developing countries like Africa.⁷

Epidemiology

It is estimated that 366 million people had DM in 2011; by 2030 this would have risen to 552 million.⁸ The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011.⁸ It is estimated that 439 million people would have type 2 DM by the year 2030.⁹ The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors.¹⁰

Literature search has shown that there are few data available on the prevalence of type 2 DM in Africa as a whole. Studies examining data trends within Africa point to evidence of a dramatic increase in prevalence in both rural and urban setting, and affecting both gender equally.¹¹

The majority of the DM burden in Africa appears to be type 2 DM, with less than 10% of DM cases being type 1 DM.¹¹ A 2011 Centre for Disease Control and Prevention (CDC) report estimates that DM affects about 25.8 million people in the US (7.8% of the population) in 2010 with 90% to 95% of them being type 2 DM.¹²

It is predicted that the prevalence of DM in adults of which type 2 DM is becoming prominent will increase in the next two decades and much of the increase will occur in developing countries where the majority of patients are aged between 45 and 64



years.¹³ It is projected that the latter will equal or even exceed the former in developing nations, thus culminating in a double burden as a result of the current trend of transition from communicable to non-communicable diseases.¹⁴

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.¹⁷ 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.¹⁹

There is a strong inheritable genetic connection in type 2 DM, having relatives (especially first degree) with type 2 DM increases the risks of developing type 2 DM substantially. Concordance among monozygotic twins is close to 100%, and about 25% of those with the disease have a family history of DM.²⁰ Recently, genes discovered to be significantly associated with developing type 2 DM, include *TCF7L2*, *PPARG*, *FTO*, *KCNJ11*, *NOTCH2*, *WFS1*, *CDKAL1*, *IGF2BP2*, *SLC30A8*, *JAZF1*, and *HHEX*. *KCNJ11* (potassium inwardly rectifying channel, subfamily J, member 11), encodes the islet ATP-sensitive potassium channel Kir6.2, and *TCF7L2* (transcription factor 7-like 2) regulates proglucagon gene expression and thus the production of glucagon-like peptide-1.²¹ Moreover, obesity (which is an independent risk factor for type 2 DM) is strongly inherited.²² Monogenic forms like Maturity-onset diabetes of the young (MODY), constitutes up to 5% of cases.²³ There are many medical conditions which can potentially give rise to, or exacerbate type 2 DM. These include obesity, hypertension, elevated cholesterol (combined hyperlipidemia), and with the condition often termed metabolic syndrome (it is also known as Syndrome X, Reaven's syndrome).²⁴ Other causes include acromegaly, Cushing's syndrome, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, cancer, and drugs.²⁵ Additional factors found to increase the risk of type 2 DM include aging,²⁶ high-fat diets, and a less active lifestyle.²⁷

Pathophysiology



Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure.^{28,29} This leads to a decrease in glucose transport into the liver, muscle cells, and fat cells. There is an increase in the breakdown of fat with hyperglycemia. The involvement of impaired alpha-cell function has recently been recognized in the pathophysiology of type 2 DM.³⁰

As a result of this dysfunction, glucagon and hepatic glucose levels that rise during fasting are not suppressed with a meal. Given inadequate levels of insulin and increased insulin resistance, hyperglycemia results. The incretins are important gut mediators of insulin release, and in the case of GLP-1, of glucagon suppression. Although GIP activity is impaired in those with type 2 DM, GLP-1 insulinotropic effects are preserved, and thus GLP-1 represents a potentially beneficial therapeutic option.³⁰ However, like GIP; GLP-1 is rapidly inactivated by DPP-IV in vivo.

Two therapeutic approaches to this problem have been developed: GLP-1 analogues with increased half-lives, and DPP-IV inhibitors, which prevent the breakdown of endogenous GLP-1 as well as GIP.³⁰ Both classes of agents have shown promise, with potential not only to normalize fasting and postprandial glucose levels but also to improve beta-cell functioning and mass. Studies are ongoing on the role of mitochondrial dysfunction in the development of insulin resistance and etiology of type 2 DM.³¹ Also very important is adipose tissue, as endocrine organ hypothesis (secretion of various adipocytokines, i.e., leptin, TNF-alpha, resistin, and adiponectin implicated in insulin resistance and possibly beta-cell dysfunction).³⁰

A majority of individuals suffering from type 2 DM are obese, with central visceral adiposity. Therefore, the adipose tissue plays a crucial role in the pathogenesis of type 2 DM. Although the predominant theory used to explain this link is the portal/visceral hypothesis giving a key role in elevated non-esterified fatty acid concentrations, two new emerging theories are the ectopic fat storage syndrome (deposition of triglycerides in muscle, liver and pancreatic cells). These two hypotheses constitute the framework for the study of the interplay between insulin resistance and beta-cell dysfunction in type 2 DM as well as between our obesogenic environment and DM risk in the next decade.³⁰

