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Vitamins and Type 2 Diabetes Mellitus

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Abstract: The present review evaluates the relationship between type 2 diabetes mellitus and individual or combined vitamins. Antioxidant vitamins A, C and E are found decreased in diabetic subjects, possibly due to an increased need to control the excessive oxidative stress produced by abnormalities in glucose metabolism. On the other hand, retinol binding protein exerts a modulating effect, as it has adipokine functions. With respect to the B group vitamins, thiamin, pyridoxine and biotin have been found decreased but the mechanisms are not clear, however supplementation has shown some improvement of the metabolic control in diabetic patients. The absorption of folic acid and vitamin B_{12} is importantly decreased by the prolongued use of metformin, which is the first choice drug in uncomplicated diabetes, thus these two nutrients have been found deficient in the disease and most probably need to be supplemented regularly. On the other hand, vitamin D is considered a risk factor for the development of diabetes as well as its complications, particularly cardiovascular ones. Although some studies have found an association of vitamin K intake with glucose metabolism further research is needed. Studies on the use of multivitamin supplements have shown unconclusive results. After reviewing the evidence, no real recommendation on the use of vitamin supplements in type 2 diabetes mellitus can be issued, however patients using metformin during prolongued periods may need folic acid and vitamin B_{12}.

Keywords: Antioxidants, type 2 diabetes mellitus, vitamins.

INTRODUCTION

Type 2 Diabetes Mellitus is a multifactorial disease that is typically linked to energy metabolism, particularly carbohydrate and fat management in the organism, however, most micronutrients are also involved in some way either as part of the cause or effect of this chronic pathology. The consequences and complications of diabetes are the result of an imbalance between free radical formation and their control by natural antioxidants [1]. Thus, those micronutrients that have an antioxidant function are very important in the development of the disease and its complications, while other non-antioxidant vitamins have also shown a relationship.

VITAMINS AND DIABETES

Vitamin A or Retinol

The term vitamin A comprises various chemical components with a structural and functional similarity. The most active form is retinol, present in animal tissues, esterified with long chain fatty acids. Carotenes that are present in vegetable tissues are enzymatically hydrolyzed into retinal and converted to retinol in the enterocyte. Some xanthines are also converted into retinol. Vitamin A participates in multiple metabolic processes such as genetic expression, cellular differentiation and growth, having a very important role in the immune system, fetal development, sight, taste, hearing, appetite and spermatogenesis. Retinoids have a very important function as antioxidants, thus helping to maintain the organism's homeostasis when subjected to various forms of stress [2].

It has also been postulated that retinoids may be involved in hepatic lipid metabolism, adipogenesis as well as pancreatic β -cell function. While retinol binding protein (RBP), a protein that transports retinoids has an important effect on insulin sensitivity, acting as an adipokine [2]. A mouse model that lacks the gene for retinaldehyde dehydrogenase 1, (Raldh1a1), that participates in the generation of retinoic acid to be utilized in lipid metabolism, shows better lipid profiles than mice with adequate Raldh1a1 production [3].

Even though further research is needed to identify the precise mechanisms by which retinoids and their pathways effect carbohydrate and lipid metabolism in health and disease, it is clear that adequate vitamin A intake, concentrations reserves should be maintained in the normal healthy individual and particularly in those subjects with chronic diseases that involve carbohydrates and lipids.

Very old age type 2 diabetic patients have lower plasma concentrations of vitamin A and carotenoids [4]. On the other hand, serum retinol concentrations have been found normal in adult diabetic subjects, with lower carotene and higher RBP than controls [5]. A nested case-control study showed that high levels of plasma beta-carotene are associated with lower risk of diabetes before adjusting for cardiovascular risk factors [6]. Urinary excretion of retinol has also been found increased in diabetic subjects vs controls in association with diagnosis of nephropathy [7].

