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RECENT DEVELOPMENTS IN THE MANAGEMENT OF DIABETES MELLITUS

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DEFINITION

Diabetes mellitus (DM) is a chronic disorder affecting carbohydrate, lipid and protein metabolism due to a relative or absolute insulin deficiency.[1]

The resultant effect is chronic hyperglycemia and other related disorders which forms the hallmark of the disease. DM prevalence appears to be steadily increasing world wide with over 200 million individuals being affected [2]. It is also common in Nigeria.

Diabetes mellitus is the commonest endocrine condition seen in medical practice in Nigeria.[3] Unfortunately a large proportion of practitioners are not well informed about the current trends in the management of the condition. This paper attempts to assist in enlightening cavers.

PATHOPHYSIOLOGY

The pathophysiologic changes seen in DM are due to absent or inadequate insulin secretion and or peripheral insulin resistance.[4] There is increased hepatic glucose production, impaired insulin mediated muscle glucose uptake which leads to hyperglycaemia and glucotoxicity. Glucotoxicity refers to the decline in function and number of B cells due to the adverse effects of hyperglycemia. Lipotoxicity (lipotoxity being a similar effect brought on by hyper triglyceridaemia and increased circulating fatty acids) also occurs and beta cells decline due to the twin effects of glucotoxicity and lipotoxicity.[5] In type 2 DM, insulin resistance predominates with a resultant hyperinsulinemia which drives some other processes like endothelial proliferation and atherogenesis.

MANAGEMENT OPTIONS

The management of DM has evolved over the years from dietary management only to the myriad of agents we currently have on ground. From the first insulin in 1922 and later oral hypoglycemic agents (sulphonyureas and biguanides) three decades later, other classes of drugs have since been developed.

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The treatment of DM is multidisciplinary in approach. It involves the physicians, nurses, nutritionists, dietitians, physiotherapist, diabetes educators and chiropodists/podiatrists. The goal of treatment often varies depending on the state of presentation and the type of DM. Treatment involves setting achievable and realistic short term and long term goals through interaction and in cooperation with the patient. Consideration should be given for age and other peculiarities of the individual (children, adolescents, elderly, and that of marital life and pregnancies) with an emphasis on maintaining a "near normal life". The educational level and the financial status are also very important factors to be considered in the management of DM in Nigeria as these dictate the methods of teaching, the type of monitoring and recreational activities relating to the patient.

DIABETES EDUCATION

Diabetes education (DE) could be in the format of individualized or group based structured education. This is best done at the initial visit and should be continued subsequently. In the individualized education, the physician educates the patient during the course of his consultation. In the group education the patient along with others are educated by a nurse, pharmacist, diabetes educator or other trained personal often before seeing the doctors or while waiting for their drugs at the pharmacy. It is done by various health professionals. DE should be repetitive and interactive. It should address causes, course of disease, complications, survival techniques and treatment.

The proven and quantifiable benefits of education include the following;[6,7]

(a) Improvement of general well being and quality of life.
(b) Improved self- care management.
(c) Improved metabolic control
(d) Decreased cost of care in the short and long term
(e) Enhanced prevention and early detection of complications.

LIFE STYLE MODIFICATION

The DM patients are advised to quit smoking and minimize alcohol consumption (if they indulge in these activities). For this they may require medical and psychological support. Regular aerobic exercise is advisable, so also is a healthy diet and weight reduction in obese patients. Sedentary lifestyle is to be discouraged.

DIETARY MANAGEMENT

The goals of dietary management are slightly different in type 1 and type 2 DM. For type 1 DM, establishment of consistent carbohydrate intake to synchronize mealtimes with insulin action is necessary. Moderate caloric restrictions must however be maintained to prevent undue weight gain or post prandial hyperglycemia. The basic dietary advice is avoidance of simple carbohydrates like sugar, sweets, honey, etc. as they tend to cause a sharp rise in the blood glucose levels due to their high glycaemic index. [8, 9] In type 2 DM weight reducing diet is often emphasized as quite a number of the patients are obese. Fats are particularly restricted due to the dyslipidemia and coronary artery disease common to the metabolic syndrome and type 2 DM [10]. Likewise salt restriction is a key area in managing the commonly associated hypertension.[11]

