MERIT RESEARCH JOURNALS
www.meritresearchjournals.org

Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 5(9) pp. 440-445, September, 2017
Available online http://www.meritresearchjournals.org/mms/index.htm

Review

Currents and future projections in diabetes managements: an update review

Umar Z. U.[1*], Isah R. T.[2] and Mainassara A. S.[3]

[1]Department of Physiology, Usman Danfodiyo University Sokoto. Nigeria

[2]School of Medical Lab Science, Usman Danfodiyo University Sokoto. Nigeria

[3]College of Health Sciences, Usman Danfodiyo University Sokoto. Nigeria.

***Corresponding Author's E- mail; zenufatee@yahoo.com**
Phone: +2348062617066

Abstract

Diabetes mellitus (DM) is now a pandemic non-communicable disease that needs emergency multifactorial interventions. Blood glucose metabolism is normally controlled by a feedback mechanism including islet beta cells, insulin sensitive cells and tissue sensitive to the insulin have higher magnitude of beta cell response. Based on various etiology and pathogenesis, there are many type of diabetes with similar symptoms and manifestations. However, diabetic-hyperglyacemia appears difficult to control within the normal range of glycaemic level and no lasting solution to this disease. Since after the discovery of standard medication for DM such as oral hypoglycaemic agents and insulin other, numerous therapeutic and technological advances have improved the lives of patients with DM. Moreover, based on the clinical trials and future focus, many antidiabetic agents and methods of good glycaemic control were found that can positively affect or normalized glucose metabolism. The decision to use any of this techniques is based on its efficacy, safety and patient factors. This article reviewed the recent therapeutic and technological advances and the future trends in the management of DM with a view to obtain possible final solution to the management of this disease.

Keywords: Diabetes, currents updates, classification, managements.

INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder of multiple aetiology characterised by persistent hyperglycaemia, polyuria, polyphagia and polydipsia with alter normal carbohydrate, fat and protein metabolism due to defects in insulin secretion, insulin action or both (IDA, 2016; IDF, 2016). DM is the most common non-communicable but life threatening diseases worldwide and study reveal its rising prevalence of DM globally, this has been observed in populations that have undergone relatively rapid transition from rural to urban lifestyles (IDF, 2016). Worldwide the number of people with diabetes is expected to rise from 382 million people in 2013 to triple by 2045 (IDF, 2015).The rising prevalence of diabetes in developing countries is due to some factors such as lifestyle, industrialization and socioeconomic development. It is the fourth or fifth leading cause of death in most high income countries and there is substantial evidence that it is epidemic in many economically developing and newly industrialized countries, is undoubtedly one of the most challenging health problems of the 21st century (WHO, 2016).

Morbidity and mortality rates are increased in diabetes, due to complications including, micro and macro vascular problems, retinopathy, nephropathy, and nonspecific macro vascular atherosclerosis, while acute metabolic complications such as diabetes ketoacidosis (DKA), hyper osmolar non ketotic stage (HONK), gynecological and obstetric complications, susceptibility to sepsis continue to be the major cause of increased mortality rate in developing countries (WHO, 2008; IDF,

2013). The blood glucose control choice depends on a number of factors including, patient preference, adverse effect profile, risk of hypoglycemia, availability, affordability and even the action on weight. Diabetes is associated with reduced life expectancy, significant mortality and diminished quality of life.

The American Diabetes association standards of care plan to provide the patients, clinicians, researchers and other interested individuals with the idea on pathogenesis of DM, management modalities and treatment goals, tools to attract more research, evaluate the quality of care to be applied in the context of excellent and with adjustments (ADA, 2016). This review will act as an eye opener in attracting more research toward finding lasting solution to patient with diabetes and reference for literature citation.

AIMS AND OBJECTIVES

The aim of this review was to narrate, update and address the currents trend in DM managements, highlight on various DM classes to open avenue for feature research.

Classification of Diabetes Mellitus

Diabetes is classified into four main categories:

Type 1 DM

Diabetes which is due to beta cell destruction or inadequate insulin secretion that usually leads to absolute insulin deficiency. It accounts for 5-10 % of Diabetes Mellitus. There is autoimmune destruction of beta cells with absolute insulin deficiency, hence formerly called Insulin Dependent Diabetes Mellitus (IDDM). It commonly occurs in childhood (< 30 yrs). The onset is usually acute and they are Ketoacidosis prone.

