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APPROACHES IN THE TREATMENT OF DIABETES MELLITUS

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Abstract: Diabetes mellitus (DM) is an endocrinological metabolic disorder resulting from a defect in insulin secretion, insulin action or both. Insulin deficiency in turn leads to chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. As the disease progresses tissue or vascular damage ensues leading to severe diabetic complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration. Thus, diabetes covers a wide range of heterogeneous diseases. Diabetes mellitus is aggravated by and associated with metabolic complications that can subsequently lead to premature death. Diet and lifestyle strategies are to reduce weight, improve glycaemic control and reduce the risk of cardiovascular complications in diabetes. Diabetes is best controlled either by diet alone and exercise (non-pharmacological) or diet with herbal or oral hypoglycemic agents or insulin (pharmacological).This review explores about diabetes mellitus and its management.

Key words: Diabetes mellitus, insulin, oral hypoglycemic agents

INTRODUCTION:

Diabetes mellitus[1] is a combination of heterogeneous disorders commonly presenting with episodes of hyperglycemia and glucose intolerance as a result of lack of insulin, defective insulin action or both. Such complications arise due to derangements in the regulatory systems for storage and mobilization of metabolic fuels including the catabolism and anabolism of carbohydrates, lipids and proteins emanating from defective insulin secretion, insulin action or both. The debilitating effects of diabetes mellitus include various organ failures, progressive metabolic complications such as retinopathy [2], nephropathy [3] and neuropathy [4]. Diabetes mellitus is accompanied by risk of cardiovascular[5], peripheral vascular, cerebrovascular diseases and ulceration [6]. Several pathogenesis processes are involved in the development of diabetes including destruction of pancreatic β-cells that lead to lowered sensitivity of insulin action.

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CLASSIFICATION OF DIABETES MELLITUS [7]:

Diabetes mellitus may be classified into several types such as type 1, type 2 and gestational diabetes. On the basis of aetiology type 1 and type 2 were widely used to describe insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) respectively.

Type-1 DM

On the basis of etiology type 1 is present in patients who have little or no endogenous insulin secretory capacity and who therefore require insulin therapy for survival. The two main forms of clinical type 1 diabetes are type 1a (about 90% of type 1 cases in Europe) which is thought to be due to immunological destruction of pancreatic ß cells resulting in insulin deficiency and type 1b (idiopathic about 10% of type 1 diabetes) in which there is no evidence of autoimmunity. Type 1a is characterized by the presence of islet cell antibody (ICA), anti-glutamic acid decarboxylate (anti-GAD), IA-2 or insulin antibodies that identify the autoimmune process with ß-cell destruction. Autoimmune diseases such as Grave's disease, Hashimoto's thyroiditis and Addison's disease may be associated with type 1 diabetes mellitus. There is no known etiological basis for type 1b diabetes mellitus. Some of these patients have permanent insulinopaenia and are prone to ketoacidosis, but have no evidence of autoimmunity. This form is more prevalent among individuals of African and Asian Origin.

Type-2 DM

Type 2 diabetes is the commonest form of diabetes and is characterized by disorders of insulin secretion and insulin resistance. There is a higher incidence of type 2 diabetes in urban than in rural areas. Its incidence is associated with population whose lifestyle has changed from traditional patterns to a modern. Type 2 diabetes is common in individuals over the age of 40. It is often associated with obesity, decreased physical activity and heredity. The disease is usually controlled through dietary therapy, exercise and hypoglycaemic agents.

Gestational Diabetes (GD) mellitus

Gestational Diabetes (GD) mellitus refers to the onset or initial recognition of glucose intolerance during pregnancy usually in the second or third trimester. It occurs in about 4% of all pregnancies. Patients with GD have a 30% to 50% chance of developing DM usually type 2 DM.Other types include genetic defects of the pancreatic ß cell or in insulin action pathways (insulin receptor mutations or post-receptor defects) as well as disease of the exocrine pancreas (e.g. Pancreatitis, pancreatic reaction, or cystic fibrosis) are less common causes of DM. Endocrinopathies producing insulin counter regulatory hormones excess (e.g. Cushing's syndrome, acromegaly) may result in DM.Certain drugs like glucocorticoids, pentamidine, niacin, and a-interferon may also lead to DM.