Total calories allowed an individual will depend on the present weight and the targeted optimal weight. In all patients the total calories prescribed should take into consideration the activity levels of the patients as well as special circumstances like growth, pregnancy and lactation. A weight maintaining diet should have 30-35kcal/kg body weight daily; weight reduction diet 20-30 kcal/kg body weight per day. [12]

Carbohydrates should constitute around 60-70% of total calories and should be in the form of complex polysaccharides with adequate amount of fiber. Twenty 30 grams of fibre daily are often prescribed and this can be obtained 3-5 servings of fruit and vegetable daily. [12,13]

Protein intake should be 12-18% of total calories. It should approximate to about 0.8gm/kg of ideal body weight. Protein intake may however need to be restricted to 0.6gm/kg of body weight in patients with nephropathy.[14] Fat should be restricted to around 20-25% of total calories. Polyunsaturated fat are preferable (vegetable oils). Omega 3 fatty acids (fish oils) are equally preferred. This in simple term translates to eating less red meat, avoiding fatty portions of meat and eating more fish. Animal fats should be reduced [15]

Micronutrients supplementation are generally not required if the diet is balanced. The uses of antioxidants like vitamins E, C, and alpha lipoic acid, have been shown to reduce risk of cardiovascular disease CVD.[16,17] and are thus encouraged.

EXERCISE

A regular exercise program tailor-made for each individual and undertaken after due fitness evaluation, is an essential part of modern diabetes management. Benefits of exercise include increased insulin sensitivity, improved long term glycaemic control, (lower glycated hemoglobin (HbA1c)). It also includes improved lipid profile, improved blood pressure control among other benefits. [18,19]

The patients will require full pre-exercise evaluation before starting exercise. Underlying heart disease should be screened for (especially if the patients are >35 years), ophthalmic evaluation, microalbuminuria and peripheral neuropathy are important parameters that should be screened for. The exercise should be aerobic and isotonic such as walking, running, dancing, and swimming. Isometric exercises, such as weight lifting arm wrestling, etc are not recommended. Exercise must be graduated from a few minutes daily to longer periods. The duration of each exercise session should be around 30-45 minutes with a five minutes warm up and five minutes cooling off period. This helps to reduce cramps and muscular/ligamentous injuries. Exercise should be individualized. Intensity of exercise is measured in terms of the percentage of the patient's maximum heart rate (MHR). MHR = 220-Age of the patient (years). Exercise can be increased to reach 60-70% of the MHR. [20]

PHARMACOTHERAPY

The diverse pharmacological agents available for the treatment of DM patients can be classified into the following; oral glucose lowering agents, insulin, insulin analogues, and newer agents.

ORAL GLUCOSE LOWERING AGENTS

Current therapy for the treatment of hyperglycaemia of type 2 Diabetes includes the following agents. The main groups are sulphonylureas, biguanides, alpha-glucosidase inhibitors, meglitinides, and thiazolidinediones.

SULPHONYLUREAS (SU)

These work primarily by stimulating the pancreatic insulin secretion which in turn reduces hepatic glucose output and increases peripheral glucose disposal. They are the 1st group of oral drugs to be used in the treatment of DM. They are divided into 1st and 2nd generation. The 1st generation ones being tolbutamide, chlorpropamide, glibenclamide and

acetohexamide. The 1st generation sulphonylureas are rarely used now due to poor safety profile. [21] The second generation SUs are gliclazide, glipizide and glimepiride. SUs all lead to weight gain and hypoglycemic episodes are common. They have little or no effect on insulin resistance, thus after some years oral agent failure manifests with increasing dose requirements before frank failure ensues.