Type 2 DM

Diabetes which is due to a progressive insulin receptor or insulin functional defect on the background of insulin resistance or gene mutation. It accounts for 90-95 % of Diabetes Mellitus. It was formerly called Non-Insulin Dependent Diabetes Mellitus (NIDDM). The pathology is mainly Insulin resistance in peripheral tissues with associated Insulin secretory defect of beta cells. There is Strong genetic predisposition in this case. The aetiology is multifactorial – interaction between genetic & environmental factors. Some risk factors for Type 2 DM includes, Genetic factors (Genetic markers, family history, “thrifty” gene), Advancing age, Ethnicity (blacks, Native Americans), Obesity, Physical inactivity, Diet, Urbanization/modernization, Metabolic determinants (Impaired glucose tolerance, Insulin resistance).

1. Gestational diabetes mellitus in which hyperglycemia develops only during pregnancy and can resolve immediately after delivery. Although, may come up with type 2 DM letter in life (CDC, 2016).
2. Other types of diabetes are due to some associated causes such as genetic defects in beta cell normal physiology, genetic defects in insulin function, diseases affecting the islets or exocrine pancreas, beta cell cytotoxic chemicals or steroid therapy (ADA, 2016; IDF, 2017).

Diagnostic Criteria

The disease is usually diagnosed based on plasma glucose criteria, either the fasting blood sugar level of ≥ 126 mg/dL (≥ 7.0 mmol/L) or the two hour plasma glucose value ≥ 200 mg/dL (≥ 11.1 mmol/L) after a 75g glucose tolerance test. Recently, an International Expert Committee has added the glycated hemoglobin level of ≥ 6.5% with any of the following symptoms, polyuria, polydipsia, weight loss (ADA, 2016; WHO, 2016).

The vivid criteria for the diagnosis of diabetes mellitus are as follows:

1. When a patient present with signs and symptoms of diabetes, namely, polyuria, polydipsia, polyphagia and unexplained weight cost, plus random plasma glucose concentration ≥200mg/d or
(11.1mmol/L), and confirmed on a subsequent day, to give a similar outcome, the diagnosis of diabetes mellitus is made.
2. When a patient presents with sign and symptoms of diabetes listed above, with fasting plasma glucose concentration of ≥ 126mg/dl (7.2mmol/L), also confirmed on a subsequent day, to give similar outcome.
3. When a patient presents with sign and symptoms of diabetes mellitus, with 2 ours plasma glucose concentration of 200mg/dl (11.1mmol/L) during an oral glucose tolerance test as described by WHO, using a glucose load containing the equivalent of 75g anhydrous glucose, dissolved in water. This however, is not routinely used in the diagnosis of diabetes mellitus.
4. An intermediate group of subjects with glucose concentration that do not meet the above criteria for diabetes, and nevertheless, too high to be considered normal exists (ADA 2016; IDF, 2016). This group of subjects had fasting plasma glucose level > 110mg/dl (6.1mmol/L), but <126mg/dl (7.0mmol/L). To avoid the stigmatization attached to the name diabetic, they are classified as subjects with impaired fasting glucose (IFG). With time, these class of subjects may progress to full blown diabetes, or revert to normal plasma glucose concentration (ADA, 2014; IDA, 2016; WHO, 2010).

Modalities of DM Managements

Lifestyle modification

This involves Lifestyle modification in the Population and those at high riskinclude diet, weight reduction and exercise. Is usually first treated by increasing physical activity, and eliminating saturated fat and reducing sugar and carbohydrate intake with a goal of losing weight. These can restore insulin sensitivity even when the weight loss is modest, most especially when it is in abdominal fat deposits. Diets that are very low in saturated fats can reverse insulin resistance (Van Realte and Diamant, 2011).

Diet

It should contain low carbohydrates, High fibre and low saturated fat. It is not different from that considered healthy for everyone

Physical activity

It improves glycemic control, assist with weight maintenance, and reduce risk of CVD. At least 150 min/week of moderate-intensity physical activity is recommended. The physical activity should be distributed over at least 3 days/week and with no more than two 2 consecutive days without physical activity (Chow et al., 2016; Van Realte and Diamant, 2011).

