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REVIEW ARTICLE

Vitamin D and Diabetes, Pathophysiology, Dietary Significance and recommendation

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ABSTRACT
There are also evidences suggesting that altered calcium and vitamin D homeostasis plays a role in the development of diabetes. Low levels of activated vitamin D are associated with glucose intolerance, diabetes, insulin resistance and metabolic syndrome; all increasing the potential for the development of type 2 diabetes Vitamins can be taken up from the foods like fish and oils but the major source is sunlight. Vitamin D exerts its effects by binding to its nuclear receptor (VDR). VDR are present on pancreatic β-cells and vitamin D is essential for normal insulin secretion. Insulin secretion is reduced in animal models with vitamin D deficiency. The Aim of this review is to emphasize the role of Vitamin D for Diabetes and Daily Recommended use for Prevention of advanced risk factors.
Key Words .Vitamin D Receptor , Diabetes Mellitus , Ergocalciferol

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INTRODUCTION

Type 1 diabetes mellitus (DM) is a catabolic disorder in which circulating insulin is very low or absent, plasma glucagon is elevated, and the pancreatic beta cells fail to respond to all insulin-secretary stimuli. The pancreas shows lymphocytic infiltration and destruction of insulin-secreting cells of the islets of Langerhans, causing insulin deficiency. Patients need exogenous insulin to reverse this catabolic condition, prevent ketosis, decrease hyperglucagonemia, and normalize lipid and protein metabolism. [1]
One theory regarding the etiology of type 1 DM is that it results from damage to pancreatic beta cells from infectious or environmental agents. In a genetically susceptible individual, the immune system is thereby triggered to develop an autoimmune response against altered pancreatic beta cell antigens or molecules in beta cells that resemble a viral protein. Approximately 85% of type 1 DM patients have circulating islet cell antibodies, and the majority also has detectable anti-insulin antibodies before receiving insulin therapy. Most islet cell antibodies are directed against glutamic acid decarboxylase (GAD) within pancreatic beta cells. [2]
Currently, autoimmunity is considered the major factor in the pathophysiology of type 1 DM. Prevalence is increased in patients with other autoimmune diseases, such as Graves disease, Hashimoto thyroiditis, and Addison disease. Approximately 95% of patients with type 1 DM have either human leukocyte antigen (HLA)-DR3 or HLA-DR4. HLA-DQs are considered specific markers of type 1 DM susceptibility. [1]
Recent evidence suggests a role for vitamin D in the pathogenesis and prevention of diabetes mellitus. Vitamin D deficiency is also an important independent predictor of development of coronary artery calcification in individuals with type 1 DM.[2]

ETIOLOGY

The etiology of type 1 DM has a strong genetic component. Nevertheless, identical twins have a concordance rate for type 1 DM of less than 50%. In studies of identical twin pairs in which 1 twin has type 1 diabetes, antibodies to the islet cell and to insulin are positive for several years in the non diabetic twin before overt diabetes develops. [3]

Extra genetic factors also may contribute. Potential triggers for immunologically mediated destruction of the beta cells include viruses (eg, mumps, rubella, coxsackie virus B4), toxic chemicals, exposure to cow's milk in infancy, and cytotoxins. As beta-cell mass declines with ongoing immunologic destruction, insulin secretion decreases until the available insulin no longer is adequate to maintain normal blood glucose levels. After 80-90% of the beta cells are destroyed, hyperglycemia develops and diabetes may be diagnosed[4].
A meta-analysis suggests a significant association between enterovirus infection and autoimmune/type 1 DM.[3] The role of enterovirus in development of type 1 DM warrants investigation in larger prospective studies.

