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REVIEW ARTICLE

CURRENT UPDATES ON ANTI-DIABETIC THERAPY

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ABSTRACT

Diabetes globally has become one of the chronic public health problems and is related to group of metabolic defects resulting due to defect in insulin secretion and its action. As the disease progress micro and macro vascular damage may lead to retinopathy, neuropathy, nephropathy and various cardiovascular like complications. It is estimated that by the year of 2030 about 439 million adults would be suffering from any form of diabetes. There are mainly two types of diabetes which is because of their occurrence rate. The current review covers the basic aspect of types of diabetes, insulin molecular, chemical basis, and its secretion, hypoglycemic drugs used and their mode of action, what are the recent advancement in terms of new drugs finding, and the herbal plants. Thus, the information will help researchers for development of combination medication which involve both recent medication and herbal medication for combating various complication associated with diabetes.
Key-Words: Hyperglycemia, insulin, glucose, phyto-constituents.

INTRODUCTION

Diabetes mellitus is defined by a group of metabolic disorder caused by altered metabolism of carbohydrate, lipid and lipoprotein resulting from the defect in insulin secretion and action; it is characterized by symptom likehyperglycemia, glycosuria, polyphagia, polyurea, polydipsia, gradual loss of weight, fatigue, cramps, blurred vision, constipation, and candidiasis are prominent.It is the most prevalent chronic disease in the world affecting nearly 100 million persons of the population where 5-10% having type 1 while 90-95% of them suffers from type 2 diabetes mellitus.Diabetes leads to many health complications such as hyperlipidemia, hypertension and atherosclerosis[1,2].

Categorization of Diabetes

There are mainly four types of diabetes mellitus i.e. Type I diabetes or insulin dependent diabetes mellitus(IDDM),type II diabetes or non insulin dependent diabetes mellitus (NIDDM),the other two diabetes mellitus are not much common i.e. gestational diabetes and genetically modified diabetes [4]. Type I diabetes can occur in any age but priorly seen in young adult. It is an immune mediated disease resulting from destruction in β-cells of pancreas which leads to insufficientendogenous insulin production. Type II diabetes or non insulin dependent diabetes mellitus (NIDDM) is the most common type affecting elderly and obese personcaused either by insulin resistance or deficient insulin secretion.It is characterized by hyperglycemia in the presence of hyperinsulinemia due to peripheral insulin resistance. Type 2 diabetes mellitus is most encountered form of diabetes accounting for more than 80% of total case of diabetes while in western countries it affects 7% of the population in particular[5].A third type of diabetes GDM (gestation diabetes mellitus) is first recognize during pregnancy where hyperglycemic condition developsin women who doesn't have diabetes result from an inadequate insulin supply to meet tissue demand for normal blood glucose regulation. Fourth type of diabetes is genetically modified DM there occur defects in β cell function or mutation of insulin receptor and may lead to diabetes. Other rare types of diabetes include those caused by surgery, drug used (e.g. antihypertensive vasodilator diazoxide, corticosteroids in high doses, lower dose of thiazides, oral contraceptives, high dose of anabolic androgens, streptozotocin, alloxan, theophylline, asprin, isoniazid, nalidixic acid), malnutrition, infection and other illness. [6]

Acute and long-term occurrence of type 1 and type 2 diabetes mellitus can result in macrovascular (coronary artery disease, atherosclerosis and peripheral vascular disease) and microvascular (retinopathy, nephropathy, and neuropathy) complications [7]. Chronic hyperglycemia is an important factor leading to complications of DM causing diverse cellular and organ dysfunctionwhich may lead to autonomic dysfunction, potential blindness, renal failure (due to nephropathy), and foot ulcers, amputation, Charcot joints (due to neuropathy).

Insulin and its secretion

The insulin is a polypeptide hormone having a molecular weight of 6000 Da. It is originally produced as a single molecule (pre-proinsulin) consists of 110 amino acids released by the pancreatic β-cells whichareresponsible for glucose homeostasis. It consists of two polypeptide chains A and B containing 21 and 30 amino acid residue respectively.[8]Two disulfide bridges (residue A 7 to B7 and A20 to B19) covalently bind the chain where chain A containsan internal disulfide bridge (residue A6 to A 11).Hormone insulin is synthesized as pre- proinsulin in rough endoplasmic reticulum further by proteolysis it convert to pro-insulin and then to insulin.The A chain has an amino terminal helix (A1 –A8) linked to an anti-parallel carboxy- terminal helix (A 12-A20). The B chain has a central helix (B8-B19), flanked by extended amino and carbonyl terminal strands. This arrangement is called the T conformation. .After pre-proinsulin has passed through the endoplasmic reticulum, 24 amino acids are removed by enzymatic action from one end of chain, leaving another

form pro-insulin that undergoesfolds and bonds to passes towardsGolgi body where the middle section (C chain) of 33 amino acids is removed by the action of the enzymes pro-hormone convertase1 and 2 converting to final structure of insulin.[9]