Antidiabetic Agents

About 8 different classes of oral medications are currently used in the treatment of DM. They either make the pancreas produce more insulin or reduce gluconeogenesis by the liver. The drugs include - Sulfonylureas (glybenclamide, gliclazide), Biguanides (metformin), Meglitinides (Repaglinide), Alpha Glucosidase Inhibitors (acarbose), Thiazolidinediones (rosiglitazone, pioglitazone), Insulin, Insulin analogues (Lispro, Glargine), Incretin Mimetics (Exenatide), Dipeptidyl Peptidase 4 (DPP-IV) Inhibitors (Sitagliptin) and Amylin Analogs pramlintide (Van Realte and Diamant, 2011).It involves Prevention of emergence of risk factors in the population. This can be achieved through health education. The importance of maintenance of normal body weight, healthy nutrition (high intake of fibre, adequate protein and low refined carbohydrates) and Physical exercise are emphasised. Good control of blood glucose protects against the development of complications. The glycemic control can be achieved with antidiabetic drugs or insulin (Boyle et al., 2010; Viollet et al., 2012). The following parameters are necessary for secondary prevention: Routine monitoring of the followings: blood glucose, Glycosylated haemoglobin, urinalysis, lipids, Blood Pressure, visual acuity, weight gain monitor and Periodic examination of the feet. Self-care: Adherence to diet and drugs (Holden et al., 2016; Hur and Lee, 2015).

New Trends in DM Managements

Incretin Mimetics

The role of intestinal peptides in the regulation of postprandial insulin secretion was first identified by the observation that insulin secretion from pancreatic ß-cells was more robust after an oral glucose bolus than after an equivalent, intravenous glucose bolus. This "incretin effect" was attributed to the insulinotropic action of gut hormones, specifically GLP-1and glucose-dependent insulinotropic polypeptide (Laux et al., 2016). The biological activities of GLP-1include (1) glucose-dependent insulin secretion to aid tissue uptake of plasma glucose, (2) suppression of postprandial glucagon to reduce hepatic glucose release, (3) slowing of gastric emptying to avoid overwhelming the circulation with glucose as food is absorbed from the gut, and (4) suppression of food intake (appetite) (5) Preserves islet integrity and decreases apoptosis. In addition, animal data suggest that GLP-1 regulates maintenance of pancreatic ß-cell mass as a normal physiologic function. Incretin mimetics are a new class of pharmacological agents with multiple antihyperglycemic actions that mimic some effects of endogenous incretin hormones, including glucose-dependent enhancement of insulin secretion. They include- Exenatide, Liraglutide and Tespoglutide (Laux et al., 2016; Nielsen, 2005).

Dipeptidyl peptidase-4 (DPP-4) Inhibitors

They increase blood concentration of the incretin GLP 1 by inhibiting its degradation by DPP-4. Examples are vildagliptin, sitagliptin and saxagliptin (Flory et al., 2016). Amylin analogues slow gastric emptying and suppress glucagon release. They have all the incretins action except stimulation of insulin action. Pramlintide is the only clinically available amylin analogue (Tiwari, 2015; Yabe et al., 2016).

The Bio-artificial pancreas

A cross section of bio-engineered tissue with encapsulated islet cells delivering endocrine hormones in response to glucose is implanted (Barkai et al., 2016). Encapsulation of the islet cells in a protective coating that has been developed to block the immune response to

transplanted cells, which relieves the burden of immunosuppression and benefits the longevity of the transplant. This approach has had very positive clinical studies and is currently underway in human trials. So far, treatment using this method of cell encapsulation has been proven safe and effective and is the first to achieve insulin independence in human trials without immunosuppressant drugs (Barkai et al., 2016; Pothuloori and Chaidarun, 2015).

Islet cell regeneration

Researchers have discovered a protein they referred to as INGAP Islet Neogenesis Associated Protein (INGAP). INGAP seems to be the product of a gene responsible for regenerating the islets that make insulin and other important hormones in the pancreas. As of 2008, the protein had undergone Phase 2 Human Clinical Trials, and developers were analyzing the results (Assouline-Thomas et al., 2015). This trial will be unique in that patients who are beyond the 'newly diagnosed' period will be included in the study. Most current trials seeking to treat people with type 1 diabetes do not include those with established disease (Flores et al., 2014).