EPIDEMIOLOGY
Internationally, rates of type 1 diabetes are increasing. In Europe, the Middle East, and Australia, rates of type 1 diabetes are increasing by 2-5% per year. Scandinavia has the highest prevalence rates for type 1 DM (ie, approximately 20% of the total number of people with DM), while China and Japan have the lowest prevalence rates, with less than 1% of all people with diabetes. Some of these differences may relate to definitional issues and the completeness of reporting.[5]

PROGNOSIS
Type 1 DM is associated with a high morbidity and premature mortality. More than 60% of patients with type 1 DM fare reasonably well over the long term. Many of the rest develop blindness, end-stage renal disease, and, in some cases, early death. If a patient with type 1 DM survives the period 10-20 years after onset of disease without fulminant complications, he or she has a high probability of reasonably good health. Other factors affecting long-term outcomes are the patient's education, awareness, motivation, and intelligence level[6].

CLINICAL PRESENTATION
The most common symptoms of type 1 diabetes mellitus (DM) are polyuria, polydipsia, and polyphagia, along with lassitude, nausea, and blurred vision, all of which are due to the hyperglycemia itself.
Common insulin regimens
Although emergency physicians rarely start new therapy for patients with diabetes, being acquainted with the various forms of insulin and the common regimens is useful.
When treating patients with type 1 DM, the goal is to provide insulin in a manner that is as physiologic as possible. Insulin replacement is given as a basal insulin (either long-acting [glargine or detemir] or intermediate-acting [NPH]) and preprandial (premeal) insulin (either rapid-acting [lispro, aspart, or glulisine] or short-acting [regular]). For patients on intensive insulin regimens (multiple daily injections or insulin pumps), the preprandial dose is based on the carbohydrate content of the meal (the carbohydrate ratio) plus a correction dose if their blood glucose level is elevated (eg, 2 additional units of rapid-acting insulin to correct the blood glucose from a level of 200 mg/dL to a target of 100 mg/dL). This method allows patients more flexibility in caloric intake and activity, but it requires more blood glucose monitoring and attention to the control of their diabetes. [8]
Common insulin regimens include the following:

1) Split or mixed, such as NPH with rapid-acting (eg, lispro, aspart, or glulisine) or regular insulin before breakfast and supper
2) Split or mixed variant: NPH with rapid-acting or regular insulin before breakfast, rapid-acting or regular insulin before supper, NPH before bedtime (designed to reduce fasting hypoglycemia by giving the NPH latter in the evening)
3) Multiple daily injections (MDI), a long-acting insulin (eg, glargine or detemir) once a day in the morning or evening (or twice a day in about 20% of patients), and a rapid-acting insulin before meals or snacks (dose adjusted based on the carbohydrate intake and the blood glucose level)
4) Continuous subcutaneous insulin infusion (CSII), rapid-acting insulin infused continuously 24 hours a day through an insulin pump at one or more basal rates, with additional boluses given before each meal, and correction doses administered if blood glucose levels exceed target levels

Insulin is sensitive to heat and exposure to oxygen. Once a bottle of insulin is open, it should be used for no more than 28 days and then discarded, even if insulin remains in the bottle. Use of old insulin can result in a lack of clinical effectiveness. Insulin in a pump reservoir for longer than 3 days may lose its clinical effectiveness (although insulin asparthas now been approved for use for up to 6 days in a pump). Sometimes, insulin distributed from the pharmacy has been exposed to heat or other environmental

factors and may be less active. If a patient is experiencing unexplained high blood sugar levels, new insulin vials should be opened and used.[9]

TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus comprises an array of dysfunctions resulting from the combination of resistance to insulin action and inadequate insulin secretion. It is disorders are characterized by hyperglycemia and associated with microvascular (ie, retinal, renal, possibly neuropathic), macrovascular (ie, coronary, peripheral vascular), and neuropathic (ie, autonomic, peripheral) complications. Unlike patients with DM type 1 patients with type 2 are not absolutely dependent upon insulin for life. This distinction was the basis for the older terms for types 1 and 2, insulin dependent and non–insulin dependent diabetes. However, many patients with type 2 diabetes are ultimately treated with insulin. Because they retain the ability to secrete some endogenous insulin, they are considered to require insulin but not to depend on insulin. Nevertheless, given the potential for confusion due to classification based on treatment rather than etiology, these terms have been abandoned [6]

Another older term for type 2 diabetes mellitus was adult-onset diabetes. Currently, because of the epidemic of obesity and inactivity in children, type 2 diabetes mellitus is occurring at younger and younger ages. Although type 2 diabetes mellitus typically affects individuals older than 40 years, it has been diagnosed in children as young as 2 years of age who have a family history of diabetes.