SYMPTOMS [8]

Symptoms develop more rapidly in type 1 diabetes and more typical. The symptoms include polyurea, polydipsia, polyphagia, weight loss, fatigue, cramps, constipation, blurred vision and candidacies. Longstanding type 1 DM patients are susceptible to micro vascular complications and macro vascular disease (coronary artery, heart and peripheral vascular diseases).Symptoms in type 2 DM are similar but insidious in onset. Most cases are diagnosed because of complications or incidentally. Type 2 DM caries a high risk of large vessel atherosclerosis commonly associated with hypertension, hyperlipidaemia and obesity.

Mostpatients with type 2 diabetes die from cardiovascular complications and end stage renal disease.

DIAGNOSTIC CRITERIA [9-11]

The diagnostic criteria and the classification of diabetes was first put forward by the World Health Organization (WHO) in 1965 then by the National Diabetes Data Group (NDDG) in 1979 and this was followed by simplified recommendations by the WHO in 1980. These WHO recommendations were modified slightly in 1985. The latest recommendations have been published by the American Diabetes Association (ADA) in 1997 and by the WHO in 1999. Both groups agree on the recommendations and criteria.

According to the ADA recommendation changes in 1997 the fasting glucose concentration should be used in routine screening for diabetes as well as epidemiological studies the threshold for fasting glucose was changed from 7.8 mmol/L (140 mg/dl) to 7.0 mmol/L (126 mg/dl) however the 2 hr glucose criterion remains as = 11.1 mmol/L (200mg/dL). For the diagnosis of diabetes at least one criterion must apply.

- Symptoms of diabetes (polyurea, polydipsia, unexplained weight loss etc) as well as casual plasma glucose concentration = 11.1 mmol/L (200 mg/dL).
- Fasting plasma glucose = 7.0 mmol/L (126 mg/dL) with no caloric intake for at least 8 hr. 2 hr plasma glucose = 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test (OGTT) with the glucose load containing 75 g anhydrous glucose in water.

The report states that diagnosis should not be based on a single glucose determination but requires confirmatory symptoms or blood/plasma determination. Ideally therefore both the 2 hr and fasting value should be used.WHO group includes for GDM the gestational impaired glucose tolerance (GIGT) and GDM fasting glucose = 7.0 mmol/L (126 mg/dL) and/or 2hr glucose = 7.8 mmol/ L (140 mg/dL) after a 75-gOGTT.

TREATMENT OPTIONS [12-15]

Sulfonylureas

Sulfonylureas work by binding to sulfonylurea receptor (SUR) on beta cells of the pancreas thus enhancing insulin secretion from the pancreas blocking hepatic glucose production when being transported through the portal vein. Sulfonylureas are divided into first and second generation agents.First generation which are less potent include: Acetohexamide (dymelor),Chlorpromazine (Diabenese), Tolazamide (Tolinase)and Tolbutamide (Orinase).Second generation include Glipizide (Glucotrol, Glucotrol XL), Glyburide (Diabeta, Micronase) and Glimepiride (Amaryl).These agents are metabolized by the liver by CYP 450 enzymes (CYP 2C9) with renally eliminated active metabolites needed dosing adjustment in patients with renal failure.

Short acting insulin secretagogues known as Metiglitinides

Nateglinide (Starlix) and Repaglinide (Prandin) are the two Metaglinides approved in the U.S. They both stimulate the secretion of insulin from the pancreatic beta cells. These two agents are though rapid-acting and have a short half-life of 1 to 1.5 hours. They are mainly metabolized by CYP 2C9 and CYP3A4. When used alone they reduce postprandial glucose levels and HbA1C levels. They should be dosed half an hour prior to each meal and one of the advantages is that they can be used in renal insufficiency as well as alternative in hypoglycemic patients with

low-dose sulfonylureas. Due to the glucose sensitive release of insulin they cause less hypoglycemia in comparison with sulfonylureas.