Stem cells

Stem cell research has been suggested as a potential avenue for a cure since it may permit regrowth of Islet cells which are genetically part of the treated individual, thus perhaps eliminating the need for immuno-suppressants. This new method autologous nonmyeloablative hematopoietic stem cell transplantation was developed by a research team composed by Brazilian and American scientists and it was the first study to use stem cell therapy in human diabetes mellitus This was initially tested in mice and in 2007 there was the first publication of stem cell therapy to treat this form of diabetes (He et al., 2015). In summary it is a kind of "immunologic reset" that blocks the autoimmune attack against residual pancreatic insulin-producing cells. It is too early to say whether the results will be positive or negative in the long run. In September 2008, scientists from the University of North Carolina at Chapel Hill School of Medicine have announced their success in transforming cells from human skin into cells that produce insulin. The skin cells were first transformed into stem cells and then had been differentiated into insulin-secreting cells (Mellado-Gil et al., 2012).

Gene therapy

Technology for gene therapy is advancing rapidly with such pathways possible to support endocrine function, with potential to practically cure diabetes. Gene therapy might eventually be used to cure the cause of beta cell destruction, thereby curing the new diabetes patient before the beta cell destruction is complete and irreversible (Zulewski et al., 2001). Gene therapy can be used to turn duodenum cells and duodenum adult stem cells into beta cells which produce insulin and amylin naturally. By delivering beta cell DNA to the intestine cells in the duodenum, a few intestinal cells will turn into beta cells, and subsequently adult stem cells will develop into beta cells (Kawser-Hossein et al., 2016). This makes the supply of beta cells in the duodenum self-replenishing, and the beta cells will produce insulin in proportional response to carbohydrates consumed. Transplants of exogenous beta cells have been performed experimentally in both mice and humans, but this measure is not yet practical in regular clinical practice partly due to the limited number of beta cell donors. Thus far, like any such transplant, it has provoked an immune reaction and long-term immunosuppressive drugs have been needed to protect the transplanted tissue (Johannesson et al., 2015).

Other experimental agents

Sodium –Dependent Glucose Transporter 2 Inhibitors – increase urinary glucose excretion. Fructose 1,6 – biphosphatase inhibitors – they decrease gluconeo-genesis by the liver (Kawser-Hossein et al., 2016; Johannesson et al., 2015).

Testosterone replacement therapy

May improve glucose tolerance and insulin sensitivity in diabetic hypo gonadal men. The mechanisms by which testosterone decreases insulin resistance is under study. Moreover testosterone may have a protective effect on pancreatic beta cells, which is possibly exerted by androgen-receptor-mediated mechanisms and influence of inflammatory cytokines (Cernea et al., 2016).

Gastric bypass surgery

Recently it has been suggested that a type of gastric bypass surgery may normalize blood glucose levels in 80-100% of severely obese patients with diabetes. The precise causal mechanisms are being intensively researched; its results may not simply be attributable to weight loss, as the improvement in blood sugars seems to precede any change in body mass. This approach may become a treatment for some people with type 2 diabetes, but has not yet been studied in prospective clinical trials (Clements et al., 2004).

Natural products

Recent findings suggest that natural approaches to the DM may help supplement current standard medications for socio-economic alleviation and good glycaemic control (Schultz et al., 2016). Thus, establishing an intellectual property protection of medical treatments comprising of natural products is existing in public domain and currently promoted as dietary supplements in the management of DM (Bulaj et al., 2016). Additionally, some flavonoids and polyphenols are found to be effective in DM management (Jung et al., 2006; Patel and Udayabanu, 2016). However, the safety and efficacy of natural products supplementation remains to be established.

CONCLUSION

There are many type of DM based on various etiology and pathogenesis, hyperglycemia appear difficult to control within the normal range and no lasting solution to this disease. Since the discovery of insulin in the 1920's, numerous therapeutic and technological advances have improved the lives of patients with DM. However, based on the clinical trials and future focus many antidiabetic agents and methods of glycaemic control can positively affect glucose metabolism. The decision to use any of these techniques is based on efficacy, safety and patient factors. This article aimed to reviewed recent therapeutic and technological advances and the future trends in the management of DM.

ACKNOWLEDGEMENTS

This work is supported by Research University Grant from Universiti Sains Malaysia (1001/PPSP/813072) and Prof Mahaneem Mohamed.

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