Section A-Research paper

A DETAILED OVERVIEW ON CURRENT DEVELOPMENTS IN TREATMENT STRATEGIES FOR DIABETES MELLITUS MANAGEMENT

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Abstract:

Diabetes mellitus is a serious public health problem, but the good news is that important advances are being made in prevention, detection, and treatment of diabetes. For the management of type 1 diabetes, patients require insulin administration 3-4 times a day throughout their lives and their blood sugar levels should be regularly monitored to avoid complications like retinopathy and risks of cardiovascular diseases. Although the value of lifestyle modification in obese youth is unquestioned, scant evidence for optimal treatment of type 2 diabetes in this age group exists. Despite recent therapeutic drug trials, metformin and insulin are the only medicines currently approved by the US Food and Drug Administration for the treatment of type 2 diabetes in youth. Because of recently amended pharmaceutical regulations, however, it is likely that more anti-diabetic medications soon will be added to the

armamentarium of therapeutic options for youth with type 2 diabetes. Recent approaches in drug discovery have contributed to the development of new class of therapeutics like Incretin mimetics, Amylin analogues, GIP analogs, Peroxisome proliferator activated receptors, and dipeptidyl peptidase-4 inhibitor as targets for potential drugs in diabetes treatment. Subsequently, the identification and clinical investigation of bioactive substances from plants have revolutionized the research on drug discovery and lead identification for diabetes management. The development of newer generation of drugs like sulphonylureas, biguanides, alpha glucosidase inhibitors, and thiazolidinediones with significant efficacy in reducing hyperglycemia.

Keywords: Diabetes mellitus, blood sugar levels, cardiovascular disease, pharmaceutical regulations, new class of therapeutics.

Introduction:

Diabetes is a major killer worldwide and its unprecedented rise poses a serious threat to mankind. According to recent estimation, 387 million people worldwide are affected from the disease with a prevalence rate of 8.3% and 46.3% still remains undiagnosed. Furthermore, maximum percentage of 387 million people lives in low and middle income countries and comprise of 40–59 age group in the population. Population survey by the Indian Council of Medical Research suggested that China leads the survey with an estimation of 98.4 million cases and India coming next with 65.1 million diabetes patients[1-3].

Insulin Dependent Diabetes Mellitus (IDDM)

It is also known as juvenile onset diabetes or type 1 diabetes, which accounts for 5–10% of the patients, resulting from cellular-mediated autoimmune destruction of the pancreatic cells. The disease can affect people of all ages but usually occurs in children or young adults. Regular supply of insulin injections is essential for the control of glucose level in blood. The rate of β cell destruction varies showing fast deterioration in infants and children while the degeneration of β cells is slower in adults. Symptoms like ketoacidosis occur in children and young individuals while others exhibit modest fasting hyperglycemia that can change to severe hyperglycemia or ketoacidosis in response to stress or infection.

Noninsulin Dependent Diabetes Mellitus

It is also referred to as adult onset diabetes, which accounts for 90–95% of all diabetes. Major metabolic syndromes like obesity, insulin resistance, and dyslipidaemia have led to an epidemic of type 2 diabetes. The treatment of this type of diabetes is through oral hypoglycemic drugs, dietary in nature. Insulin resistance as well as loss of insulin secretion contributes to the onset of disease. Type 2 diabetes mellitus is the most common form of diabetes and is the fourth leading cause of death in developed countries with a twofold excess mortality and two- to fourfold increased risk of coronary heart disease and stroke[4-9].

Gestational Diabetes Mellitus

It is defined as any degree of glucose intolerance resulting in hyperglycaemia of variable severity that is diagnosed during pregnancy. GDM, or impaired glucose intolerance which is first diagnosed during pregnancy, is a major type affecting 14% women during pregnancy or 135,000 women a year in the United States and is a risk factor for type 2 diabetes in mothers [28]. The magnitude of the reported risk varies due to variations in ethnicity, selection criteria, and tests for GDM and type 2 diabetes. Gestational diabetes can lead to respiratory distress syndrome, neonatal hypoglycemia, and fetal macrosomia.