Diabetes mellitus is a chronic disease that requires long-term medical attention both to limit the development of its devastating complications and to manage them when they do occur. It is a disproportionately expensive disease; in the United States in 2002, the per-capita cost of health care was $13,243 for people with diabetes, while it was $2560 for those without diabetes. The emergency department utilization rate by people with diabetes is twice that of the unaffected population.[7]

Pathophysiology

Type 2 diabetes is characterized by the combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. Insulin resistance, which has been attributed to elevated levels of free fatty acids in plasma,[5] leads to decreased glucose transport into muscle cells, elevated hepatic glucose production, and increased breakdown of fat.

For type 2 diabetes mellitus to occur, both defects must exist. For example, all overweight individuals have insulin resistance, but diabetes develops only in those who cannot increase insulin secretion sufficiently to compensate for their insulin resistance. Their insulin concentrations may be high, yet inappropriately low for the level of glycemia.

Beta cell dysfunction is a major factor across the spectrum of pre-diabetes to diabetes. A study of obese adolescents by Bacha et al confirms what is increasingly being stressed in adults as well: Beta cell function happens early in the pathological process and does not necessarily follow stage of insulin resistance.[7] Singular focus on insulin resistance as the "be all and end all" is gradually shifting, and hopefully better treatment options that focus on the beta cell pathology will emerge to treat the disorder early

In the progression from normal glucose tolerance to abnormal glucose tolerance, postprandial blood glucose levels increase first; eventually, fasting hyperglycemia develops as suppression of hepatic gluconeogenesis fails.

During the induction of insulin resistance, such as is seen after high-calorie diet, steroid administration, or physical inactivity, increased glucagon levels and increased glucose-dependent insulinotropic polypeptide (GIP) levels accompany glucose intolerance; however, postprandial glucagonlike peptide-1 (GLP-1) response is unaltered. This has physiologic implications; for example, if the GLP-1 level is unaltered, GLP-1 may be a target of therapy in the states mentioned above. [9]

The high mobility group A1 (HMGA1) protein is a key regulator of the insulin receptor gene (*INSR*).[6] Functional variants of the *HMGA1* gene are associated with an increased risk of diabetes. These variants were shown to lead to reduction in protein content of both *HMGA1* and *INSR*.

Although the pathophysiology of the disease differs between the types of diabetes, most of the complications, including microvascular, macrovascular, and neuropathic, are similar regardless of the type of diabetes.

Role of Vitamin D in Diabetes

Vitamin D refers to vitamin D2 (Ergocalciferol) or vitamin D3 (cholecalciferol). Ergocalciferolis produced from irradiated fungi or yeast. Cholecalciferol is produced in skin or found naturally in fatty fish such as salmon or mackerel. Both forms of vitamin D can be used to fortify food, however only cholecalciferol can be made endogenously in skin. When the skin is exposed to ultraviolet B (UVB) radiation between the

wavelengths of 290 and 315 nm, 7-dehydrocholesterol, a compound present in the skin, is converted to previtamin D3[10]. Then it isomerizes to form vitamin D3.

Once vitamin D enters the circulation bound to vitamin D–binding protein. This complex is transported to the liver, where vitamin D undergoes hydroxylation in the 25 position to form 25-hydroxyvitamin D (25[OH]D), which then circulates to the kidney and is hydroxylated at the 1 position by the 1-α-hydroxylase to form the hormonal form of vitamin D, 1,25-dihydroxyvitamin D (1,25[OH]2D). 1, 25(OH) 2D circulates bound to vitamin D–binding protein, enters the target cell and binds to the vitamin D receptor (VDR) in the cytoplasm, which then enters the nucleus and then increase the transcription of vitamin D–dependent genes for the regulation of bone metabolism, calcium absorption[11]

Circulating 1, 25(OH) 2D is catabolized by the 24-hydroxylase to form 1, 24, 25(OH) 2D, an inactive vitamin D compound. 1, 25(OH) 2D increases its own catabolism by increasing expression of the 24-hydroxylase. Recently, researchers discovered that medications such as anticonvulsants and rifampin can increase the catabolism of 1, 25(OH) 2D by activating the pregnane X receptor, resulting in increased expression of the 24-hydroxylase[12].