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Retinol binding protein (RBP), particularly RBP4, together with transtyrethin (TTR) transports retinol from the liver to peripheral tissues by binding to specific cell receptors and has been linked to lipid metabolism and insulin sensitivity. Retinol status modifies RBP4 expression, and their ratio is used as a marker for retinol sufficiency [8]. Increased plasma concentrations of RBP4 have been observed in diabetic subjects also associated to plasma TTR levels [9]. Increased concentrations of RBP4 have been shown to lead to low glucose uptake by skeletal muscle and high glucose liver production in mice, with a consequent increase in insulin resistance [10].

Complications of diabetes include retinopathy, cardio-vascular disease, nephropathy and non-alcoholic fatty liver, among others; some studies have linked RBP4 to these diseases, however the results are still controversial.

Akbay *et al*. [11] compared RBP4, retinol and TTR levels in diabetic and healthy BMI-matched subjects; they found no differences between those who had retinopathy of macrovascular disease, with lower values of all three markers associated to micro and macro-albuminuria, concluding that retinopathy and cardiovascular disease are not related to RBP4 status. On the other hand, after measuring serum RBP 4 in diabetic patients with and without non-alcoholic fatty liver disease (NAFLD), Wu *et al.* [12] found increased levels of RBP4 in subjects with NAFLD, particularly in males, suggesting a participation in the pathogenesis of the disease. An increase in the risk for type 2 diabetes in the Dutch population has been associated to the RBP4-803A allele, but the authors indicate that this is not clearly related to retinoid status [13].

Additional to retinol blood concentrations or urinary excretion, an important measurement of retinol metabolism its relation to retinol binding protein (RBP) concentrations, and although this ratio is high in diabetic patients, the cause of this is not yet clear. For instance, Erikstrup *et al.* [14] measured RBP and retinol concentrations in type two diabetic, normal or impaired glucose tolerant subjects with or without obesity; diabetic subjects had lower levels of RBP and retinol as well as a higher RBP to retinol ratio. Whereas retinol and retinol/RBP ratio have also been found higher in diabetic than in control subjects, implying and excess of retinol in these type of patients [15]. The administration of retinoic acid in diabetic mice has been demonstrated to reduce RBP4, decreasing the retinol to RBP4 ratio, improving insulin sensitivity [16].

B Vitamins

Thiamine, Riboflavin, Niacin, Panthotenic acid, Pyridoxine, Biotin, Cobalamin and Folic acid are usually grouped as B vitamins, and although most of them have been linked to type 2 diabetes mellitus, there is not much information on Riboflavin or Panthotenic acid.

Thiamine or B_1

Thiamine acts as a coenzyme in the active transference of aldehyde groups and glycation, as well as in neuro-transmission and neuronal conductivity, and may have effects on the development of various diabetic complications [17].

Polizzi *et al*. found increased DNA-glycation in leukocytes from diabetic patients with nephropathy, which were decreased after a 5-month thiamine and pyridoxine supplement trail [18].

Low levels of thiamine and increased renal clearance have been found in both Type 1 and type 2 diabetic patients [19]. In a cross-sectional comparative study of normal controls, microalbuminuric and macroalbuminuric DM patients, thiamine was lower in diabetics, with a progressive decrease with albuminuria, more so in macroalbuminuria. A negative correlation between thiamin and lipid profile was observed in microalbuminuria [20].

Various thiamine supplementation studies have been conducted with positive results. For instance, the administration of thiamine during one month has been shown to decrease glucose and leptin in diabetic patients when compared to controls [21]. Rabbani *et al.* [22] conducted a double-blind placebo-controlled study of diabetic patients with microalbuminuria with a consequent reduction in urinary albumin excretion after a three-month intervention.

Pyridoxine or B_6

Vitamin B_6 comprises a group of three related compounds: Pyridoxal, pyridoxine and pyridoxamine, and their corresponding phosphorilated forms. The active form of this vitamin is pyridoxal-5'-phospate (PLP). It is an aminotransferase, also acting as a coenzime for glucose-phosphorilase for the utilization of glucogen in liver and muscle, thus participating actively in glucose metabolism [23].