Catamenial Hyperglycaemia

Diabetic ketoacidosis (DKA) is a condition, arising due to infection, inadequate insulin or poor insulin compliance, acute pancreatitis, stroke, drugs, metabolic disturbances within the body, or negligence with the treatment. The uncontrolled hyperglycaemia with DKA occurring before the menstrual cycle in females is known as catamenial diabetic ketoacidosis or catamenial hyperglycaemia. The uncontrolled hyperglycemia resulted in increased insulin requirement, up to 4 times. The condition is aggravated even after continuous insulin infusion, resulting in vomiting, and leading to significant acidosis, ketonuria, and hyperglycaemia.

Type 2 diabetes in children and adolescents is a new disease that has emerged over the last 2–3 decades. Prior to this rise, almost all children and adolescents with diabetes were diagnosed with type 1 diabetes mellitus, with type 2 diabetes accounting for only a tiny fraction of all new cases of diabetes in this age group. Type 2 diabetes is a chronic, progressive state of beta cell dysfunction characterized by insulin resistance and hyperglycemia. Prediabetic states (Impaired Fasting Glucose – IFG /and Impaired Glucose tolerance - IGT) are typically present prior to the diagnosis of type 2 diabetes, and lead to frank diabetes in affected children[10-15].

The selection and application of a glucose lowering therapy are dependent on a number of considerations like the severity of hyperglycemia, hepatic and renal associated functions, risks of hypoglycemia, body mass index, ability to self monitor the blood glucose level, and also the cost of the medication. The therapeutics for type 1 diabetes includes stimulation of insulin secretion through GLP analogues like Exenatide and Liraglutide, insulin injections to compensate for β cell defects, dipeptidyl peptidase-4 (DPP-4) inhibition by Sitagliptin, and increased islet survival and islet cell regeneration through islet neogenesis associated protein (INGAP) peptide therapy aiming at islet cell regeneration among others.

The treatment approach for type 2 diabetes includes several conventional therapeutics, namely, sulfonylureas and repaglinide enhance insulin secretion, troglitazone increases insulin action in fat and muscle, metformin promotes insulin mechanism in liver tissue, and miglitol and acarbose enact delayed carbohydrate absorption from food intake, respectively. The drugs used for the treatment of type 2 diabetes poses limitations in the sense that they have significant side effects. The other major medications strategies constitutes combinational therapy of insulin with sulfonylureas which reduced the daily requirement of insulin and insulin and metformin

combination therapy (approved by FDA); minimizing weight gain due to insulin therapy and troglitazone-insulin in combination efficiently reduced insulin requirement and improved glycemic control[16-21].

Epidemiology of Type 2 diabetes in Youth

As noted, the incidence and prevalence of type 2 diabetes in children and adolescents have increased, compared to just a few decades ago, especially in certain racial/ethnic populations. Estimates indicate that 8–45% of cases of recently diagnosed diabetes in children and adolescents are due to type 2 diabetes [4]. The SEARCH for Diabetes in Youth Study from the United States estimated the prevalence of type 2 diabetes as 0.22 cases per 1000 persons under the age of 20 years.

Risk Factors for Type 2 Diabetes

Many of the risk factors for developing type 2 diabetes in childhood are similar to those for adults. Obesity is the most important modifiable risk factor for developing type 2 diabetes in children, and children with type 2 diabetes are virtually always overweight and usually profoundly obese. A history of type 2 diabetes in a first or second degree family member is often present, with up to 90% of children and adolescents with type 2 diabetes having at least one affected relative.

Pathophysiology

In full-blown diabetes, insulin stimulated glucose disposal is impaired by approximately 30%, first phase insulin is impaired by approximately 75%, and second phase insulin is impaired by approximately 65% compared with children with normal glucose tolerance. Beta cell dysfunction relative to reduced insulin sensitivity (glucose disposition index or GDI) also was lower in those with IFG, IGT, and IFG plus IGT (40, 47, 47% respectively); this decreased further to 80% in those with type 2 diabetes[22-28].

Treatment options

The primary prevention still remains the ideal modality, and lifestyle modification is the safest and most commonly used intervention. Once type 2 diabetes in youth develops, lifestyle changes are exceedingly difficult to effect, emphasizing the urgency for the development of safe and effective anti-diabetic drugs in youth. Although insulin is almost uniformly effective in lowering blood sugars, the need for injections and the risk of hypoglycemia render it rarely the first modality to consider, unless metabolic decompensation is present at the time. Few oral medications have been tested in children with type 2 diabetes; only metformin has been approved by the US FDA for use in children (to the age of 10 years). Although many anti-diabetic drugs are available, the great majority has been studied for safety and efficacy only in adults. Although off label use of non-approved drugs in youth with type 2 diabetes is common, this practice requires taking a risk that such use may be associated with unexpected side effects, complications, or ineffectiveness related to physical or metabolic immaturity. Bariatric surgery has emerged as a new avenue for surgical treatment of Type 2 diabetes in the adult literature but there is limited experience with its use in pediatrics.

