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REVIEW ARTICLE

Vitamins and Type 2 Diabetes Mellitus

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Abstract:

The present review evaluates the relationship between type 2 diabetes mellitus and vitamins. Oxidative stress has been implicated in the development of type 2 diabetes and its several complications. Antioxidant vitamins A, C and E are found decreased in type 2 diabetes and there is increasing evidence that antioxidants may have role not only in reducing development of diabetes and its complications, but also in improving glycaemic control. Several B vitamins e.g. Thiamine, Pyridoxine, Biotin, B_{12} are also found decreased in type 2 diabetes. Thiamine has beneficial role in diabetic nephropathy while Pyridoxine may have a role in the treatment of diabetic retinopathy. Metformin, when used for long term, has been found to cause deficiency of Folate and B_{12}. Vitamin D deficiency is considered a risk factor for the development of type 2 diabetes as well as its complications particularly cardiovascular ones; moreover, vitamin D supplementation has favourable effects on glycaemia. There are no current recommendations of routine supplementation of vitamins above the recommended dietary allowances either to prevent development of type 2 diabetes or to improve outcomes in people with type 2 diabetes unless there is underlying deficiencies. However, patients taking metformin for long time may need folic acid and B_{12} supplementation.

Introduction

Diabetes mellitus (DM) is a metabolic disorder of multiple aetiologies characterised by chronic hyperglycaemia together with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action or both. Worldwide most prevalent type of diabetes is type 2 diabetes. Diabetes is associated with the development of the specific micro- and macro-vascular complications. Vitamins have multi-dimensional roles in type 2 diabetes. Some of the vitamins are found to have preventive role; while several others have contribution in the development of diabetic complications. Supplementation of the vitamins may have positive effects on the development and progression of diabetes and specific diabetic complications. Several studies have found diminished levels of some of the vitamins in people with type 2 diabetes than in general population.

Antioxidants

The consequences and complications of diabetes are the result of an imbalance between free radical formation and their control by natural antioxidants[1–3]. So the vitamins with antioxidant function may have role in the pathogenesis of diabetes and its complications. Oxidative stress may contribute to the pathogenesis of type 2 diabetes by increasing insulin resistance or impairing insulin secretion[4]. Development of type 2 diabetes may be reduced by the intake of antioxidants in the diet[5]. Though diabetes management has largely focused on control of hyperglycaemia, the rising burden of this disease is mainly correlated to its vascular complications. Oxidative stress has also been suggested to be a common pathway for the pathogenesis of cardiovascular disease and other complications in diabetes[2,3,6]. Consequently, the question of whether antioxidants could have a beneficial effect on reducing the risk of these conditions, especially cardiovascular disease, has been intensively investigated. Antioxidants such as N-acetyl cysteine, vitamin C and α-lipoic acid have been found to be effective in reducing diabetic complications[7]. Diet rich in fruits can improve some antioxidants which are likely to reduce oxidative stress in type 2 diabetes and regular consumption of fruits can improve glycaemic status in these patients[8]. But it remains inconclusive whether it may be beneficial in preventing diabetic complications either by ingestion of natural antioxidants or through dietary supplementation[6,9].

Vitamin A

Vitamin A, its analogs and metabolites are collectively called retinoids[10]. Vitamin A has important role not only in the pancreas development and islet regulation, but also in adult pancreas[11,12]. In animal model, decreased pancreatic vitamin A caused increased α-cell to β-cell mass ratios, hyperglycaemia and hyperglucagonaemia which were restored by reintroducing dietary vitamin A[13]. Though some investigators found lower concentration of serum vitamin A and its binding protein, RBP, in patients with type 2 diabetes than in normal control subjects[14]; the data regarding serum vitamin A levels in these patients are ambiguous[15,16]. Retinol supplementation as applied to diabetes has not been explored to a large extent in humans, owing to a relatively recent elucidation of its role in type 2 diabetes. Intake of α- and β-carotene and lycopene has been shown to improve glucose metabolism in subjects at high risk of type 2 diabetes[17].

Vitamin C or Ascorbic Acid

Ascorbic acid acts a co-factor in a number of reactions, particularly acting as a potent antioxidant; in collagen, neuropeptide and carnitin synthesis; increasing iron absorption, inhibiting histamine release; and stimulating immune system[18]. Vitamin C level was found to be lower in type 2 diabetes cases in comparison to healthy controls[19–21]. Plasma vitamin C concentrations have been inversely correlated to glycosylated haemoglobin, fasting- and postprandial blood glucose and oxidative stress[22,23]. Higher plasma vitamin C levels and increased fruits and vegetables consumption have been found to reduce the risk of developing type 2 diabetes[24]. Therapeutic supplementation of vitamin C was found to improve not only blood glucose but also hypertension, lipid profile and urea nitrogen[25,26]. In a study, the incidence of diabetic retinopathy was 50% lower in subjects with a high fruit and vitamin C intake[27].