Screening and Diagnosis

Tests for screening and diagnosis of DM are readily available. The test recommended for screening is the same as that for making diagnosis, with the result that a positive screen is equivalent to a diagnosis of pre-diabetes or DM.³² Although about 25% of patients with type 2 DM already have microvascular complications at the time of diagnosis suggesting that they have had the disease for more than 5 years at the time of diagnosis.³³ It is still



based on the American Diabetic Association (ADA) guidelines of 1997 or World Health Organization (WHO) National diabetic group criteria of 2006, which is for a single raised glucose reading with symptoms (polyuria, polydipsia, polyphagia and weight loss), otherwise raised values on two occasions, of either fasting plasma glucose (FPG) ≥ 7.0 mmol/L (126 mg/dL) or with an oral glucose tolerance test (OGTT), two hours after the oral dose a plasma glucose ≥ 11.1 mmol/L (200 mg/dL).³²

The 1997 ADA recommendations for diagnosis of DM focus on the FPG, while WHO focuses on the OGTT.³² The glycated hemoglobin (HbA1c) and fructosamine is also still useful for determining blood sugar control over time. However, practicing physicians frequently employ other measures in addition to those recommended. In July 2009, the International Expert Committee (IEC) recommended the additional diagnostic criteria of an HbA1c result $\geq 6.5\%$ for DM. This committee suggested that the use of the term pre-diabetes may be phased out but identified the range of HbA1c levels $\geq 6.0\%$ and $< 6.5\%$ to identify those at high risk of developing DM.³⁴

As with the glucose-based tests, there is no definite threshold of HbA1c at which normality ends and DM begins.³² The IEC has elected to recommend a cut-off point for DM diagnosis that emphasizes specificity, commenting that this balanced the stigma and cost of mistakenly identifying individuals as diabetic against the minimal clinical consequences of delaying the diagnosis in a patient with an HbA1c level $< 6.5\%$.³⁴

Management

Through lifestyle and diet modification. Studies have shown that there was significant reduction in the incidence of type 2 DM with a combination of maintenance of body mass index of 25 kg/m^2 , eating high fibre and unsaturated fat and diet low in saturated and trans-fats and glycemic index, regular exercise, abstinence from smoking and moderate consumption of alcohol.^{5,16,35-37} Suggesting that majority of type 2 DM can be prevented by lifestyle modification. Patients with type 2 DM should receive a medical nutrition evaluation; lifestyle recommendations should be tailored according to physical and functional ability.³⁸

Pharmacological Agents

Biguanides

Biguanides, of which metformin is the most commonly used in overweight and obese patients, suppresses hepatic glucose production, increases insulin sensitivity, enhances glucose uptake by phosphorylating GLUT-enhancer factor, increases fatty acid oxidation,



and decreases the absorption of glucose from the gastrointestinal tract.³⁹ Research published in 2008 shows further mechanism of action of metformin as activation of AMP-activated protein kinase, an enzyme that plays a role in the expression of hepatic gluconeogenic genes.⁴⁰ Due to the concern of development of lactic acidosis, metformin should be used with caution in elderly diabetic individuals with renal impairment. It has a low incidence of hypoglycemia compared to sulfonylureas.³⁹

Sulfonylureas

These generally well tolerated but because they stimulate endogenous insulin secretion, they carry a risk of hypoglycemia.³⁸ Elderly patients, with DM who are treated with sulfonylureas have a 36% increased risk of hypoglycemia compared to younger patients.⁴¹ Glyburide is associated with higher rates of hypoglycemia compared to glipizide.⁴² Some of the risk factors for hypoglycemia are age-related impaired renal function, simultaneous use of insulin or insulin sensitizers, age greater than 60 years, recent hospital discharge, alcohol abuse, caloric restriction, multiple medications or medications that potentiate sulfonylurea actions.⁴³ Use of long acting sulfonylurea such as glyburide should be avoided in elderly patients with DM and use of short-acting glipizide should be preferred.³⁸

Meglitinides

Repaglinide and nateglinide are non-sulfonylurea secretagogues which act on the ATP-dependent K-channel in the pancreatic beta cells thereby stimulating the release of insulin from the beta cells, similar to sulfonylurea, though the binding site is different.⁴⁴ Meglitinides have a rapid onset and a short duration of action (4-6 hrs) and thus lower risk of hypoglycemia. Meglitinides are given before meals for postprandial blood glucose control. Pre-prandial administration allows flexibility in case a meal is missed without increased risk of hypoglycemia.⁴⁵ Repaglinide is mainly metabolized in the liver with very minimal amounts excreted via the kidneys and thus dose adjustment is not necessary in patients with renal insufficiency except those with end-stage renal disease.⁴⁴

Thiazolidinediones

Thiazolidinedione is an insulin sensitizer, selective ligands transcription factor peroxisomes proliferator-activated gamma. They are the first drugs to address the basic problem of insulin resistance in type 2 DM patients,⁴⁶ whose class now includes mainly pioglitazone after the restricted use of rosiglitazone recommended by Food and Drug Administration (FDA) recently due to increased cardiovascular events reported with rosiglitazone.³⁶ Pioglitazone use is not associated with hypoglycemia and can be used in



cases of renal impairment and thus well tolerated in older adults. On the other hand, due to concerns regarding peripheral edema, fluid retention and fracture risk in women, its use can be limited in older adults with DM. Pioglitazone should be avoided in elderly patients with congestive heart failure and is contraindicated in patients with class III-IV heart failure.⁴⁷