Lifestyle modification

Lifestyle modification, also referred to as behavioral weight control, includes 3 essential components: diet, exercise, and behavioral therapy. The goal of lifestyle modification is gradual and sustained weight loss. Dietary recommendations include limiting consumption of foods with high levels of fat, sugar, and salt; absolute elimination of high calorie beverages from the diet; decreasing portion sizes; and a combination of these interventions. Increased consumption of healthy alternatives, particularly fruits and vegetables, is recommended. The American Diabetes Association recommends a balanced diet rich in fiber, whole grains, and legumes; contains less than 7% saturated fat and reduced trans fats; and is limited in calories and foods with a high glycemic index. A ketogenic, low calorie diet in children has been shown to be effective in a sample of 20 adolescents with type 2 diabetes. After about 2 months on average, the mean A1c decreased from 8.8% to 7.4% and all the patients came off their prior antidiabetic treatment with metformin or insulin. Obese individuals can lose weight on a variety of diets varying widely in macronutrient composition, although caloric restriction is common to all effective diets. A successful diet is defined as one in which 5–10% of the initial weight is lost over several months. Greater weight loss is linearly associated with greater improvements in many risk factors including A1C and cardiovascular risk.

Physical activity also plays an integral role in the treatment of type 2 diabetes in children. Improved insulin sensitivity, increased uptake at the level of the muscle and a decreased need for insulin therapy are all benefits seen with increased physical activity. Patient and family education with focus on diet and exercise with the psychological needs of the youth in mind should be done in a culturally sensitive and age appropriate manner. Healthy behaviors need reinforcement in order to lead to a permanent change in lifestyle.

Oral Medications

In addition to lifestyle intervention, many pediatric patients require glucose lowering medication in order to achieve normalization of blood glucose and A1C levels. Although many oral glucose lowering medications have been approved for adults with type 2 diabetes, only metformin has been approved by the FDA for use in pediatric patients aged 10 years and older. Metformin, an oral biguanide insulin sensitizer, binds to insulin receptors in liver, muscle, and fat tissue. Its mechanism of action is twofold: 1) the primary effect of metformin is to reduce hepatic glucose production. 2) metformin also increases glucose uptake of peripheral tissues (muscle and fat), with a net effect of improving insulin sensitivity and reducing both pre- and postprandial blood glucose levels. Metformin rarely if ever causes hypoglycemia in type 2 diabetes patients, a distinct advantage of metformin over most other oral medications. Appropriate counseling and gradual titration of dose is helpful in dealing with its most common adverse effects (GI intolerance - nausea, abdominal discomfort and diarrhea) - symptoms which tend to improve with continued use. Metformin is contraindicated in patients with impaired renal function, cirrhosis, hepatitis, alcoholism, cardiopulmonary insufficiency. These potential risk factors should be evaluated for each individual patient before initiating therapy. One of the most serious risks of metformin is lactic acidosis, although it only occurs in the context of renal failure and its

incidence in youth is extremely low. Patients taking metformin are advised to take daily multivitamins due to a possible poor absorption of vitamin B12 and/or folic acid. Metformin also should be withheld before radiographic studies requiring the administration of iodinated contrast dye, because of the potential for renal deterioration in its immediate aftermath. Metformin should be initiated at 500 mg orally daily or twice daily with meals and slowly titrated up over 3–4 weeks to 1000mg orally twice daily with meals as tolerated. Some suggest that metformin should be temporarily discontinued during a gastrointestinal illness[29].