BIGUANIDES (BG)

These were the next group of drugs to be discovered after the sulphonylureas. They are often prescribed for obese type 2 DM patients. BGs work mainly by suppressing hepatic glucose production and increasing glucose utilization in peripheral tissues. They also reduce appetite and intestinal glucose absorption. They often lead to modest weight loss and gastro intestinal upset is common. They may cause lactic acidosis and diarrhea. The only BG available now is metformin. [22]

ALPHA GLUCOSIDASE INHIBITORS

These drugs came to use in the late eighties. They are fairly new drugs. The prototype is acarbose. It is an intestinal, brush border enzyme inhibitor, thus preventing the last phase of carbohydrate digestion. It improves insulin sensitivity and also leads to reduction in weight. It however causes bloating and diarrhoea like the biguanides. [23]

MEGLITINIDES

These drugs are derivatives of sulfonylurea. They are ultra short acting insulin secretagogues. They stimulate the beta cells of the pancreas directly and demonstrate a mild improvement in insulin sensitivity. There is a low risk of hypoglycemia with these drugs and they are given with each meal. [24] An example of drugs in this group is repaglinide.

THIAZOLIDINEDIONES

These are the newest class of oral antidiabetic drugs available in markets. They are quite expensive. They reduce insulin resistance significantly and preserve pancreatic beta cells. They improve fat distribution by reducing visceral adiposity and improve cardiovascular risk profile. There is no risk of hypoglycemia when used as monotherapy. They act via the Peroxisome Proliferator Activator Receptor (PPAR) Gamma.[25] Examples are troglitazone, rosiglitazone, and pioglitazone. Troglitazone, the first to be used has now been withdrawn worldwide due to hepatotoxicity[26]. Rosiglitazone and pioglitazone have done well in trials and the only adverse effects of note are fluid retention and transient non specific elevation of transaminases.

INSULIN THERAPY

Understanding of insulin biosynthesis secretion and action is necessary for the application of the principles of insulin therapy.

Biosynthesis, Secretion and Action of Insulin

Insulin is produced by the B cells of the pancreas from the precursor preproinsulin. Proinsulin is in turn cleaved to C-peptide and insulin. Glucose is the key regulator of insulin secretion by the pancreatic beta cell while other regulators include amino acids, ketones, gastrointestinal peptide and some neurotransmitters.

Normal Insulin Secretion

In non-diabetic persons, insulin secretion can be divided into 2 basic components basal and stimulated insulin secretion. Basal insulin is insulin that is continually secreted between meals and throughout the night at a rate of 0.5- 1U/hour in adults. The low basal concentration reduces hepatic glucose production (gluconeogenesis and glycogenolysis) but allows for glucose levels sufficient for cerebral energy utilization. Normally, stimulated insulin secretion occurs in response to a meal and results in serum insulin concentration of 60-80 micro-unit ml from just before to 30 minutes after meals. The insulin concentration returns to basal levels in 2-4 hours. Thus the regimens of regular insulin attempts to mimic the stimulated insulin secretary pattern while the regimens of long or intermediate acting insulin mimic basal secretion. [27,28]

Indications for Insulin Therapy

Type 1 DM; all type 1 DM patients require insulin for survival and glycaemic control; hyperglycaemia despite maximum doses of oral agents (secondary oral agent failure); decompensation of glycaemic control due to intercurrent events (e.g. infection, acute injury, stress); complications like myocardial infarction, cerebrovascular accident etc, all necessitate conversion of oral agent to insulin due to the refractoriness of such cases to adequate control or the need for better glycaemic control. This refractoriness is occasioned by rising stress hormones; severe hyperglycaemia with ketonemia or ketonuria is always treated with insulin. Renal disease (diabetic or non diabetic) is best managed by replacing oral agents with insulin because of the risk of impaired renal excretion and also because tight control is required to stem further nephropathy. For elective surgery, it is essential to put patients on

insulin and thus tighten control and preempt loss of control that goes with the increased stress hormones that characterize the physiological response to trauma/surgery. In pregnancy, most oral agents have not been proven to be safe in pregnancy. Their safety in pregnancy has not been established as no trials are done in such pregnant women. Allergy or other serious reaction to oral agents. [29,30]

Duration of Action of Insulin

Various insulin preparations are available with different pharmokinetic profiles. Some are listed below [28]