Biguanides

Glucophage or Glucophage XR (metformin) is the only biguanide approved in the U.S. Mechanism of action is through reducing glucose production by the liver, reducing absorption of glucose, and enhancing uptake of glucose into skeletal muscle. Glucophage is not extensively metabolized and it is eliminated by renal tubular secretion and glomerular filtration.

Thiazolidinediones (TZDs)

Pioglitazone (Actos) and Rosiglitazone (Avandia) are the two FDA approved TZDs for Type 2 diabetes. They act by binding to the peroxisome proliferative insulin activated receptors enhancing sensitizing effects of insulin at liver, muscle as well as fat tissues also by inhibiting glucose formation by liver. This class of drugs has shown to be metabolized in the liver through CYP 450 isoenzymes 2C8 (Pioglitazone,rosiglitazone), 3A4 (pioglitazone) and 2C9(rosiglitazone).

AlphaGlucosidase inhibitors

Acarbose (Precose) and miglitol (Glyset) were approved in mid 1999 in the U.S. They competitively inhibit alpha-glucosidase enzymes in the small intestine which delays the breakdown of complex carbohydrates and sucrose thus decreasing postprandial glucose increase. These agents target patients with high postprandial blood glucose with almost normal values of HbA1C and fasting blood glucose and minimal effect on body weight.

Combination products

The use of combination therapies improved patient's compliance to the use of the oral diabetic agents. Glucovance is an example of a combination of glyburide and metformin. This combination was proven to reduce fasting plasma glucose by 50 to 60 mg/dl and HbA1C by 1.7 % to 1.9 %. This effect was greater than that of each agent as Monotherapy. Other combinations include glipizide/metformin (Metaglip),rosiglitazone/metformin (Avandamet), pioglitazone/glimepiride (Duetact).

Dipeptidyl peptidase4 Inhibitor (DPP4 Inhibitor)

The first FDA approved DPP-4 inhibitor in october 2006 in the United States is Sitagliptin (Januvia).Incretin hormones released in the intestine in response to meals play a role in regulation of glucose homeostasis. These hormones are deactivated by DPP-4 enzymes. Sitagliptin inhibits the inactivation of incretin hormones by inhibiting the DPP-4 enzyme increasing incretin levels. This process leads to an increase in the release of insulin and a decrease in the levels of glucagon in the blood. Vildagliptin (Galvus, Novartis) is a new DPP-4 taken once daily that has been approved in Europe, Iceland and Norway. It is approved for the use along with sulfonylureas, thiazolidinediones and metformin.This medication has been shown to lower blood sugar levels without causing weight gain or high incidence of hypoglycemia.

Newer approaches Peroxisome Proliferator Activated Receptors (PPARs)

Peroxisome proliferator activated receptors (PPARs) are transducer proteins belonging to nuclear receptor [16]. Three major types of PPARs encoded by separate genes have been identified: they are PPARα, PPARBβ/δ andPPAR $\gamma 2$. Peroxisome proliferators activated gamma (PPARγ)is a transcription factor activated by thiazolidinediones (TZDs). In transactivation , which is DNA-dependent, PPARγ forms a

heterodimer with the retinoid X receptor(RXR) and recognizes specific DNA response elements called PPAR response elements (PPRE) in the promoter region of target genes. This results, ultimately in transcription of PPARs undergo conformational changes, which lead to recruitment of cofactor proteins and co activators. The co activators interact with nuclear receptors in a ligand dependent way and influence the set of genes transcribed.

Glucagon like Peptide -1(GLP-1) Hormone

It is the incretin hormone acting via GLP-1 receptor (a G-Protein coupled receptor)When blood glucose levels are high this hormone stimulates insulin secretion and biosynthesis and inhibits glucagon release leading to reduced hepatic glucose output. In addition, it serves as an 'ileal brake', slowing gastric emptying and reducing appetite. GLP-1 has a number of effects on regulation of β -cell mass: stimulation of replication and growth inhibition of apoptosis of existing β -cell and neogenesis of new β $-$ cells from precursors.