To increase the efficiency of calcium absorption optimal vitamin D levels are necessary.Without adequate vitamin D, the body absorbs no more than 10% to 15% of dietary calcium. In the vitamin D–sufficient state, the intestinal calcium absorption increases to 30% to 40%[13]

Over the past few years the definition of vitamin D insufficiency has changed from less than 20 ng/mL to less than 32 ng/mL.[13] According to the clinical trials established that optimal calcium absorption occurs with a 25(OH) D level greater than 32 ng/mL and most protection from fracture comes from a 25(OH)D level greater than 30 ng/mL. An optimal 25 (OH)D should be at least 32 ng/mL to prevent secondary hyperparathyroidism and fracture [14]

In another study a large percentage of patients with osteoporosis were included. A study of 1536 postmenopausal osteoporotic women from osteoporosis clinics, evenly distributed across southern and northern latitudes of the United States, found that over half of these women (52%) were vitamin D insufficient (25[OH]D < 30 ng/mL)[15].

Vitamin D insufficiency is spreading in all age groups and it is not limited to elderly and osteoporotic patients. A study from Boston demonstrated that over two thirds of healthy young adults were vitamin D insufficient .Using cross-sectional data from the Third National Health and Nutrition Examination Survey, we found that more than 92% of black and 61% of white Americans had vitamin D insufficiency defined by 25(OH)D less than 32 ng/mL[16]

Vitamin D repletion improves insulin sensitivity and insulin secretion in many animal and human studies[16]

Experimental and epidemiological evidences suggested that proper calcium and vitamin D intake also reduces the development of diabetes[17]

Calcium is essential for insulin-mediated intracellular processes in insulin-responsive tissues such as skeletal muscle and adipose tissue with a very narrow range of [Ca2+] needed for optimal insulin-mediated functions Changes in [Ca2+] in primary insulin target tissues may contribute to peripheral insulin resistance via impaired insulin signal transduction. Associations between low vitamin D level and decreased insulin sensitivity have been reported in cross-sectional studies[18,19]

A high HbA_{1c} represents poor glucose control. However, a 'good' HbA_{1c} in a patient with diabetes can still be riddled with a history of recent reduce glucose or, alternatively, spikes of hyperglycemia. Regular blood glucose monitoring is still the best method for the analysis of overall vascular health with respect to blood sugar control. Improved control over the long-term is likely to prevent falls. Although, the benefits of glycemic control are well established in diabetic adults. Current guide lines recommend an AIC goal of 7% or less for older diabetic adults[20]

As well as assisting glycemic control, increasing your levels of vitamin D can also:[21]

Aid weight loss; studies has been reported that good vitamin D potentially helps to decrease the parathyroid hormone (PTH) levels, which in the long-term may help in weight reduction and reduce risk of obesity, which is a major risk factor for type 2 diabetes.

Regulation of appetite – vitamin D greatly effect on serum leptin level andraised body's levels of the hormone leptin, which controls body fat storage thus lowering hunger levels.

Reduce belly or abdominal fat ;some studies shown an raised in vitamin D can help lower levels of cortisol, a stress hormone produced in the adrenal glands. Cortisol is involved in a number of important functions, including the body's response to stress and regulation of blood pressure. But higher and more prolonged levels of the hormone in the blood can lead to increased abdominal fat, which is linked to various health conditions including diabetes type 2[22]

CONCLUSION

Vitamin D help in reduction of Body fat as well as parathyroid hormone to help in long term reduction of boy Weight in Diabetic Patient. It is recommended to enhance the use of vitamin D in Daily life to protect from hazardous effects of Diabetes Neuropathy.

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