Newly diagnosed diabetic patients have lower PLP concentrations when compared to non-diabetic subjects [24] Even though a long-term placebo-controlled trial of combined folic acid, pyridoxine and B12 supplementation found no differences in the risk of developing type 2 diabetes in women with high risk of CVD, although homocysteine levels were lower in the supplemented group [25].

Even though vitamin B6 status is not clearly associated to the development of type 2 diabetes mellitus there is evidence that its deficiency may be effecting negatively the progression of some of its complications once the disease is present. In this sense, an experimental model of pyridoxamine supplementation showed decreased insulin concentration and insulin sensitivity with no effect on blood glucose levels [26]. In humans, the combination of pyridoxine with thiamine, but not alone, has been shown to decrease DNA glycation in leukocytes of diabetic patients [18]. A six-month supplementation trial showed a decrease in retinal edema and an increase in light sensitivity in diabetic patients with non-proliferative retinopathy [27].

Niacin or B_3

Nicotinic acid is a component of NAD and NADH, which are essential for ATP production and energy efficiency at the cellular level [28]. Not much research has been done in

relation to diabetes, however niacin supplementation has been found to increase HDL-cholesterol, decreases tryacilglycerides and LDL cholesterol [29]. It is used as a lipid-lowering drug either alone or in association with other lipid-lowering drugs, however its effect on reducing cardiovascular disease is still not clear [30]. These lipid-modifying effects may have a role in diabetes-induced atherosclerosis; cell-adhesion molecules (CAM), which mediate processes that result in atherogenesis, the expression of CAM's is increased in diabetes. Niacin supplementation has been found to reduce monocyte adhesion to endothelial cells from diabetic patients [31]. On the other hand, negative effects have been identified with niacin supplementation, as with the Coronary Drug Project, where niacin was supplemented in men with previous myocardial infarction and normoglycemia or impaired fasting glucose (IFG), showed a slightly increased risk for type 2 diabetes mellitus in subjects with IFG [32]. While Zhou *et al.* [33] suggest that nicotinamide excess from an increase in niacin, thiamin and riboflavin population intake, through food fortification, may be associated with oxidative stress and insulin resistance, thus exerting a negative effect on the development of complications related to type two diabetes mellitus.

Biotin

Biotin is a cofactor for carboxilases such as acetyl CoA carboxylase that participates in biosynthesis and elongation of fatty acids, pyruvate carboxylase involved in gluconeo-genesis, metilcrotonil CoA carboxylase essential for the degradation of leucine and propyonil CoA carboxylase. Although mammals do not produce biotin, its deficiency is rare due to its presence in a wide variety of animal and plant origin foods [34]. Not much research has been done in relation to type 2 diabetes mellitus. A study of biotin and chromium piccolinate supplementation of type 2 diabetic rats resulted in anti-diabetic effects, apparently preventing insulin resistance in skeletal muscle by an increase in the expression of the glucose transporter protein GLUT4 [35, 36].

Cobalamin or B_{12}

Vitamin B12 is a coenzyme in the single-carbon metabolic pathways, involved in the synthesis of methionine, pyrimidine and purine bases. Its deficiency due to DNA damage or faulty repair is involved in cancer, vascular diseases and some birth defects, while a consequent hyperhomocysteinemia, also related to folic acid deficiency; it has been identified as a risk factor for hypertension and atherosclerosis [37].

The Women's Antioxidant and Folic Acid Cardiovascular Study, where women with or without cardiovascular disease risk factors were supplemented with folic acid, pyridoxine and B12 or placebo during approximately 7 years, showed no differences in the incident development of type 2 diabetes mellitus [25]. While Movva S, *et al*. suggest that subjects at risk of developing diabetes should be screened specifically for the MTHFR C6771 mutation, as this polymorphism confers and increased risk of developing the disease, and vitamin B12, B6 and folic acid supplementation might help reduce the risk in these individuals [38]. However, Rafnsson *et al*. [39] concluded in their systematic review of cohort studies that there is scarce evidence that cobalamin deficiency can be considered a risk factor for mortality from cardiovascular diseases or diabetes, and that supplementation is not necessary. Thus, the use of profilactic vitamin B12 to decrease the risk of developing diabetes is still controversial.

