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Diagnostic Approaches to Diabetes Mellitus and the Role of Vitamins

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Abstract

Diabetes mellitus is a group of heterogeneous disorders commonly characterized by chronic hyperglycemia and glucose intolerance, as a result of defects in insulin secretion, defective insulin action, or both. Based on the aetiology and clinical presentation, diabetes mellitus is classified as either immune-mediated (Type 1 diabetes), insulin resistance (Type 2), gestational or others (environment, genetic defects, infections, and certain drugs). The major types of diabetes are type 1 and type 2. Type 1 diabetes is immune mediated and is caused by destruction to the islets cells of the pancreas while type 2 diabetes is caused by a combination of genetic factors related to impaired insulin secretion, insulin resistance and environmental factors such as obesity, overeating, lack of exercise and stress, as well as ageing. The progression of the disease there occurs tissue and vascular damages. This damage ultimately causes severe complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration. As diabetes mellitus is associated with severe medical complications it ultimately leads to premature death. The complications of diabetes are due to multiple factors, cellular pathways etc. Oxidative stress is one of the factors that cause this complication by generation of free radicals. The damage caused by these reactive free radicals can be minimized by the antioxidant capacity of vitamins especially vitamin C, E, A and others. Besides these the role played by some minerals is also critical. There are several parameters which can serve as a diagnostic to diabetes. Utilizing the methods for the measurement of these biomarkers is thus very critical and of utmost importance. Some of the diagnostic markers which can be utilized for the type of diabetes a patient is suffering from are blood sugar, HbA1c, c-peptide, GADA, glycated albumin and glycated proteins.

The main idea and concern of writing this review is to explores diabetes mellitus in terms of its past historical perspective, biochemical basis, economic burden, management steps along with the future perspectives which needs to be taken to minimize the great loss of damage caused by this metabolic disorder.

Keywords: Diabetes mellitus; Resistance; Complications; Oxidative stress; Hyperglycemia; Markers

Introduction

Diabetes mellitus is a metabolic disorder of carbohydrate metabolism characterized by chronic hyperglycemia due to defect in insulin secretion, insulin action or both. Due to the deficiency of insulin there occur disturbances in carbohydrate, fat and protein metabolism. Further progression of the disease causes tissue or vascular damage and ultimately causes severe complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration. Thus, diabetes covers a wide range of heterogeneous diseases. It has been reported that the most common endocrine disorder is diabetes and by the year 2010, it is estimated that more than 200 million people worldwide will have DM [1] and 300 million will subsequently have the disorder by 2025 [2]. According to the worldwide survey carried on diabetes it has been reported that diabetes is affecting nearly 10% of the population [3]. According to a report by World Health Organization (WHO) that the prevalence of diabetes is likely to increase by 35% by the year 2025 [4]. The prevalence of diabetes in India is very high and the numbers are increasing at an enormous rate. A study which has been carried out in India reported that diabetes is expected to increase from 40.6 million in 2006 to 79.4 million by 2030 [5].

Based on the clinical presentation and aetiology of the disease, diabetes mellitus is classified into four types: Type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types [6]. But the two main types of diabetes are type 1 and type 2. Type 1 diabetes mellitus is immune mediated in which body's own cells cause destruction of the beta islet cells of pancreas and as a result there is less secretion of insulin. Type 1 diabetes mellitus is due to an autoimmune reaction to proteins of the islets cells of the pancreas [7]. According to a report carried out by American Diabetes Association about 10% of all cases of diabetes, approximately 20 million people are affected worldwide [8]. It has been found that all the age groups are affected by type 1 diabetes, the majority of individuals are diagnosed either at around the age of 4 to 5 years, or in their teens and early adulthood [9]. The commonest form of diabetes is type 2 which is caused by defective insulin secretion and insulin resistance [10]. Alone type 2 diabetes accounts for at least 90% of all cases and is the most predominant form of diabetes mellitus [11]. It has been found that the rate of prevalence of Diabetes is higher in developing countries than in developed countries (69 vs. 20%) [12].

Gestational Diabetes (GD) mellitus

During pregnancy especially in the second or third trimester there occurs an onset of glucose intolerance. GD has been reported in 4% of all pregnancies. About 30% to 40% of patients with GD have a chance of developing type 2 DM [13]. Other types of DM are due genetic defects of the pancreatic ß cell or in the pathways of insulin action (insulin receptor mutations or post-receptor defects) [14] as well as disease of the exocrine pancreas (e.g., Pancreatitis, pancreatic reaction, or cystic fibrosis) are less common causes of DM [13]. Endocrinopathies producing insulin counter regulatory hormones excess (e.g., Cushing's syndrome, acromegaly) may result in DM [13]. Certain drugs like glucocorticoids, pentamidine, niacin, and a-interferon may also lead to DM [15].