$\beta-$3- Adrenoreceptor Agonits3-Adrenoreceptor Agonits

β3- Adrenoreceptor Agonist showed marked selectivity for stimulation of lipolysis and hence for oxygen and energy consumption in skeletal muscle and adipose tissue. SR-58611 (Sanofi-Synthelabo) and TAK-677 (Takeda) are some of the compounds in this series. In certain types of fat cells the β adrenergic receptor (β3AR) which belongs to the superfamily of G-protein coupled receptor (GPCRs) functions in a manner contrary to the general adrenergic system in which activation of β3AR actually induces the waste of metabolic energy. Agonists of this receptor activate the coupled protein (UCP) which causes the expenditure of metabolic calories as heat [17].

α-Lipoic Acid

LA functions naturally as a cofactor in several mitochondrial enzyme complexes responsible for oxidative glucose metabolism and cellular energy production. LA pretreatment maintains the intracellular level of reduced glutathione (the major intracellular antioxidant) in the presence of oxidative stress and blocks the activation of serine kinases that could potentially mediate insulin resistance.The protective effects of LA might be related to its ability to preserve the activation of inhibitory stress-sensitive serine kinases including IKKbeta. This stress-sensitive kinase is a crucial regulator of the transcription factor i.e., necrosis factor-kappaB (NF-kappaB), a major target of hyperglycemia,cytokines, reactive oxygen species, and oxidative strss. LA and other agents that interfere with the persistent activation of the NF-kappaB pathway appear to be promising approaches to increase insulin sensitivity and perhaps even as treatments for complications of diabetes in which NF-kappaB avtivation has been implicated.

Liver Selective Glucocorticoid Antagonists:

Glucocorticoids[18] raise blood glucose levels by functionally antagonizing the action of insulin, thereby inhibiting glucose production and output. So the approaches towards liver selective glucocoticoid antagonist have a potential role in the management of Type-II Diabetes Mellitus. Mifepristone has shown glucocorticoid antagonist action and few other similar compounds have been tested in which showed reduction in glucose levels and improved lipid profiles in an animal model of diabetes.

Dipeptidyl PeptidaseIV Inhibitors:

DPP-IV inhibitors stabilize endogenous GLP-! And induce insulin secretion in a glucose-dependent manner in contrast to insulin tropic agents which release insulin in glucose independent manners which manifest the

hypoglycemia as a residual effect. Thus, the use of DPP-Iv inhibitors increases the circulating levels of endogenous GLP-! Leading to increased insulin secretion, biosynthesis and inhibiting glucagon release. Example-salagliptin, dulogliptine, gemigliptin, alogliptinr, linagliptine.

Protein Tyrosine Phosphatase-1b (PTP-1b)

PTB-1B, belongs to non transmembrane class of enzymes. PTP-1B is an abundant enzyme expressed in nearly all tissues. PTP-1B acts as negative regulator of insulin signaling[19]. It acts by causing dephosphorylation of insulin receptor. It also causes negative regulation of insulin signaling. It is involved in Type-2 diabetes and obesity. Administration of PTP-1B antisense oligonuclotides to diabetic obese mice reduces plasma glucose and brings insulin level to normal.

Glycogen synthase kinase(GSK-3)

The key enzyme involved in glycogen metabolism is now known to regulate a wide range of cell functions its ability to phosphorylate and inhibit glycogen synthase(GS), deactivation of GS and decrease its affinity to allosteric activation by glucose-6-phosphate.It is reported that GSK-3 can also phosphorylate insulin receptor[20] substrate. Lithium ion (Li) has been found to cause relatively specific inhibition of GSK-3 and has been reported to have insulin like effects.

Fructose-1, 6-bisphosphate as a therapeutic target for Type 2 diabetes[21]

Fructose-1,6-bisphosphatease(FBPase) has provided new insights into the therapeutic utility of gluconeogenesis inhibitors the potential of FBPase inhibitors as a new class of antidiabetic drugs and increasedendogenous glucose production (EGP).

Estrogen receptors [22]

Estradiol regulates energy metabolism and opens new insights into the role of the two estrogen receptors, ERα to ERβ in this context. New findings on gene modulation by ERα to ERβ of insulin sensitive tissues indicate that estradiol participates in glucose homeostasis by modulating the expression of gene that are involved in insulin sensitivity and glucose uptake.