Alpha-Glucosidase Inhibitors

Acarbose, Voglibose and Miglitol have not widely been used to treat type 2 DM individuals but are likely to be safe and effective. These agents are most effective for postprandial hyperglycemia and should be avoided in patients with significant renal impairment. Their use is usually limited due to high rates of side-effects such as diarrhoea and flatulence.³⁸ Voglibose, which is the newest of the drugs, has been shown in a study to significantly improve glucose tolerance, in terms of delayed disease progression and in the number of patients who achieved normoglycemia.⁴⁸

Incretin-Based Therapies

Glucagon-like peptide 1 (GLP-1) analogues are the foundation of incretin-based therapies which are to target this previously unrecognized feature of DM pathophysiology resulting in sustained improvements in glycemic control and improved body weight control.⁴⁹ They are available for use as monotherapy, as an adjunct to diet and exercise or in combination with oral hypoglycemic agents in adults with type 2 DM. Examples are Exenatide, an incretin mimetic, and Liraglutide.³⁸

There is no risk of hypoglycemia with the use of GLP-1 therapies (unless combined with insulin secretagogues). In addition, emerging evidence suggests incretin-based therapies may have a positive impact on inflammation, cardiovascular and hepatic health, sleep, and the central nervous system.⁴⁹

Dipeptidyl-Peptidase IV Inhibitors

Dipeptidyl-peptidase (DPP) IV inhibitors inhibit dipeptidyl peptidase-4 (DPP-4), a ubiquitous enzyme that rapidly inactivates both GLP-1 and GIP, increase active levels of these hormones and, in doing so, improves islet function and glycemic control in type 2 DM.⁵⁰ DPP-4 inhibitors are a new class of anti-diabetogenic drugs that provide comparable efficacy to current treatments. They are effective as monotherapy in patients inadequately controlled with diet and exercise and as add-on therapy in combination with metformin, thiazolidinediones, and insulin. The DPP-4 inhibitors are well tolerated, carry a low risk of producing hypoglycemia and are weight neutral. However, they are relatively



expensive.⁵⁰ The long-term durability of effect on glycemic control and beta-cell morphology and function remain to be established.^{50,51}

Insulin

Insulin is used alone or in combination with oral hypoglycemic agents. Augmentation therapy with basal insulin is useful if some beta cell function remains. Replacement of basal-bolus insulin is necessary if beta cell exhaustion occurs. Rescue therapy using replacement is necessary in cases of glucose toxicity which should mimic the normal release of insulin by the beta cells of the pancreas.⁵² Insulin comes in injectable forms - rapid acting, short acting, intermediate acting and long acting. The long acting forms are less likely to cause hypoglycemia compared to the short acting forms.

Insulin analogues

Insulin therapy was limited in its ability to mimic normal physiologic insulin secretion. Traditional intermediate- and long-acting insulins (NPH insulin, lente insulin, and ultralente insulin) are limited by inconsistent absorption and peaks of action that may result in hypoglycemia.^{53,54} The pharmacokinetic profiles of the new insulin analogues are distinct from those of the regular insulins, and their onset and durations of action range from rapid to prolonged. Currently, two rapid-acting insulin analogues, insulin lispro and insulin aspart, and one long-acting insulin analogue, insulin glargine, are available.^{53,54}

Future in Drug Therapy Inhaled Insulin

The inhaled form of rapidly acting insulin which became available in 2006,⁵⁵ after it was approved by both the European Medicines Evaluation Agency and FDA for treatment of type 1 and type 2 DM in adults.⁵⁵⁻⁵⁷ It is a rapid acting form of insulin that was indicated for use in adults with type 1 and type 2 DM and has the advantage of delivery directly into the lungs. Studies have however shown that inhaled insulin is as effective as, but not better than short acting insulin.⁵⁵ It was withdrawn from the market by the manufacturer in October 2007 due to poor sales.

Bromocriptine

Quick-release bromocriptine has recently been developed for the treatment of type 2 DM. However, the mechanism of action is not clear. Studies have shown that they reduce the mean HbA1c levels by 0.0% to 0.2% after 24 weeks of therapy.⁵⁸

Others



Inhibitors of the sodium-glucose cotransporter 2, which increase renal glucose elimination, and inhibitors of 11 β -hydroxysteroid dehydrogenase 1, which reduce the glucocorticoid effects in liver and fat. Insulin-releasing glucokinase activators and pancreatic-G-protein-coupled fatty-acid-receptor agonists, glucagon-receptor antagonists, and metabolic inhibitors of hepatic glucose output are being assessed for the purpose of development of new drug therapy for type 2 diabetic patients.⁵⁹

Conclusion

Type 2 DM is a metabolic disease that can be prevented through lifestyle modification, diet control, and control of overweight and obesity. Education of the populace is still key to the control of this emerging epidemic. Novel drugs are being developed, yet no cure is available in sight for the disease, despite new insight into the pathophysiology of the disease. Management should be tailored to improve the quality of life of individuals with type 2 DM.

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