Table 1: Type 2 diabetes medications currently approved for adults as antidiabetic agents

Class	**Examples**	**Mechanism**
Biguanide (insulin sensitizers)	Metformin, Metformin ER, Metformin Solution	Primarily decrease hepatic glucose production; increase muscle glucose uptake
Thiazolidinedione (insulin sensitizers)	Rosiglitazone, Pioglitazone	Selective PPAR-gamma antagonists; increase glucose transport into adipose, muscle, and liver cells
Sulfonylurea (insulin secretagogues)	Glimepiride, Glipizide, Glyburide	Enhance insulin secretion by their interaction with ATP sensitive K channel on the Beta Cell Membrane.
Glucosidase inhibitors	Acarbose, Miglitol	Interferes with alpha glucosidase, thereby inhibiting the hydrolysis and absorption of carbohydrates in the GI tract.
Amylin analog	Pramlintide-Acetate	slows gastric emptying, promotes satiety, and suppresses the abnormal postprandial rise of glucagon
Meglitinide	Repaglinide, Nateglinide	blocks ATP-dependent potassium channels; stimulates insulin release from the pancreatic beta cells.
DPP-4 inhibitor	Saxagliptin, Linagliptin, Sitagliptin	prolonged active incretin levels; increasing insulin synthesis and release from pancreatic beta cells and decreasing glucagon secretion from pancreatic alpha cells.
GLP-1 Analog	Exenatide , Exenatide ER injection	dose dependent and glucose-dependent augmentation of insulin secretion. slows gastric emptying, suppresses

Class	Examples	Mechanism
		inappropriately elevated glucagon levels, and leads to weight loss
Dopamine D2 Agonist	Bromocriptine-Mesylate	mechanism of action is unknown; may reset hypothalamic circadian activities which have been altered by obesity

Sulfonylureas: Glimepiride & Glyburide

Sulfonylureas are the major drugs in the family of insulin secretagogues. They exert their actions by stimulating insulin release from intact and functioning beta cells through an interaction with ATP-sensitive potassium channels on the beta cell membrane. In addition, these drugs increase insulin sensitivity in peripheral tissues indicating that extra pancreatic effects are also involved in the activity. Pharmacokinetic studies of these drugs in pediatrics are limited. One study examined children 10–17 years of age with type 2 diabetes who were given single oral doses of 1 mg of glimepiride. These children demonstrated pharmacokinetics comparable to those described previously in adults. In other studies, glimepiride therapy has been shown to reduce A1C, but less so than that associated with metformin use. Although efficacy as an anti-diabetic drug has been demonstrated, the glimepiride pediatric trial failed to demonstrate non-inferiority to metformin in reducing A1C; thus, it has not received FDA approval in this age group. In addition, glimepiride stimulates weight gain more than that associated with metformin.

Insulin Therapy

Insulin therapy is a key component in the treatment of youth with type 2 diabetes, in part because of a familiarity of pediatricians with the use of insulin from experiences in treating children with type 1 diabetes, and in part because of the paucity of oral drugs studied in children, as noted above. Many care providers prefer insulin at the time of diagnosis for all patients with type 2 diabetes, and its use is essential for those with significant hyperglycemia or ketosis. For patients treated with oral medications, insulin is often the first step toward intensification of therapy, once oral medications and lifestyle interventions are insufficient for achieving optimal glycemic control.

Rapid acting Insulin Analogues

The faster absorption of rapid acting insulin analogues results in higher and sharper peaks and shorter duration of action compared to regular insulin. This helps to control early postmeal hyperglycemia and to reduce late postprandial hypoglycemia. Aspart (Novolog), lispro (Humalog), or glulisine (Apidra) are the three types of rapid acting insulin analogues available on the market currently. All are commonly used in children before meals, and no major differences in pharmacokinetics compared with those of adults have been noted, although a reduced biologic action because of the insulin resistance of puberty have been described in children with Type 1 diabetes. All three insulins can be used in insulin pumps and all have been shown to be safe and effective in children with type 1 diabetes. Mixing with any of the long

acting insulins is not recommended. All can be given intravenously, although none has been found to be superior to regular insulin[30].

Intermediate-acting Insulin Analogues

NPH is the only available intermediate acting insulin on the market currently. With its delayed peak of action it provides the means to cover lunchtime glucose excursions, and some insulin coverage throughout a full 24 hour period on a twice daily injection regimen. However, its duration of action typically is too short to provide adequate overnight basal insulin replacement without causing hypoglycemia. With the advent of long-acting insulin analogues, NPH has largely been replaced in multiple-daily insulin regimens by the long-acting insulin analogs in all children with all types of childhood diabetes.