Salsalate

It is a non- steroidal anti-inflammatory drug (NSAID).Salsalte belongs to a class of drugs called salicyaltes. Salsalate may work by inhibiting the production of and release of prostaglandins. It is used for Type2 diabetes. It also reduces blood sugar in obese adults who don't have diabetes, apparently by making insulin work better. Side effects are ringing in the ears, loss of hearing, difficulty in breathing or swallowing, shortness of breath, hoarseness, unexplained weight gain.

Resveratrol [23]

Resveratrol possesses hypoglycemic and hypolipidemic effects both in streptozotocin (STZ)-induced diabetic rats. Resveratrol ameliorates common diabetes symptoms such as polyphagia, polydipsia and bosy weight loss. Other diabetic animal model studies by different researchers have alos demonstrated the ant diabetic effects of resveratrol.

DiaPep277

It is a synthetic peptide of 24 aminoacids derived from the sequence of the human heat shock protein 60(Hsp60). The peptide modulates the immune response that leads to autoimmune diabetes by diminishing or blocking the immunological destruction of beta cells. Treatment of Type1 diabetes patients with

DiaPep277 may have several medical benefits including prevention of disease deterioration, improved glycemic control, reduction of daily insulin dose requirements, and delay or reduction of diabetic complications.

Gene therapy [24]

Gene therapy in Diabetes Mellitus (DM) is to maintain euglycemia in face of wide variations in dietary intake. The risk-benefit ratio of gene therapy in DM is better than that of lifelong injections of insulin and islet transplantation, which faces the problems of donor shortage and rejection.The gene delivery systems by viral vectors, since most gene therapy approaches for DM involves the use of viral vectors, paying special attention to current efforts to overcome the disadvantages of adenovirus, adenovirus-associated virus and retrovirus vectors and targeting gene delivery for optimal efficiency of gene expression.

Anakinra [25]

The arthritis drug Kineret (anakinra) helped to control blood glucose levels in diabetes. The drug is known as a recombinant human interleukin-1-receptor antagonist.Kineret blocks the production of interleukin-1, which is a typer of cytokine associated with joint inflammation. In diabetes, interleukin-1 beta is produced in the pancreas. High glucose levels appear to trigger the release of interleukin-1 beta .

Otelixizumab [26]

Otelixizumab is a monoclonal antibodies that targetCD3 a T-lymphocyte receptor involved in normal cell signaling. Otelixizumab targets the epsilon chain of CD3. Data suggest that the drug works by blocking the function of effector T-cell, which mistakenly attack and destroy insulin producing beta cells while stimulating regulatory T-cells, which are understood to protect against effector T-cell damage, thus preserving the beta cells' normal ability to make insulin.

Teplizumab

Teplizumab is a monoclonal antibody which is used as an immunosuppressive drug. It is a humanized Fc-engineered monoclonal antibody. It targets at protecting the remaining beta cells in newly diagnosed T-1 diabetics. These agents (anti-CD3-antibodies) alone do not restore normal glucose control. They must be combined with other anti-diabetic drugs.

Stem cell therapy [27]

Stem cell therapy is alternate therapy for diabetes mellitus. Stem cells from chord blood to re-educate a diabetic's own T cells and consequently restart pancreatic function reducing the need for insulin. Stem Cell Educator therapy slowly passes lymphocytes seperated from a patient's blood over immobilized chord blood stem cells (CBSC) from healthy donors. After two to three hours in the device the re-educated lymphocytes are returned to the patient.

Diet and exercise

It has been shown that weight reduction and an increase in daily energy expenditure decrease insulin resistance and increase glucose tolerance. In fact advice on diet and exercise are an important part of the treatment of type 2 DM. Overweight patients are advised to restrict calorie intake, consume food with low total fat content (especially saturated fat) and high (predominately unrefined) carbohydrate content. Regular physical activity[28] is an important component of the prevention and management of type 2 diabetes mellitus.

CONCLUSION:

To prevent diabetes related morbidity and mortality, it is needed to take food choices, physical activity, proper medications intake and blood glucose monitoring from the patients. The role of future new chemical entities can target the metabolic disorder through multi facet mechanisms. The new anti-diabetic treatment strategies may in the future not only control symptoms and modify the natural course of diabetes, but also potentially prevent or cure the disease.

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