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***Review article***

# A REVIEW ON MANAGEMENT OF BLOOD GLUCOSE IN TYPE 2 DIABETES MELLITUS

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**ABSTRACT:** Type 2 diabetes mellitus is a chronic metabolic disorder in which prevalence has been increasing steadily all over the world. As a result of this trend, it is becoming an epidemic in some countries of the world. The number of people affected are expected to become double in the next decade due to increase in ageing population, there by adding extra burden to already existing burden for healthcare providers, especially in poor developed countries. This review is based on a search of medicine, 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 currents treatment. Only articles in English were included. Screening and diagnosis is still based on World Health Organisation (**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 hypoglycaemic agents, and insulin sensitizers like metformin, a biguanide that reduces insulin resistance, is the still recommended first line medication especially for obese patients. Other effective medications include non-sulfonylurea secretagogues, thiazolidinediones, alpha glucoside inhibitors, and insulin. Recent research in the pathophysiology of type 2 DM has led to the introduction of new medications like glucagon-like peptide 1 analogues: dipeptidyle peptidase-IV inhibitors, inhibitors of sodium glucose cotransporter 2 and 11 beta-hydroxy steroid dehydrogenase 1, insulin releasing glucokinase activators and pancreatic-G-protein-coupled fatty-acid-receptor agonists, glucagon-receptor antagonists, metabolic inhibitors of hepatic glucose output and quick – release bromocriptine. Inhaled insulin was licensed for use in 2006 but has been withdrawn from market because of low patronage.
**Keywords:** Diabetes mellitus-Diagnosis-Epidemology-Management.

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## 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. Type 2 DM was first described as a component of metabolic syndrome in 1988 [2]. 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. Type 2 DM results from interaction between genetic, environmental and behavioural risk factors [3]. People suffering with type 2 DM are more vulnerable to various forms of short-trem 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 [4].

## EPIDEMIOLOGY

It is estimated that 366 million people had DM in 2011; by 2030 this would rise to 552 million. The number of people with type 2 DM are 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. It is estimated that 439 million people would have type 2 DM by the year 2030 [5]. The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors [6]. 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 dramatic increase in prevalence in both rural and urban setting, and affecting both gender equally. 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. Centre for Disease Control and Prevention (CDC) 2011 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.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 [7]. It is projected that this latter will equal or even exceed the former in developing nations, thus culminating in a double burden trend of transition from communicable to non-communicable diseases [8].

## Lifestyle, Genetics and Medical Condition

Type 2 DM is due to different lifestyle factors and genetics [9]. A number of lifestyle factors are known to be important to the development of type 2 DM. These are physical inactive, sedentary lifestyle, cigarette smoking and generous consumption of alcohol [10]. 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 lead to the increase in type 2 DM in children and adolescents. Environment toxins may contribute to the recent increase in the rate of type 2 DM. A weak positive correlation has been found between concentrations in the urine bisphenol A, a constituent of some plastics, and the incidence of type 2 DM [11]. There is a strong inheritable genetic connection in type 2 DM; having relatives (especially first degree) with type 2 DM increases the risk 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 [12]. Recently , genes discovered to be significantly associated with developing type 2 DM, include TCF7L2 ,PPARG, FTO, KCNJ11, NOTCH2, WFSI, CDKAL1, LGF2BP2, SLC30A8, JAZF1, and HHEX.KCNJ11(potassium rectifying channel, subfamily J ,member 11),encodes the islets ATP- sensitive potassium channel Kir6.2 and TCF7L2( transcription factor 7-like 2)regulates pro glucagon gene expression and thus the production of glucagon-like peptide-1[13]. Moreover, obesity (which is an independent risk factor type 2 DM) is strongly inherited [14]. Monogenic forms like maturity-onset diabetes of the young (MODY), constitutes up to 5%of cases [15]. There are many medical conditions which can potentially give raise to exacerbate type 2 DM. These include obesity, hypertension, elevated cholesterol (combined hypolipidemia) and with the condition often termed metabolic syndrome (it is also known as Syndrome X, Reaven's syndrome) [16]. Other causes include acromegaly, Cusing's syndrome, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, cancer, and drugs. Additional factors found to increase the risk of type 2 DM include aging, [17] high fat diets, and less active lifestyle [18].

## Pathophysiology

Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure [19, 20]. This leads to a decrease in glucose transport in 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 recognised in the phathophysiology of type 2 DM [21]. As a result of this dysfunction, glucagon and hepatic glucose levels that raise during fasting are not suppressed with a meal. 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 [21]. 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 [21]. Both classes of agents have shown promise, with potential not only to normalise 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 [22]. 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 and possibly beta-cell dysfunction) [21]. A majority of individual suffering from type 2 DM are obese, with central visceral adiposity. Therefore, adipose tissue plays a crucial role in the pathogenesis type 2 DM.

Although the predominant theory used to explain this link is 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 muscles, 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 [21].