Clinical features of diabetes mellitus

General symptoms:

- Polyuria.
- Nocturia.
- Salt and water depletion: thirst, dizziness, cramps.
- Tiredness.
- Altered visual activity.
- Symptoms of infections: Purities, infection of skin and nails, Diarrhoea.

Clinical features of Type I diabetes:

- Sudden appearance of weight loss accompanied by polyuria, nocturia and polydipsia.
- Usually appears in young mean individuals typically 10–12 years.
- Overwhelming fatigue, increase appetite.
- Muscular atrophy in thigh.
- Smell of acetone.

Clinical features of Type II diabetes:

- Usually affects overweight persons.
- Most are over 40 years of age.
- Genital candidiasis, urinary tract infections/skin infections.

Diagnostic Approaches for Diabetes

To prevent the complications which are related to diabetes it is very important to diagnose diabetes at an early stage. The tests which are mostly used in diagnosing diabetes are fasting blood glucose, postprandial blood glucose and HbA1c. A large number of experimental and clinical observations have demonstrated that the formation of excess free radicals may be directly or indirectly associated with hyperglycemia [16].

Blood sugar as a biomarker for diabetes

In Clinical practice major basis for diagnosis of diabetes mellitus is to determine the fasting plasma glucose (120 mg/dl) or 2 h post prandial plasma glucose levels greater than 200 mg/dL [17]. To prevent the long term, life threatening complications of diabetes, it is necessary to control glucose levels [18].

HbA1c as a biomarker for glycemic control

Glycated hemoglobin (HbA1c) is the best measure of long-term glycemic control, since it represents the average blood glucose levels over several months [19]. Glycemic control is defined as excellent if the measured HbA1c is <6.5%, very good if HbA1c is 6.5-7.0%, good if HbA1c is 7.1-7.5%, acceptable if HbA1c is 7.6-8.0% and poor if HbA1c is >8.0% [20].

C-peptide as a biomarker for differential diagnosis of type 1 and type 2 diabetes

Type 1 diabetes is distinguished from type 2 diabetes on the basis of the need for exogenous insulin for survival [21]. C-peptide level may be used to distinguish people with new-onset type 2 diabetes from those with type 1 diabetes in addition to obesity, family history of type 2 diabetes and absence of Glutamic Acid Decarboxylase (GAD)-65 antibodies [22]. C-peptide has been widely accepted as the most appropriate measure of residual β-cell function because it is secreted on a basis equimolar to insulin and unlike the latter, is not removed in the first pass through the liver [23]. Because C-peptide is secreted from islet cells into the circulation in equimolar concentrations with insulin and is not extracted by the liver, many investigators have used C-peptide levels as a biomarker of β-cell function [24]. Fasting C-peptide level <0.6 ng/ml is considered as an indicator of poor insulin reserve. Hence, C-peptide is a useful guide in initiating therapy to prevent complications [25].

GADA positivity as a biomarker for differential diagnosis of type 1.5 and type 2 diabetes

Based on the clinical features type 1.5 diabetes can be distinguished from type 2 diabetes, but to a large extent there still exists an overlap. However the gold standard for identifying type 1.5 diabetic patients involves the use of immunogenetic markers for the measurement of autoantibodies. Identification of these patients is clinically relevant to their management as the early use of insulin resulted in β-cell preservation in several pilot studies [26]. Blood tests for the detection of antibodies could be used to distinguish type 1.5 diabetes from type 2 diabetes. Type 1.5 diabetes is diagnosed by the presence of pancreatic auto-antibodies, such as glutamic acid decarboxylase (GAD) antibodies in an adult initially presenting with non-insulin dependent diabetes [27].

Fructosamine test

The main component of plasma proteins is Albumin. As albumin also contains free amino groups, non- enzymatic reaction with glucose in plasma occurs. Therefore glycated albumin can be considered as a marker to monitor blood glucose. Glycated albumin is usually taken to provide a retrospective measure of average blood glucose concentration over a period of 1 to 3 weeks. The reference interval of albumin is 205-285 μmol/L.

Glycated proteins

Proteins in blood react with glucose to form glycated derivatives. The extent of glycation of proteins is controlled by the concentration of glucose in blood and by the number of reactive amino groups present in the protein that are accessible to glucose for reaction. All proteins with reactive sites can be glycated and the concentration of the glycated proteins that can be measured in blood is a marker for the

fluctuation of blood glucose concentrations during a certain period. From a clinical diagnostic point glycated proteins with a longer life time in blood are of interest, since they reflect the exposure of these proteins to glucose for longer periods.