Long Acting Insulin Analogues

At the current time, two commercially available long-acting insulin analogs are available: glargine (Lantus) and detemir (Levemir). Both address basal insulin requirements for coverage of hepatic glucose production. Although few head-to-head comparisons in children have been reported, a more consistent pharmacodynamic profile with detemir compared with glargine has been reported in children with type 1 diabetes. On the other hand, detemir may have a shorter duration of action compared to glargine, suggesting that twice daily dosing with detemir may be necessary for some patients. In children with type 2 diabetes needing intensification of therapy, one common starting place is the addition of a long-acting insulin injection at bedtime. When this regimen is not effective, other approaches may be employed, including the addition of rapid acting insulin injections at mealtime plus basal insulin coverage with a long-acting insulin at bedtime, or the use of combination insulins (such as 75/25 or 70/30 insulins in a twice-daily regimen). Intensive lifestyle changes and oral medications remain a key part of the treatment regimen and the goal should be to keep the patient on the regimen (including the one with the best chance for adherence for each individual patient) most likely to achieve glycemic target[31].

Bariatric Surgery

The overweight and obese children, like adults, are at risk for progressing from insulin resistance (associated with obesity *per se*) to impaired glucose tolerance, and eventually to type 2 diabetes. Bariatric surgery consists of two main types of surgical interventions, resulting in weight loss caused by either physically restricting deposition of food into the stomach or creating a malabsorptive state or both. Restrictive bariatric procedures include gastric banding and sleeve gastrectomy. Malabsorptive procedures include gastric bypass and biliopancreatic diversion. Malabsorptive procedures have been shown to be superior in producing dramatic weight loss along with a rapid resolution or improvement in type 2 diabetes, even prior to any significant weight loss, indicating that hormonal mechanisms are likely involved.

Newer treatment options for management of diabetes mellitus

Nanotechnology and Diabetes

The interface of nanotechnology in the treatment of diabetes has introduced novel strategies for glucose measurement and insulin delivery. Researchers have demonstrated the advantages of glucose sensors and closed-loop insulin delivery approaches in facilitating the diabetes treatment

to make it beneficial in both type 1 and type 2 diabetes. A nanomedical device is a microcapsule containing pores which has been a promising tool in the drug delivery approach. These pores are considerably large to allow the passage of small molecules such as oxygen, glucose, and insulin but are small enough to allow the movement of larger immune system molecules such as immunoglobulins and graft-borne virus particles. Microcapsules containing replacement islets of Langerhans cells, mostly derived from pigs, could be implanted beneath the skin of diabetes patients. This could temporarily restore the body's delicate glucose control feedback loop without the need for powerful immunosuppressants that can leave the patient at serious risk for infection[32-35].

Statin Therapy

Statins are defined as inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A and inhibit the crucial process of LDL cholesterol in liver, thereby decreasing its level in the blood besides increasing healthy blood vessel lining. Since the long term effect of diabetes include the high risk of cardiovascular diseases, statins (HMG-CoA reductase inhibitor) are a main line of therapy in reducing cardiovascular risk in the patients suffering from type 2 diabetes. The lipid lowering agents, popularly known as statins, cause inhibition of HMG-CoA reductase specifically and reversibly. The enzyme catalyzes the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in the formation of cholesterol. These compounds are highly effective in reducing cholesterol levels as compared to dietary supplements.

Statin therapy reduces low density lipoprotein (LDL) cholesterol to a significant level thereby greatly decreasing the chances of developing a coronary artery disease. National Institute for Health and Clinical Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) diabetes guidelines showed lipid lowering therapy as primary prevention (when used regularly) for patients with type 2 diabetes, aged over 40 (Grade A recommendation), as well as its consideration for patients aged over 40 with type 1 diabetes (Grade B recommendation).

Statins have good efficacy and are effective in lowering cardiovascular events in people with modest levels of cholesterol and without cardiovascular disease. However, the HMG-CoA reductase inhibitors or statin therapy also has some disadvantages. The therapy has some side effects like renal dysfunction and muscle disorders from myositis to frank rhabdomyolysis and hepatic dysfunction which is rare and can be tolerated by the patient.

Stem Cell Technology

The interest to find a possible therapeutic for diabetes has eventually explored various new scientific areas of research, with the stem cell technology being one of them. It is known that both type 1 and type 2 diabetes result from the β cell deficiency of the pancreatic cells, resulting in insufficient insulin secretion. The strategies should aim at either removing the defects in pancreatic β cell or enhancing the sensitivity of the body cells to the action of insulin. β cell replacement strategies offer a novel source while current strategies aiming at islet cells and pancreas transplantation are limited due to shortage of donor organs[36-37].