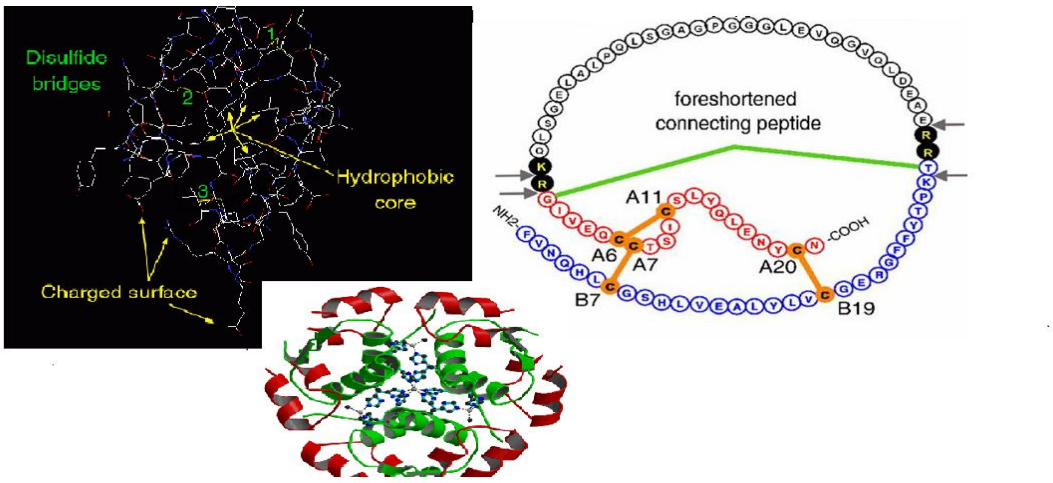

Figure 1: Insulin structure showing its disulfide bridge, its hexameric structure and describing its A and B chain with its amino acid sequence

Insulin stimulates hepatocytes, mycocytes and adipocyte to uptake glucose for circulatory system. Insulin is needed to move blood glucose into cell where it stored (and depending on the need glucose can either be stored as glycogen inside muscles or liver cells. The inappropriate utilization of insulin leads to insulin resistance, which is characterized by inability of cells to respond to normal level of circulating insulin, thus leads to occurrence of disease. Histologically there is not much difference in islet of diabetic pancreas and the normal pancreas apart from the presence of amyloid [4, 6].

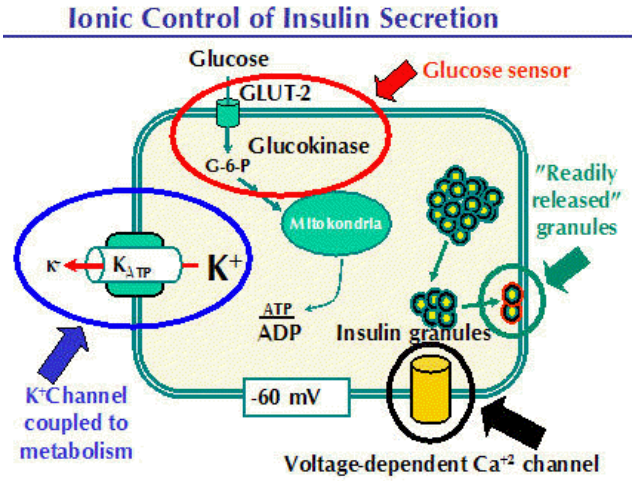

Figure 2: Insulin Releasing Pathway

The insulin release is a complex process involving the integration and interaction of multiple external and internal stimuli. Glucose is mediated into the β cell with the help of GLUT- 2 for the glycolysis (energy producing pathway). Glucose is further phosphorylated with the help of glucokinase enzyme and further metabolized to form ATP. Elevation in ATP ADP ratio causes the ATP-gated potassium channels in cellular membrane to close, preventing potassium ions from being shunted across the cell membrane. This increase intracellular conc. of potassium ions lead to depolarization of cell. This in turn activates the voltage gated calcium channel and facilitates extracellular calcium influx into the β cell. Ultimately by the process of exocytosis insulin is exported from the insulin storing granules and diffuses into nearby vessels.