Complications of diabetes

If the blood sugar levels are not controlled over a period of time it can result in severe long term complications of eye, heart, kidney and foot [27]. The complications associated with diabetes are of two types I microvascular complications that include retinopathy, nephropathy, neuropathy and peripheral vascular disorders and macrovascular complications that include cardiovascular and cerebrovascular disorders.

Causes of diabetic complications

In particular a number of multiple factors, cellular pathways etc. are responsible for causing complications that are related to diabetes. One factor in particular i.e., oxidative stress has been linked responsible for these complications [28]. Oxidative stress leads to the generation of reactive free radicals in the body which in turn causes major damage to the body. Oxidative stress reduces the insulin sensitivity and destroys the cells producing insulin thereby promoting the onset of diabetes. The damage to the β-cells of pancreas is caused by ROS which easily penetrates through the cell membrane [29]. Impaired pancreatic β-cell function and damage to the mitochondrial DNA is caused by ROS that in turn are released by a diet rich in fat or free fatty acids [30]. The development of diabetes has been related with reduction in the levels of mitochondrial proteins and mitochondrial DNA [31].

Vitamins

Vitamins are the organic compound which is required by the organism for the proper growth and development. Vitamins are required in limited amounts by the organism. Vitamins are classified as either water soluble (B, C) or fat soluble (A, D, E, K). Of all the vitamins only vitamin D can be synthesized by the body through direct exposure to sunlight. Therefore all other vitamins must be provided in diet. Some of the vitamins have antioxidant properties. As diabetes is associated with the oxidative stress and as a result there is formation of free radicals which cause damage to the body. To minimize the damage caused by the generation of free radicals, some of the vitamins could play a key role in this process. The vitamins which have potential antioxidant activity are vitamin C, E and A. Therefore by utilizing the antioxidant property of these vitamins the damage caused by these reactive species can be reduced.

Role of Vitamins

The oxidative stress and free radicals cause damage to the blood vessels and organs. This damage can be decreased by antioxidant potential of vitamin C, E, A etc. The role which these vitamins can play is as Vitamin C.

Vitamin C (Ascorbic acid) is found in citrus fruits like lemons, oranges and amla etc. According to study which was carried out by Tanaka et al. [32] found a 50% reduction in cases of retinopathy in subjects with a high fruit and vitamin C intake. A study which was carried out by Hegde et al. [33] found that diets rich in fruit can improve dietary antioxidant intake, which in turn, is likely to reduce oxidative stress in people with type 2 diabetes. The foods that are rich in antioxidants give protection against the damage that occurs in any inflammatory condition and from exacerbating factors caused by obesity, smoking and physical inactivity. A report by Harding et al. [34] about plasma vitamin C and fruit and vegetable consumption in association with the prevention of type 2 diabetes. They found that there was a decreased risk of developing diabetes in those which had higher levels of vitamin c levels in plasma, and to a lesser extent intake of fruits and vegetable. Also in some trials which were given higher doses of vitamin C to determine a possible link with reducing inflammation, although results have been inconclusive [35].

Vitamin E

The most important lipid-soluble antioxidants are Vitamin E. It inhibits the peroxidation of lipids thereby protecting the integrity of the membranes. It has been reported that by giving vitamin E supplementation has no beneficial effect in improving glycaemic control in all people with type 2 diabetes, however it was also found that in people with inadequate glycaemic control or low serum levels of vitamin E it may decrease HbA1c levels [36]. This shows the importance of targeting therapy. Higher doses of vitamin E supplements more than 400 international units [IU] per day should be avoided as it may increase all-cause mortality [37].

Vitamin A

Vitamin A is a fat soluble vitamin which has antioxidant property. The important properties of vitamin A involves boosts cell growth, contributing to better vision, healthy immune system. Pleiotropic role in cell regulation through its action on gene regulation, maintenance of epithelial cell integrity, and resistance to infection. Studies have also found a role of vitamin A in up-regulating the antioxidant enzyme functions in the body. Additionally, a link has been found between diabetes and deficient vitamin A levels indicating vitamin A supplementation may have a role in T2DM biology.

Management of Diabetes

It has been found and reported that in new cases of diabetes diet and lifestyle advice alone is required to maintain glucose levels in approximately 50%, of cases, while as 20-30% will require oral anti-diabetic treatment and insulin will be needed in 20-30% cases. The adequacy of functioning of the residual β-cell determines the choice of treatment. The type of treatment required depends upon the clinical features besides age and weight of the patient should be kept under consideration.

Diet and Lifestyle

It has been observed that diet and lifestyle to a certain extent does play an important role. By undergoing life style changes like doing regular physical activity, a good healthy diet and by decreasing alcohol consumption could be ideal to control glycaemic levels. Besides this encouragement should be given to patients to stop smoking.

Composition of the Diet

A healthy and a proper diet management plan should be followed. A good diet should consist of fresh fruits and vegetables.