Vitamin E

Vitamin E, one of the most important antioxidant vitamins, protects the integrity of cell membranes by inhibiting lipid peroxidation. Vitamin E demonstrated beneficial effect in the prevention of type 2 DM[28]. Below-median plasma vitamin E levels has been found to be associated with a 3.9-fold higher relative risk of diabetes[29]. Moreover, people with diabetes were also found to have lower serum vitamin E level in comparison to healthy persons[20,21]. Vitamin E supplementation has shown to improve insulin sensitivity in overweight healthy subjects[30,31]. There is no proven beneficial effect of vitamin E supplementation in improving glycaemic control in people with type 2 diabetes. Vitamin E supplementation may decrease HbA1c in people with

inadequate glycaemic control with low serum levels of vitamin E[32]. A recent meta-analysis suggested that high-dosage (≥400 IU/day) vitamin E supplements may increase all-cause mortality and should be avoided[33].

Vitamin B Complex

Thiamine, Riboflavin, Niacin, Pantothenic acid, Pyridoxine, Biotin, Cobalamin and Folic acid are usually grouped as B vitamins, and most of them have been linked to type 2 diabetes.

Thiamine or B_1

Vitamin B_1 (Thiamin) is an essential co-factor in carbohydrate metabolism which may have an impact on glucose homeostasis. Several studies have shown reduced blood levels of thiamine in people with diabetes than in controls[34,35]. These low levels are thought to be a result of increased renal clearance[35]. Thiamine deficiency may augment hyper-glycaemia-induced tissue damage[34]. Thiamine supplementations have demonstrated positive effects on blood glucose[36,37]. Thiamine in high dose (300 mg/day) has shown to reduce urinary albumin excretion and may prevent and reverse early stage nephropathy[37,38]. Daily intake of thiamine was positively correlated with the circulating level of endothelial progenitor cells and vascular endothelial function in patients with type 2 diabetes[39]. High dose of thiamine therapy (70 mg/kg) prevented increase in plasma cholesterol and triglycerides in diabetes-induced rats but it did not reverse the decrease of high-density lipoprotein (HDL)[40]. Though in rat model benfotiamine, a thiamine derivative, showed improvement in diabetic peripheral neuropathic pain, its high dose long-term supplementation showed no significant effects on peripheral nerve function in patients with type 1 diabetes[41,42].

Niacin or B_3

Niacin or Nicotonic acid is a component of nicotinamide adenine dinucleotide (NAD) and NADH, which are essential for adenosine triphosphate (ATP) production and energy efficiency at the cellular level[43]. High-dose niacin is used to treat dyslipidemia as it decreases HDL cholesterol and triglycerides, while it increases HDL cholesterol level. It is often used in combination with other lipid lowering drugs e.g. statin. In a post hoc analysis, niacin supplementation was found to be associated with a modest increase in the risk of new-onset type 2 diabetes; but had a potential for reduction in cardiovascular (CV) risk which was independent of baseline glycaemic status[44]. In another study, 3 years use of niacin in people with normal baseline glucose was found to be associated with increased glycaemia and a risk of developing impaired fasting glucose, but not diabetes[45].

Pyridoxine or B_6

Pyridoxine act as a coenzyme for glucose phosphorylase that is necessary for the utilization of glycogen in liver and muscle, thus have an important role in glucose metabolism[46]. Patients with type 2 diabetes were found to have lower Pyridoxal-5′-Phosphate (PLP, the active form of B_6) in comparison to healthy controls[47,48], and the deficiency was more pronounced in patients with microalbuminuri[a47]. Long-term B_6 supplementation along with folic acid and B_{12} was not associated with reduction in developing diabetes[49]. The combination of pyridoxine with thiamine, but not alone, has been shown to decrease DNA glycation in leukocytes of patients with diabetes[50]. In an experimental model, pyridoxine supplementation increased insulin sensitivity and decreased insulin concentration with no effect on blood glucose levels[51]. B_6 deficiency was not found to be a factor in the aetiology of diabetic peripheral neuropathy and treating diabetic peripheral neuropathy with high dose vitamin B_6 or placebo resulted in a similar frequency of symptomatic improvement[52]. A six-month supplementation trial of B_6, Folate and B_{12} showed a decrease in retinal oedema and an increase in light sensitivity in patients with diabetic non-proliferative retinopathy[53].