On the other hand, type 2 diabetes mellitus is an oxidative stress disease; vitamin B_{12} and folic acid deficiencies in diabetic subjects have been found associated to oxidative stress, in relation to a resulting hyperhomocysteinemia [40]. As a result of this association, it is conceivable that vitamin B_{12} deficiency should be considered a risk factor for diabetic complications. One of the most frequent complications related to type 2 diabetes mellitus is peripheral neuropathy, and its development has been associated to hyper-homocisteinemia, which is more frequently found in patients with diabetes [41-45].

Retinal edema and increased light sensitivity in diabetic retinopathy have been found to improve with the supplementation of pyridoxine, folate and B12 combined supplementation [27] also in association with hyper-homocysteinemia [46]. Type 2 diabetic Nigerian individuals showed higher levels of total homocysteine and low plasma concentrations of vitamin B12 than normal controls [47]. Atherosclerosis is another frequent complication related to diabetes, Shargorodsky *et al*. [48] found a significant association between increased levels of homocysteine and arterial stiffness.

Vitamin B_{12} deficiency is not common in the general population as it is present in most animal food sources, being frequently present in strictly vegetarian individuals. However, the prolonged use of metformin, the drug of choice in uncomplicated diabetes causes cobalamin malabsorption, increasing the risk of deficiency [49-54]. For instance a cross-sectional study found lower plasma levels of vitamin B_{12} in type 2 diabetic patients who were using metformin, while a retrospective review of medical records also showed this association [55, 56] Short term metformin therapy has been found to decrease cobalamin in elderly patients [57] On the other hand, vitamin B12 deficiency has also been reported in diabetic patients not taking metformin [58]. Diabetic subjects who were using metformin showed worse cognitive performance than those without metformin or non-diabetic individuals. The authors suggest the use of Vitamin B12 supplementation to improve cognitive performance [59]. Obeid *et al*. measured intracellular and extracellular markers of vitamin B12 metabolism. They found normal extracellular but decreased intracellular vitamin B12 in type 2 diabetic subjects, whereas metformin use reversed the effect [60].

Supplementation studies have shown a rapid recovery from this deficiency and its effects in diabetic subjects [61-64]. Data from NHANES also showed an association between metformin therapy and vitamin B12 deficiency in diabetic subjects, which led to the recommendation of supplementation with the amount available in general multivitamins, however, this is not necessarily monitored or practiced regularly [65-67]. A meta-analysis of seventeen studies showed that supplementation with lipoic acid and methylcobalamin improve nerve conduction velocity and diabetic neuropathy [68].

After reviewing the information, we can conclude that diabetic patients who are using metformin are at a higher risk of developing vitamin B12 deficiency and its consequent hyperohomysteinemia that may lead to neuropathy and other complications, thus, it seems wise to recommend cobalamin supplementation in these subjects.

Folate, Folic Acid or B_9

The term folate includes 150 components of the family of pteroilglutamate, which participate in cell replication by enzymatic activity in purine base synthesis for DNA and are an important co-factor for transamination in the conversion of aminoacids, particularly homocysteine to methionine. Folates are present in animal tissue, leafy vegetables, legumes and nuts and their deficiency has been associated to megaloblastic anemia, neural tube defects, cardiovascular disease, cancer and senile dementia [69].