Gene Therapy in Diabetes

The series of experiments leading to cloning and expression of insulin in the cultures cells in the 1970s was a tremendous revolution in the field of medicine and application of gene therapy in the treatment of diabetes was suggested as a possible cure. Regulating the sugar levels is the most important aspect in the treatment which also reduces the complications associated with the disease. Somatic gene therapy involving the somatic cells of the body includes two methods of gene delivery. The first one known as *ex vivo* gene therapy is described as the one in which the tissues are removed from the body; the therapeutic gene is inserted *in vitro* and then reimplanted back in the body while the *in vivo* therapy involves the insertion of gene therapy vectors directly to the patients by subcutaneous, intravenous, or intrabronchial routes, or by local injection. The application of *ex vivo* therapy aims at the generation of cells which possess the properties of β cells, for example, insulin producing cells. This therapy has also been used to generate β cells for transplantation. However, the concern lies in the aspect of surgically removing the tissue from the patient and reimplantation of the genetically modified tissues back into the body of the patients. Furthermore, type 1 diabetes results from autoimmune destruction of insulin synthesizing pancreatic β cells and islet transplantation has been explored as a possible solution for the treatment. The invention of insulin gene therapy substitutes β cell function by generating insulin secretory non-β cells, not vulnerable to autoimmune reactions, offering a prospective therapeutic approach for type 1 diabetes. The *in vivo* gene therapy is the method of choice as a therapeutic strategy because it is simpler and the vector containing the desired gene is directly inserted into the patient, but the development of safe (not toxic to host) and effective vectors remains as a challenging task for gene therapist. Presently, the strategies for *in vivo* therapy involve three methods: genetic transfer of glucose lowering genes which are noninsulin in nature. Presently, the strategies for *in vivo* therapy include genetic transfer of glucose lowering genes which are non-insulin in nature and application of blood sugar lowering genes: an enhancer of glucose utilization by liver or skeletal muscles and an inhibitor of glucose production by the liver. The genetic transfer of glucokinase had been used as an adjuvant therapy in the treatment of diabetes. In another strategy which was carried out to regulate the glucose production in liver, a gene known as "protein targeting to glycogen" (PTG) was used to convert glucose to glycogen. The PTG protein belongs to the family of glycogen targeting subunits of protein phosphatase-1 which regulated the metabolism of glycogen. Experiments performed in rats have indicated that adenoviral mediated PTG transfer stimulates glycogen synthesis in the liver and decreases blood glucose levels in rats. This has been considered as a therapeutic approach for diabetes.

Other areas of genetic engineering include transfer of genes which show response to glucose and the use of gene therapy to induce β cells production in the liver. The glucose responsive genes that have been manipulated to enhance conversion of proinsulin to insulin and those which after modification exhibit expression show responses to blood glucose level. The liver cells do not produce hormones which convert proinsulin to insulin; therefore, new proteolytic cleavage sites

have been incorporated into the proinsulin molecule, recognized by a protease, furin that is present in many tissue systems, including liver.

Medical Nutrition Therapy

Medical nutrition therapy in prevention and management of diabetes puts forth numerous advances in clinical research, aiming to use nutrition therapy for the treatment of disorders and illnesses. American Diabetes Association in 1994 coined the term "medical nutrition therapy" constituting 2 phases, namely, adjudging the nutritional requirement of a person and treatment through counseling and nutrition therapy, respectively. The objectives of nutritional therapy in diabetes is to regulate optimal level of lipids in blood, ideal body weight, and blood glucose level in normal range. Nutrition therapy as a therapy for diabetes depends on certain factors such as patient's age-based nutritive requirements and food preferences as well as other medical conditions together with an exercise regime and recommended nutritional requirement depending upon the patient's abilities and health conditions. Calorie requirement to maintain ideal body weight for moderately active individual is 30–35 kcal/kg/day; for obese people it is 20–30 kcal/kg/day. It is estimated that gradual weight loss of 1 lb per week should occur, if the calorie intake is reduced by 500 calories/day.