Insulin is the sole therapy currently available to treat acute hyperglycemia. It's have multiple metabolic and cellular actions firstly it lowers plasma glucose level, along with that it helps in maintaining normal cell metabolism by increasing glucose uptake and adenosine triphosphate (ATP) production in by glycolysis. Insulin provides protection from endothelial dysfunctioning, inflammation (by reducing levels of proinflammatory cytokines, adhesion molecule) and thrombosis. Insulin injections is effective in T2DM for controlling blood sugar prescribed when glucose target cannot be attained with standard regimen, it causes weight gain specifically abdominal fat which can lead to insulin resistance and various cardiovascular risk.

Hypoglycemic Drugs

Anti-diabetic drug acts through two main mechanisms by stimulating β-cells of pancreatic islet to release insulin and increase the sensitivity or number of insulin receptor. Preoperatively, oral hypoglycemic agents, especially those that stimulate insulin secretion, such as sulfonylureal and meglitinide agents, have potential for producing hypoglycemia during fasting prior to surgery.

The sulfonylurea agents (e.g. glipizide, glyburide, glimepiride) are commonly prescribed oral hypoglycemic agents for the treatment of type 2 diabetes. These agents act by bind to the ATP-dependent potassium (KATP) channel in the pancreatic s-cells, leading to closure of these channels and stimulating insulin release. Thus, pancreatic β-cells are increasingly responsive to glucose concentrations and insulin release is augmented.

Metformin, a biguanide oral hypoglycemic agent, is commonly used for treatment of type II diabetes mellitus.

Metformin primary mode of action appears to be that of increasing hepatic insulin sensitivity, resulting in decreased hepatic glucose output through suppression of gluconeogenesis and glycogenolysis. [16]. Sulfonylurea and metformin are used although they have several side effects (weight gain, hypoglycemia) because they are cost effective.α-glucosidase inhibitors are another class of drugs that includes compound like acarbose which delay the intraluminal production of monosaccharide (glucose). Acarbose competitively inhibits α-glucosidase that is associated with the brush border membrane of the small intestine and are responsible for the digestion of complex polysaccharides and sucrose. This slows carbohydrate digestion and lowers post-prandial hyperglycemia. Biguanides (metformin), suphonyl urea, thiazolidine and meglitinides are the main class of drugs used in diabetes they have various side effects like weight gain, lactic acidosis, heart failure and hepatotoxicity which will lead to other serious complications.Natural compounds may be analternative treatment as they can be included in daily diet and can be taken in larger amount without any risk. Many plants areknown in folk medicine of different culture to be used for their antidiabetic property. The plant and biomolecule have been reviewed for prophylaxis and treatment of type 2 diabetes.

Recent advancement in Diabetes treatment

Rimonabant is first drug which act through endocannabinoid system (ECS) that play an important role in appetite and carbohydrate and fat metabolism in brain as well as adipose tissue. Animal studies show that it acts through blocking the ECS leading to weight loss and improve insulin sensitivity by reducing the level of adiponectin. It result in weight loss, improve insulin release and sensitivity and suppresses appetite andacts by blocking CB 1and CB 2receptor[14].

Exenatide, a synthetic version of Exendin-4a peptide discovered in the salivary secretions of the reptile *Heloderma suspectum*. Exenatide belongs to GLP 1 class that plays an important role in weight loss and as seen in animal studies it act by HbA1c reduction. Exeratide resulted in a hemoglobin A1c (HbA1c) reduction reduction of 1.0% with placebo treatment.It is used with metformin and sulfonyl urea alone or in combination.[15]

Sitagliptin, a DPP- IV inhibitor it hypoglycemic action is due to increase in GLP 1 and GIP level. It act by suppressing appetite it target prandial and fasting glucose level, improve marker of β cell function. Vildagiptin also belongs to DPP-IV inhibitor group which is well tolerated drug. [16]

Another new anti- hyperglycemic used in T1DM is the injectable pramlintide(amylin mimetics), a synthetic analogue of human amylin, a β cell peptide cosecreted with insulin act as. It suppresses glucagon secretion from pancreatic α cells, thereby attenuating glucose production. RYpramlintide in T2DM is not so clear. Liraglutide is an acrylated human GLP 1 analogue while is nearly identical to it with lysine 34 to argentine substitution ans an addition of a C-16 free fatty acid derivative at lysine 26. The free fatty acid side chain promotes binding to albumin and other plasma proteins leading to delayed absorption rate from the injection site and extended plasma half life of 11-13 h. Dapagliflozin anew drug for treatment of T2DM aims to lower blood sugar by improving glycemic control independent of insulin action. The drug reduces renal glucose reabsorption and increases glucose elimination in urine.