Carbohydrate

Previously patients with type 1 diabetes were advised to maintain a regular intake of carbohydrates in the daily diet. However with the development of modern regimens of insulin has permitted a greater relaxation in the timing and choice of intake of carbohydrates. The insulin regimens used are insulin analogues or Continuous Subcutaneous Insulin Infusion (CSII). Patients with type 2 diabetes are advised to limit the intake of carbohydrates and restrict total caloric intake.

FAT

Patients with diabetes should take fat restricted to an amount of less than 35%, of which saturated fat should be 10% and 10-20% fat should be monounsaturated.

Diabetic Foods and Sweeteners

The use of sugar free drinks and low calorie diet is considered as very useful for diabetic patients. These drinks usually contain non-nutritive sweeteners. The sweeteners that are used in sugar free drinks should be less expensive, low in calories and should not cause any side effect.

Salt

The people with diabetes are advised to reduce the intake of sodium in the daily diet. The quantity of sodium intake should not be more than 6 g.

Weight Management

It has been reported that the reduction in weight is a key factor in the management of diabetes. People with type 2 diabetes are found to be overweight or obese and by administration of many anti-diabetic drugs including insulin results in weight gain. Obesity particularly around waist may predict insulin resistance and cardiovascular risk. Therefore it becomes very important to lose weight that in turn can be achieved by taking less calorie intake and by increasing energy expenditure through physical activity.

Exercise

Diabetic patients should be strongly encouraged to take regular physical activity, in the form of walking, gardening, swimming or cycling, for around 30 min daily and by doing this it improves insulin sensitivity, lipid profile and lowers blood pressure.

Alcohol

The consumption of alcohol should be reduced as it suppresses gluconeogenesis and can precipitate or protract hypoglycemia, particularly in patients taking insulin or sulphonylureas.

Anti-Diabetic Drugs

Patients with type 2 diabetes are treated with a number of drugs which are effective in reducing hyperglycemia. Metformin and sulphonylureas have been used for many years and have the strongest evidence of preventing complications of diabetes.

Insulin Treatment

Insulin a polypeptide secreted by the pancreatic B cells is usually composed of 51 amino acids. Normally it is secreted in the body after a meal is taken, but in case of diabetes particularly type 1 diabetes it is secreted in lesser quantity and in type 2 diabetes there occurs resistance to the insulin levels due to a defect in the insulin receptors. Thus in diabetic patients insulin is a pre-requirement for survival. The insulin used may be short acting or long acting insulin.

Short-Acting Insulin

Multiple dose regimens of short-acting insulin's are used for pre-meal injection particularly for continuous intravenous infusion in labour or during medical emergencies, and in patients using insulin pumps. It has been found that after subcutaneous injection of human insulin, it is absorbed slowly, reaching a peak 60–90 min after, and further after meals its action still persists predisposing to hypoglycemia.

Longer-Acting Insulin's

Longer acting insulin is also used and their action is enhanced by the addition of zinc or protamine. NPH (isophane insulin) is a pre-mixture consisting of 30% soluble insulin and 70% NPH is the most widely used form. The structures of the long acting insulin analogues are modified to delay absorption or to prolong their duration of action.

Future challenges

Due to the high prevalence of diabetes at the population level, it imposes great financial problems both on healthcare system and the individuals living with this metabolic disorder. It is important that each country in the world should implement preventive and curative measures. Lifestyle modification to a greater extent will play a key role in the ultimate solution to the problem of diabetes, and more definitive solutions will depend on the ability. The realization that diabetes mellitus is a "metabolic curse" should be a trigger for desire to seek understanding of the biochemical and molecular basis of this metabolic disorder. Such an understanding will inform efforts to elucidate more effective management interventions against diabetes mellitus. The oral hypoglycemic agents, which are apparently bedeviled by side effects, need to be optimized to mitigate these demerits. Lifestyle management needs to be optimized to achieve the intended goal of lowering the glycemic index in diabetics. Gene therapy will doubtlessly address the complications of diabetes mellitus. The pioneering gene therapy approach to diabetes mellitus was occasioned by the cloning of the insulin gene. The strategy was based on the premise that non-insulin producing cells could be manipulated to produce insulin using a suitable promoter and insulin gene construct. Further studies needs to be carried out on the role of vitamins with potential antioxidant capacity and how could they be utilized in minimizing the damage. Also the role of minerals should be considered side by side. The use of insulin in the treatment of diabetes is very vital and plays a key role in the life of diabetic patients. However the use of insulin along with the dietary management should be strictly followed by the diabetic patients. The short acting or long acting forms of insulin have been used. As far as the future perspective is concerned, the development of inhaled forms of insulin with good clinical results and better bioavailability in the circulation could change the life of diabetic patients.

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