## 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 a result that a positive screen is equivalent to a diagnosis of pre-diabetes or DM [23]. Although about 25% of patients with type 2 DM already have micro vascular complications at the time of diagnosis suggesting that they would have had the disease for more than 5 years by the time of diagnosis [24]. It is still based on the American Diabetic Association (ADA) guide lines of 1997 or World Health Organisation (WHO) National diabetic group criteria of 2016, 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) 7.0mmol/L (126mg /dL) or with an oral glucose tolerance test (OGTT),two hours after the oral test after the oral dose a plasma glucose 11.1 mmol/L (200mg/dL) [23]. The 1997 ADA recommendations for diagnosis of DM focus on the FPG, while WHO focuses on the OGTT [23]. The glycated haemoglobin (HbA 1c) and fructosamine is also still useful for determining blood sugar control over time. However, practicing physicians to frequently employ other measures in addition to those recommended. In July 2009 the International Expert Committee (IEC) recommended the additional diagnostic criteria of HbA 1c results 6.5% for DM. This committee suggested that the use of the term pre-diabetes may be phased but identified the range of HbA 1c levels 6.0% and < 6.5% to identify those at high risk of developing DM [25] .As with the glucose-based tests, there is no definite threshold of HbA 1c at which normality end and DM begins [23]. The IEC has elected to recommend a cut-of 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 HbA 1c level < 6.5% [25].

## 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 diet, low in saturated glycaemia index ,regular exercise, abstinence from smoking and moderate consumption of alcohol [3,26,28]. Suggesting that majority of type 2 DM can be prevented by life style modification. Patients with type 2 DM should receive a medical nutrition evaluation and life style recommendations should be tailored according to physical and functional ability [29].

## PHARMACOLOGICAL AGENTS

### (i) Biguanides

Bigunides, of which metformin is the most commonly used in over weight 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 gastro intestinal tract [30]. 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 [31]. Due to the concern 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 sulphonylureas [30].

### (ii) Sulphonylureas:

These are generally well tolerated but as they stimulate endogenous insulin secretion, they carry a risk of hypoglycemia. Elderly patients, with DM who are treated with sulphonylureas have a 36% increased risk of hypoglycaemia compared to younger patients [32]. Glyburide is associated with higher rates hypoglycemia compared to glipizide [33]. 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 medication or medications, potentiate suphonylurea actions [34]. Use of long acting sulphonylurea such as glyburide should be avoided in elderly patients with DM and use of short acting glipizide should be preferred [29].

**(iii) Meglitinides**:
Repaglinide and nateglinide are non-sulphonylurea secretagogues which acts on the ATP dependent k-channel in the pancreatic beta-cells thereby stimulating the release of insulin from the beta-cells, similar to sulphonylurea though the binding site is different [35]. Meglitinides have a rapid onset and short duration of action(4-6 hours)and thus lower risk of hypoglycaemia. Meglitinides are given before meals for postprandial blood glucose control.Preprandial administration allows flexibility incase a meal is missed without increased risk of hypoglycaemia [36]. Repaglinide is mainly metabolized in the liver with very minimal amounts excreted via the kidneys and thus those adjustment is not necessary in patients with renal insufficiency except those with endostage renal disease [35].

**(iv) Thiazolidinediones**:
Thiazolidineodiones is an insulin sensitizer. They are the first drugs to address the basic problem of insulin resistance in type 2 DM patients [37], whose class now includes mainly pioglitazone after the restricted use of rosiglitozone recommended by Food and Drug Administration (FDA) recently due to increased cardio vascular events reported with rosiglitazone [27]. Pioglitazone use is not associated with hypoglycaemia 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 [38].

## 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 postprondial hyperglycemias and should be avoided in patients with significant renal impairement. Thier use is usually limited due to high rates of side-effects such as diarrhoea and flatulence [29]. Voglibose, which is the newest of the drugs, has been shown in a study to significantly improve glucose tolereance,in terms of delayed disease progression and in the number of patients who achieve normoglycemia [39].

## 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 glycaemia control and improved body weight control [40]. They are available for use as mono therapy, 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 [29]. There is no risk of hypoglycaemia with the use of GLP-1 therapies (unless combine with insulin secreatogogues) .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 [40].

## 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 [41]. DPP-4 inhibitor are a new class of anti-diabetogenic drugs that provide comparable efficacy to current treatment. They are effective as mono therapy 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 [41]. The long term durability of effect on glycaemia control and beta-cell morphology and function remain to be established [41, 42].

## Insulin
Insulin is used alone or in combination with oral hypoglycaemia 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 [43]. 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 physiological 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 [44,45]. The pharmacokinetic profiles of the new insulin analolgues are distinct from those of the regular insulins, and their onset and durations of action range are from rapid to prolonged. Currentely, two rapid-acting insulin analogues, insulin lispro and insulin as part, and one long-acting insulin analogue, insulin glargine are available [44,45].

### Future in drug therapy inhaled insulin

The inhale form of rapidly acting insulin which became available in 2006 [46], after it was approved by both the European Medicines Evaluation Agency and FDA for treatment of type 1 and type 2 DM in adults. 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 [46]. 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 Hb A 1c levels by 0.0% to 0.2% after 24 weeks of therapy [49].

### Others

Inhibitors of the sodium-glucose cotransporter 2,which increase renal glucose elimination, and inhibitors of 11β-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 antagonist, and metabolic inhibitors of hepatic glucose output are being assessed for the purpose of development of new drug therapy for type 2 diabetic patients.

## CONCLUSION

Type 2 DM is a metabolic disease that can be prevented through lifestyle modification, diet control, control of overweight and obesity. Education of the population 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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