A Scottish medicine consortium have work on lixisentide (brand name Lyxumia) a short-acting GLP-1-receptor agonist is a modified exerdin 4 base molecule with 2-4 hr short half life it shown beneficial effects on HbA1c when combined with commonly used anti-diabetic agents on the health care service to people suffering from T2DM, studies shows that adding lixisenatide to insulin or taking it with other glucose lowering medicine controlled patient diabetes and also reduction in body weight.A series of clinical trials with 5000 participants began in May 2008. Results showed that lixisenatide was well-tolerated, with mild nausea and vomiting being the most common side effects.It is recommended for patients whose existing treatments, combined with a calorie-controlled diet and exercise; do not provide adequate glycemic control. By maintaining blood sugar level as near to normal as possible is vital to reduce the risk of long term complications such as heart disease, blindness, strokes and kidney failure. Gemingliptin is another DPP4 that has been approved by the Korean food and drug administration on june 2012 as a treatment for T2DM patient and is under phase III clinical trial to be approved by US FDA for its safety and efficacy.

Herbal remedies for treatment of diabetes

Plants have been a good source of drugs. There are more than 800 plants that possess potent anti-diabetic activity and have been used as a dietary adjuvant or as a drug which have a traditional history in India. This treatment is the safe, cost effective and with least of side effect than that of synthetic hypoglycemic agent. The plant originated products act through two mechanism either insulinomimetic or as secretagogues. There are various types of phytoconstituents like alkaloids, flavonoids and saponins glycosides present in the plants responsible for its anti-diabetic activity.. Alkaloids acts by inhibiting α – glucosidase and decrease glucose transport through intestinal epithelium. Flavanoids suppresses glucose level, reduces plasma cholesterol and triglyceride significantly and increases hepatic glucokinase activity probably by enhancing insulin from β cells.

Achyranthes aspera L produced a significant dose-related hypoglycemiceffect in normoglycaemic in alloxan-induced diabeticrabbits. In these animals, water and methanol extracts alsodecreased blood sugar levels.[21]

Aloen(A.*barbidensis*) leaves orally (500mg/kg) along with its bitter principle(5 mg/kg) .i.p. was very highly significant in reducing plasma glucose level and significant effect was seen within 5 days it work by stimulating synthesis and release of insulin from cell of langerhans [22]. Andrographis paniculata results in significant reduction of blood glucose compare to un-treated it acts by inhibiting glucose absorption. Aronia melenocarpa berries possess numerous biological and medicinal effects[23] they are rich in phenolic antioxidants, especially anthocyanins. Their fruit juices have significant effect on plasma glucose and lipid level in streptozotocin induced diabetic rat.it act by lowering triglyceride level [24].

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Artemisia dracunculus L. has been reported to have hypoglycaemic effects by several researchers [25, 26]. Wang *et al*.found that *Artemisia dracunculus* L. improved insulin sensitivity and IR signaling in insulin-resistant KK-Ay mice models. 4,5-di-O-caffeoylquinic acid, 6-demethoxycapillarisin, and 2',4'-dihydroxy-4-methoxy-dihydrochalcone was extracted from the ethanolic extract of *Artemisia dracunculus* L.[27] The compounds showed inhibitory effects towards the enzyme aldose reductase (enzyme involved in diabetic complications), which may explain the antidiabetic effect. Oral administration of extract of *Asteracantha longifolia* (20 g/kg of starting material) can significantly improve glucose tolerance in healthy human subjects anddiabetic patients. Dried Allium cepa when extracted in petroleum ether control diabetes in alloxan induced diabetes rat.