Type	Onset	Peak	Effective Duration	Maximum Duration
Regular	0.5-1hrs	2-3hrs	3-6hrs	4-6hrs
Lispro	10-15mins	1-15hrs	4-5hrs	
Aspart	10-15mins	1-2hrs	4-6hrs	
NPH	2-4hrs	4-10hrs	10-16hrs	14-18h
Lente	3-4hrs	4-12hrs	12-18hrs	16-20hrs
Ultra lente	6-10hrs	8-10hrs	18-20hrs	20-30hrs
Glargine	2-3hrs	no peak	upto 30hrs	
Detemir	2-3hrs	no peak	upto 24hrs	

Modes of Delivery of Insulin

There are various modes of insulin delivery. The commonest are needles and syringes and insulin pen devices. However other modes of delivery exist. They include insulin jet (pressure) injector which are no longer readily available worldwide and are losing popularity; Insulin Pump which delivers continuous basal insulin that can be increased pre meals. They are expensive and not yet in use in Nigeria. Insulin closed loop system (Artificial pancreases) remains mainly experimental but it attempts to deliver insulin based on glycemia, which is monitored by an implantable sensor. Inhaled insulin is administered in powder or nebulized solution format utilizing the wide surface are provided by the alveoli. Two types are exubera (powder) and AERX insulin delivery systems (uses solution). [31-33] Other types are in the pipeline.

Side Effects of Insulin Therapy

Like any chemical or agent insulin use is accompanied in some patients by side effects, some of which include hypoglycaemia which occurs when blood sugars drop to less than 45mg/dl or when it drops from a very high level to relatively lower ones, e.g. like a decline from 350mg to 70mg/dL in a few hours will give symptoms of hypoglycaemia; weight gain; lipodystrophy and lipoatrophy which usually occurs around injection sites is seen in a few patients; Pain at the injection site following the use of blunt needles or from infection due to aseptic technique; Pruritus and urticaria may result from insulin allergy; fluid retention may follow fairly large or frequent insulin doses.

INSULIN ANALOGUES

These are substances obtained from modification of amino acid sequence of human insulin. They aim to either shorten or prolong the action of the naturally occurring insulin. They are all clear solutions like regular insulin. Presently the following are available in most countries (but not yet in Nigeria): Short-acting insulin analogues e.g. Insulin aspart and Insulin lispro, Long-Acting insulin analogues e.g. Insulin determir and Insulin glargine, and Biphasic containing mixtures of short and long acting analogues [34,35]. Insulin aspart has an onset of action of 10-20 minutes and shorter duration (3-5 hours) of action compare with soluble human insulin. The maximum effect is seen at 1-3 hours after subcutaneous injection.

Advantages of Insulin Analogues over Insulin

The incidence of severe hypoglycaemia is markedly reduced so also is the incidence of nocturnal hypoglycaemia. Weight gain is not as common as seen in regular insulin. Allergy is uncommon hence allergic patients can use analogues where the human or porcine insulin are not tolerated. Convenience of dosing is also a key advantage as insulin analogues can be given just before or with meals as opposed to insulin which is given 30min-1hr before meals [35].

OTHER NEWER AGENTS AND MODALITIES.

PPAR alpha

PPAR alpha is a lipoprotein regulator expressed in tissues such as the liver, kidney heart and skeletal muscle. PPAR alpha plays an important role in oxidation of fatty acids in the liver. [36-37] PPAR alpha activation stimulates fatty acid oxidation. Its ligands are clofibrate, fenofibrate and bezafibrate. It down regulates vascular cell adhesion molecule-1 (VCAM-1). Fibrate treatment reduces weight gain and thus obesity which is a risk factor for insulin resistance. [38,39]

Dual Agonists

These are molecules able to activate both PPAR alpha and PPAR gamma and thus can potentially exhibit the positive effects of both. KPP-297 and tesaglitazar

are dual agonists still in the phase of clinical trials. Likewise muriglitazaar which may be well suited for treating type 2 DM and metabolic syndrome has reached advanced stages in clinical trials.[40,41] Medaglidasen is not strictly a PPAR agonist. It is selective peroxisome proliferator activator receptor modulators. It has shown great promise and is devoid of the side effects of PPAR gamma such as oedema and weight gain