Folate, Folic Acid or B_9

Folate is essential for synthesis for DNA and is an important co-factor for transamination in the conversion of amino acids, particularly homocysteine to methionine[54]. Like B_{12} deficiency, folate deficiency

can also result in hyper-homocysteinemia (a risk factor for cardiovascular disease) and supplementation of folic acid or B vitamins in a high-risk patient population significantly lowered homocysteine level, but this did not attenuate progression to type 2 diabetes[55]. Plasma folate level of patients with type 2 diabetes (both newly diagnosed and previously diagnosed) was significantly higher than that of subjects with normal glucose tolerance.[6]. As well as in the case of vitamin B_{12}, metformin may also cause folate deficiency[57]; and folic acid supplementation in diabetic men on metformin, showed an improvement in homocysteine levels, total antioxidant capacity and malondialdehyde[58]. A systematic review and meta-analysis revealed that folic acid supplements may decrease homocysteine levels, and there was a weak link with improved diabetes control[59]. The folate status could play a role in the development and progression of diabetic retinopathy[57], and positive effects on signs and symptoms of diabetic retinopathy have been found with supplementation of pyridoxine, folate and vitamin B_{12}[53]. Women with pre-existing diabetes contemplating a pregnancy should take 5 mg folic acid before conception and for the first 12 weeks of pregnancy for protection from neural tube defects of foetus[60].

Biotin

Biotin acts as a cofactor in biosynthesis and elongation of fatty acids, pyruvate carboxylase involved in gluconeogenesis, metilcrotonil CoA carboxylase essential for the degradation of leucine and propyonil CoA carboxylase[61]. Not much research has been done in the field of diabetes-biotin relationship. Serum biotin concentration in the type 2 diabetes patients was found significantly lower than that in the healthy controls and inversely correlated with the fasting blood glucose level. The oral administration of biotin, 9 mg daily, corrected the hyperglycaemia in patients with no change in their serum insulin level[62]. A study of biotin and chromium picolinate supplementation of type 2 diabetic rats has shown anti-diabetic effects[63]. In individuals with type 2 diabetes, this combination, administered as an adjuvant to current prescription anti-diabetic medication, improved glycaemic control in one study[64].

Cobalamin or B_{12}

Vitamin B_{12} acts as a co-factor in the methylation process of homocysteine to methionine; thus plays an essential role in maintaining the integrity of the nervous and haematopoietic systems[65]. B_{12} deficiency produces hyperhomocysteinemia which is an independent risk factor for atherosclerotic disease[66]. Vitamin B_{12} is needed for synthesis of DNA bases and for synthesis of neurotransmitters like serotonin and dopamine[67]. Vitamin B_{12} deficiency induced neuronal damage manifests as severe peripheral or autonomic neuropathy, subacute combined degeneration of the spinal cord, delirium and dementia[65,68]. Various studies have shown increased prevalence of vitamin B_{12} deficiency in patients with type 2 diabetes[69–72]. Metformin use has been implicated as a cause of vitamin B_{12} deficiency in patients with diabetes[70,71]; but vitamin B_{12} deficiency has also beenfound in patients not taking metformin[69]. Though some studies found low serum B_{12} levels among recently diagnosed patients with type 2 diabetes[72]; a recent study in Bangladesh revealed that newly diagnosed patients with type 2 diabetes before receiving any medication had sufficient B_{12} level[73]. Peripheral neuropathy (PN) caused by diabetes mellitus and B_{12} deficiency may produce overlapping clinical pictures. Moreover, nondiabetic neuropathies may be present in patients with diabetes and may be treatable[74]. Moreover, therapeutic supplementation with B_{12} or vitamin B complex mixtures containing B_{12} have shown significant improvement in symptoms of diabetic peripheral neuropathy[75,76].

Vitamin D

Vitamin D plays a major role in bone metabolism and in the regulation of intestinal absorption of calcium and phosphate. Vitamin D deficiency is thought to affect glucose metabolism, lower beta cell function, increased insulin resistance and glucose intolerance. Evidence generated from various epidemiological studies worldwide showed that a significant inverse relationship exists between vitamin D levels and risk for type 2 diabetes[77,78]. Vitamin D level was found to be lower in patients of type 2 diabetes than the

healthy controls[79,80]. Vitamin D supplementation has been found to reduce insulin resistance and fasting plasma insulin but has demonstrated variable results on fasting plasma glucose and HbA1c[81–84]. High dose intramuscular administration of Vitamin D has been found to have significant improvement in the symptoms of painful diabetic peripheral neuropathy[85].

Recommendations of diabetes guidelines

There are no current recommendations of routine supplementation of vitamins above the recommended dietary allowances (RDAs) to improve outcomes in people with diabetes unless there is underlying deficiencies[86,87]. And long-term therapeutic use of antioxidant vitamins are not recommended as there may be safety concerns[86]. As metformin has been linked with B_{12} deficiency, B_{12} levels should be checked periodically in patients on metformin therapy[86,87]. The higher prevalence of vitamin D deficiency and insufficiency warrants case finding by measurement of 25-hydroxyvitamin D levels in population at risk[87].

Conclusion

Due to lack of clear-cut benefits of routine supplementation and the risk of potential toxicity, vitamin supplementations should not be taken routinely by the patients with type 2 diabetes. The best strategy should be to consume adequate quantities of those foods that contain vitamins in sufficient amounts in order to guarantee an appropriate nutritional status.

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