Azadirachta indica has been used in ayurvedic medical tradition as a treatment for diabetic mellitus its in-vivo antidiabetic activity was seen in streptozotocin-nicotinamide induced diabetes mice. It contains meliacinolin; apotent α-Glucosidase and α-Amylase inhibitor [28] which reduces oxidative stress and act as an insulogenic. It acts by inhibiting glucose absorption.

Anemarrhena asphodeloides exhibits antidiabetic effect in streptozotocin induced mice model. It contain prototimosaponin A-III and pseudo-prtotimusaponin A –III they act by inhibiting hepatic glyconeogensis and glycogenolysis.

Ethanolic extract of the root part of *Bambusa arundinacea* (Poaceae) was evaluated for its hypoglycemic potential in normoglycemic rats followed by alloxan and glucose loaded hyperglycemic rats by single dose and multidose administration; the plant extract significantly reduces blood glucose level both in normoglycemic and hyperglycemic rats induced by alloxan and oral glucose loaded methods till the end of the course of experiment. The preliminary phytochemical study report revealed that the test extract contain flavonoids, tannins and phenolic compounds as phytoconstituents[29].

Hot water extract of *Bixa orellana* plant have potent inhibitory activity toward rat lens aldose reductase [30].*Bougainvillea spectabilis* leaves oral administration significantly lowers hyperglycemic response in alloxan-induced diabetes rats reduce blood sugar level and increase insulinlevel [31].

Seeds of *Coriandrum sativum* L(Coriander), when supplied in the diet (6.25 % by weight) and infusion (1 g/400 ml) in place of drinking, reduced the hyperglycemia during the development of streptozotocin-induced diabetes in mice[30, 32].

In a study conducted over type 2 diabetic mice, administration of *Curcuma longa* L. rhizomes extract led to the activation of the peroxisome proliferator-activated receptor-γ (PPAR-γ) [33] through the ligand binding activity of the extract towards the receptor. PPAR-γ is a key receptor in lipid and glucose homeostasis because of its ability to reduce the plasma free fatty acids (FFAs) [34, 35]. The receptor is currently used as a target for the treatment of T2DM [36]; the antidiabetic thiazolidinediones drugs exert their insulin sensitizing action through their high affinity for the receptor PPAR-γ. Thus, *Curcuma longa* is a promising therapeutic agent in the prevention and/or amelioration of T2DM. Lee *et al*. (2008) tested a combined hypoglycaemic mixture of *Melissa officinalis* L., *Morus alba*L., and *Artemisia capillaris* Thunb that resulted in changes in the expression of the PPAR-α, another key receptor in lipid and lipoprotein metabolism[37]. By conducting *in vitro* experiments on rat pancreatic β-cells using *Cornus officinalis* extracts, Chen *et al*. (2008) found that the extracts possessed insulin-mimetic activity and stimulated β-cell function by enhancing insulin secretion and protecting β-cells against toxic damage [38, 39].

Daucus carota L extractwas prepared by boiling the dried material with water or macerating it with 80 % ethanol. It was shown that the extract improved the glucose tolerance [40].

*Emblica officinalis*fruits and seed extractedin different solvent act as α- amylase and α- glucosidase inhibitors have significant hypoglycemic activity[41]. *Ficus bengalensis* (banyan tree) result in significant decrease in blood and urine sugar level, certain lipid content in serum [42]. *Fructus arctii* was investigated to its hypoglycemic activity in alloxan induced diabetic mice amd hyperglycemic hyperlipidemic diabetic rats. It shows significant reduction in plasma glucose, triglycerides and total cholesterol after treatment with total lignin from plant.

Hibiscus vitifolious flower petals contain 3, 4, 6, 8 tetrahydroxy flavonol -5- (-methyl ether 7-0 neosperidoside) which as an active compound having hypoglycemic activity well demonstrated in albino rats[43].

Ginseng Radix (GR) to normal and adrenaline-induced hyperglycemic mice caused a significant decrease in blood glucose level 4 h after its administration. The hepatic content of the facilitative glucose transporter isoform 2, liver type glucose transporter (GLUT 2) protein significantly increased in the orally GR-treated healthy and adrenaline-induced hyperglycemic mice compared to that in the controls. Recently, ginseng, which is among five crude drugs included in the traditional Chinese prescription, Byakkoka- ninjin-to, was investigated using genetically obese diabetic KK-CA(y) mice and alloxan-diabetic mice[44]. The water extract of ginseng, when individually tested, markedly lowered blood glucose level in diabetic animals.