Incretins

They are previously referred to as "Gut hormones". They are produced by cells in the intestinal tract in response to absorption of food. Glucagons- like peptide-1 (GLP-1) are the best characterized incretins. Research has demonstrated its positive effect on blood glucose control and they are known to improve pancreatic islet function. Incretins stimulate pancreatic B-cells to produce insulin especially when glucose levels are high. Incretins reduces secretion of glucagons from A-cell in the pancreatic islets. [42] It increases B-cell growth and cell mass and thus helps in maintaining insulin production and slow progression of type 2 diabetes mellitus. They also delay gastric emptying, which slows the rate at which nutrient are absorbed in the intestines, potentially helping stabilize blood glucose levels.[43] They appear to be active in the brain, affecting satiety and regulation of food intake. [43]

Incretins as a potential therapy for Type 2 DM

GLP -1 (Incretin) effectively lowers blood glucose. This makes it an attractive target for new therapies for type 2 diabetes. Incretins in the bloodstream are rapidly broken down by the enzyme dipeptidly/peptidase-4(DPP-4). This rapid breakdown results in a very short, natural half-life of approximately 2 minutes. Incretin hormones are proteins, making them too large to be taken orally. To address these challenges, two novel approaches are being developed. These include the following: incretin enhancers and GLP-1 analogues.

Incretin Enhancers

These are new class of oral anti diabetic medications; they increase level of the body's own GLP-1 and works by blocking DPP-4. Incretin enhancers currently under investigation for treatment of type 2 diabetes include vildagliptin (previously known as LAF 237) (44) which increases the circulating levels of GLP-1 in humans and animals and currently being evaluated as monotherapy in phase III trials and orally administered; and MK 431.[45] MK 431 is orally administered and currently in phase III trail for treatment of type 2 DM. It increases insulin secretions and lower glucagon level. It reduces HbA1c level significantly.

GLP-1 Analogues

These are new class of injectables antidiabetic therapies. They mimic natural GLP-1. GLP-1 analogues are slightly different in protein structure compared with natural GLP-1. Examples include Exenatide, Liraglutide and DAC: GLP-1.

Exenatide (exendin-4) is a hormone in the saliva of the gila monster, a lizard native to several southwestern American states. The synthetic version of exendin-4 is Exenatide. It displays properties similar to human GLP-1 and has potency up to 10 times greater than that of natural GLP-1 and has a longer half life. It is administered by a pen similar to insulin pens, twice daily. The main side effect is nausea and vomiting with consequent weight loss. [42, 46]

Liraglutide [46] is a series of acylated derivatives of GLP-1 that has long acting effects, works by self-associated and non-covalent binding of plasma albumin fatty acid binding sites. It decreases the level of glucagon, increases the B-cell mass in animal models of type 2 diabetes, leading to speculations against B-cell regeneration capacity. It is given once daily intravenously.

DAC: GLP-1 is another GLP-1 analogue currently in phase II clinical trail for treatment of type 2 DM. Recent trials results demonstrated that diacyglylcerol DAC: GLP-1 reduces glucose level in patients all the time of the day, including morning fasting period. It has a long duration of activity.[41-43]

Whole Pancreas Transplantation

Transplantation of whole pancreas may normalize glucose tolerance. It is an important therapeutic option in people with type 1 DM. However its limitations include side effect of immunosuppressant and requirement of great expertise.[47]

Pancreatic Islet Transplantation

This is an area of active clinical investigation. However pancreatic islet isolation graft survival is often poor except with very special techniques.[48,49]

REGIONALLY AVAILABLE TREATMENT OPTIONS OF TREATMENT OF DIABETES MELLITUS

Now that many of the mechanisms for metabolic dysfunction are understood, researchers can develop better drugs to alleviate adverse effects. Future drug development aims to increase the duration of drug action thus decreasing the amount of times the drug

needs to be administered for effectiveness. Researchers are also focused on developing the most efficient and easy methods of administration to target areas. By improving these current problems with the development of new drugs, hopefully future treatment of diabetes mellitus will be a more efficient And satisfying experience for patients in the developing and developed nations worldwide.

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