Natural Products and Diabetes

Literature has suggested the utilization of herbal medications for the treatment of insulin dependent and noninsulin dependent diabetes since time immemorial. Plants possessing antidiabetic properties may be suitable as adjunct to the existing therapies or as a prospective source of new hypoglycemic compounds. Since time immemorial, naturopathic therapies have been applied for a number of health ailments and continue to gain popularity in the present arena as well. Ancient literature revealed that diabetes was a known disease since Brahmic period and finds a mention in Ayurvedic literature, Sushruta samhita written in fourth and fifth centuries BC. Two forms of diabetes were described: one genetic in nature and the other due to dietary indiscretion. Herbal medicines are becoming immensely popular among the masses for being cost effective and with relatively few side effects. Although plant based medicines have been used traditionally in treating diseases throughout the world, the mechanism of most of the herbs is still to be defined and standardized. Many new bioactive drugs isolated from plants having hypoglycaemic effects demonstrate antidiabetic activity equal to and sometimes even more potent than known oral hypoglycaemic agents such as daonil, tolbutamide, and chlorpropamide. The bioactive constituents found in many plant species are isolated for direct use as drugs lead compounds, or pharmacological agents. These traditional approaches might offer a natural key to unlock diabetic complications. The chemical structures of a phytomolecule play a critical role in its antidiabetic activity.

Future Perspectives

Diabetes has remained as one of the most challenging health problems in the 21st century accounting for a global presence. Diabetes is a serious public health problem, but the good news is that important advances are being made in prevention, detection, and treatment of diabetes. For the management of type 1 diabetes, patients require insulin administration 3-4 times a day

throughout their lives and their blood sugar levels should be regularly monitored to avoid complications like retinopathy and risks of cardiovascular diseases. It has been estimated that around 1300 patients with type 1 diabetes receive whole organ (pancreas) transplant and do not require insulin infusion but the demand for organs transplantation is higher than supply[38].

For the management of type 2 diabetes, a well monitored glycemic control is required. The need to control the progressive deterioration of β cell function is essential since it can lead to a loss of glycemic control. Conventional drugs and insulin are effective but cannot repair the associated metabolic and glucoregulatory dysfunctions. The menace of diabetes is increasing day by day and aggressive and targeted combinational therapy is the need of the hour particularly incretin based therapy and peptide analogs. This may restore and preserve β cell function and halt the progression of type 2 diabetes. In the present era, the effectiveness and the success of the new drug will depend on its ability to treat/relieve one or more of the metabolic disturbances whether increased production of insulin or enhancement in glucose uptake and utilization by the peripheral tissues particularly skeletal muscle. Besides new generations of therapeutics, several other classes have also been reported as alternative strategies alone or in combinations to provide an effective treatment for diabetes.

The prospects of leptin therapy are one of the emerging trends in the treatment of diabetes. It is a hormone secreted by adipocytes, which acts on the neurons within the central nervous system. The multiple actions of this hormone include control of excessive increase in weight, by suppressing the intake of food and increasing the expenditure of energy. Leptins also regulate glucose homeostasis through the activation of leptin receptors (LEPRs). It has been shown that the central nervous system regulates the sugar lowering effect of leptins; it was assumed that the antidiabetic action of leptins could have been influenced by neurons in the brain with reference to type 1 diabetes.

Conclusion

Diabetes is a serious public health problem, but the good news is that important advances are being made in prevention, detection, and treatment of diabetes. For the management of type 1 diabetes, patients require insulin administration 3-4 times a day throughout their lives and their blood sugar levels should be regularly monitored to avoid complications like retinopathy and risks of cardiovascular diseases. The rapid prevalence of type 2 diabetes in youth over the past 20 years parallels and follows the worldwide epidemic of childhood obesity. Predisposing factors for the development of type 2 diabetes in the context of obesity in youth include obesity, family history, ethnicity, and an abnormal prenatal metabolic environment. Once diagnosed, type 2 diabetes in youth is exceeding difficult to treat effectively; thus, primary prevention should be a major target of health care efforts and resources. Ideal management of youth with type 2 diabetes requires an expert diabetes team, experienced in delivering requisite diabetes education and aggressive care and monitoring. The only oral medication approved for use in youth with type 2 diabetes is metformin; thus metformin is the preferred first-line oral agent in stable patients. The discovery of new drug molecules and the future development of novel therapeutics approaches could lessens the diabetes mellitus health problems.

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