Holarrhena antidysentrica bark aqueous and alcoholic extract reduces the blood sugar level in normal and alloxan -induced diabetic rats[45]. *Inula racemosa* root petroleum extract result in lowering plasma insulin and glucose level when administered in adrenaline –induced hyperglycemia in albino rats. [46]

Juniperus communis lowers the glycemic level by increasing peripheral glucose consumption and potentiation of glucose induced insulin secretion. *Lagerstroemia specisoa* showed slow glucose activity. *Momordica charantia* ethanolic extract decreases blood sugar in normal and diabetic rat model. *Morinada lucida* aqueous extract have potent hypoglycemic effect in normoglycemic and alloxan induced diabetic mice. *Momordica dioica* fruit ethanolic and ethyl acetate extract has been found to have hypoglycemic activity when studied in alloxan induced diabetic rat which was due to

presence of steroids, triterpenoids and their glucoside[48].*Nymphaea pubescens* ethanolic extract have significant activity in reducing blood glucose when study was conducted on diabetic rat histopathological examination of pancreas shows regenerative potential corroborating its anti diabetic potency. *Nicotiana glutinosa* leaves contain sucrose fatty acid compounds which are helpful in treatment of disease associated with diabetes.[49, 50, 51]

Ocimum sanctum alcoholic extract led to mark reduction of blood sugar in glucose fed hyperglycemic and streptozotcin induced diabetic rat. Ocimum gratissimum methanolic extract have shown lowers the blood glucose level in diabetic male wistar rat [52]. *Papaver somniferum* extract seed extract when given orally reduces blood glucose level in alloxan induced diabetic rats. Paspalum scrobiculatum aqueous and ethanolic extract reduces blood glucose level and lipid parameters in diabetic rats. Methanolic extact of *Phyllantus amarus* was found to have potent anti diabetic activity and it also inhibits lipid peroxidation and reduces blood sugar level in diabetic rats.*Scoparia dulcis* and *Scopari adulcis* extractsignificantly reduces lipid peroxidation and possess anti diabetic activity and are widely used in Indian folk medicine. Sephaernthus indicus flower head petroleum ether extract anti diabetic activity was studied in alloxan induced diabetic wistar rat by reducing blood glucose level [54].

Terminalia chebula, Emblica officinalis and *Terminalia belerica* combination named triphala (equal portion of all the three) are found to inhibit lipid peroxidation and scavenge hydroxyl and superoxide free radical in vitro. Oral administration of the extract reduces the blood sugar level in normal and alloxan induced diabetic rats. Tinospora cordifolia stem extract significantly lowers blood glucose level, reduce glycosylated hemoglobin level, reduced glucokinase and increases G6-P activity. And along with that it increases insulin and C- peptide level which regenerates β cells activity [49, 50, 51].

Trigonella foenum-graecum(fenugreek) seeds contains alkaloid trigonelline that counterected to hyperglycemic effect of cortisone in non diabetic rabbit by lowering blood glucose capacity. Other hypoglycemic compound present in the seeds are nicotinic acid, coumarin, and scopletine[53].

Vernonia amygdalina aqueous extract when given intraperitoneally produces a dose related fall in blood glucose when compared it effect along with tolbutamide by enhancing insulin secretion.

Zaleya decandra root ethanolic extract significantly restore the level of glucose, Total cholestrol, Triglycerides, Total protein, urea, cretinine , lipid peroxidation level and antioxidant enzyme when histopathological studies was conducted on alloxan induced diabetic rats[54].

Management of disease

Diabetes mellitus requires multidisciplinary approach for the management. It requires proper diet monitoring, exercise and stress management as a non-pharmacological approach.

A proper monitoring of diet is needed for diabetic patient. In type I and II DM caloric distribution of energy should be 55-60% carbohydrate, 10-15% protein and 20-25% from fat. Calories intake should be monitored by restricting diet. Fiber rich food should be included in the diet specially cellulose or hemicelluloses which are having beneficial effect on intestinal transit time and thereby slow down glucose absorption thus decreasing hyperglycemia. Fruits should be taken in moderate while very sweet fruits should be avoided. Fish oil has been reported for beneficial omega 3 which plays important role in reducing plasma triglycerides and lipoproteins level. Along with that alcohol and tobacco should be avoided. Artificial sweetener like saccharin and aspartame are advised in replacement of sugar. Further there is evidence that regular exercise and yoga can reduce the risk of obesity and further helps in controlling diabetes.

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