The implication of folic acid in the pathogenesis of type 2 diabetes is associated to vitamin B12 deficiency and its consequent hyperhomocysteinemia, and although its deficiency is not widespread, supplementation trials have been carried out in diabetic patients. A case-control study showed that low intakes of folate and B-12 in type 2 diabetic patients were associated with hyperhomocysteinemia [36] DNA damage as measured by the presence of micronuclei can be reverted by folic acid supplementation, thus reducing the effect of oxidative stress in diabetic patients [70]. Additionally, folate supplementation has also been shown to improve glycemic control by reducing glycosylated hemoglobin fasting blood glucose, serum insulin and insulin resistance as well as homocysteinemia in type 2 diabetes patients [71]. Positive effects on signs and symptoms of diabetic retinopathy have also been found with supplementation of pyridoxine, folate and vitamin B_{12} [27].

As well as in the case of vitamin B_{12}, metformin may also cause folate deficiency; a double blind randomized clinical trial of 8-week supplementation with folic acid of diabetic men on metformin, showed an improvement in homocysteine levels, total antioxidant capacity and malondialdehyde [72].

Vitamin C or Ascorbic Acid

Asorbic acid participates as a co-factor in multiple reactions, particularly acting as a potent antioxidant, in collagen, neuropeptide and carnitin synthesis, increasing iron absorption, inhibiting histamine release and stimulating the immune system. The main cause of increased requirements of vitamin C in type 2 diabetes mellitus is the high levels of oxidative stress caused by hyperglycemia [73].

Vitamins C and E concentrations as well as antioxidants have been found reduced in diabetic patients with respect to healthy controls [74]. Newly-diagnosed cases of type 2 diabetes mellitus have been found to increase lipid peroxidation and decrease antioxidant enzymes as well as vitamins C and E during the first two years of the disease [75].

Plasma vitamin C concentrations have been inversely correlated to glycosylated hemoglobin and fasting and postprandial blood glucose and oxidative stress, but not on lipid profiles [76, 77]. Diabetes has also been associated to periodontal disease and vitamin C supplementation together with dental maneuvers has been shown to improve chronic periodontitis in newly diagnosed type 2 diabetic subjects [78]. Vitamin C has also been shown to reduce anxiety levels but not stress and depression scores in diabetes [79]. Three month supplementation of vitamins C and E decreased hypertension, blood glucose while increasing superoxide dismutase and glutathione levels [80].

Vitamin D

Vitamin D or calciferol is an unsaponifiable heterolipid of the steroid group, it has two basic forms, D_2 (ergocalciferol) found in plants as a product from ultraviolet B radiation on ergosterol; and D_3 which originates as dehydrocholesterol produced by ultraviolet B radiation, after becoming pre-vitamin D_3. Vitamin D_3 can be synthesized in the human epidermis or ingested through fish oil, egg yolk, fortified foods or supplements [81].

Vitamin D is converted into 25-hydroxivitamin D [25 (OH)D] in the liver, which is the main circulating metabolite. When it is measured it reflects intake and endogenous production; the active form is 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] or dihydroxycholecalciferol, which is a hormone produced mainly in the kidney and regulated by parathyroid hormone, calcium and phosphorous concentrations [82].

Vitamin D receptors are present in most tissues, including the endothelium, vascular smooth muscle and myocardium; the first two are able to convert 25(OH)D in $1,25(OH)_2D$. Directly or indirectly $1,25(OH)_2D$ has a role in the regulation of many genes, such as those involved in insulin production and development of vascular smooth muscle cells, which is the reason it is thought to be an important contributing factor to cardiovascular diseases [83].

Epidemiologic data suggest that 9 out of 10 cases of T2DM can be attributed to modifiable lifestyles [67, 68], however, changes in these are hard to accomplish and maintain in the long term. There is recent evidence in humans and animal models suggesting that vitamin D may play an important role in modifying the risk of diabetes [84, 85].

Vitamin D receptors are present in pancreatic β and in immune system cells. Additionally, its role in the regulation of calcium absorption is well known; vitamin D participates in the activity of β-cell endopeptidases dependent on calcium and can act through two main pathways, directly inducing β-cells to secrete insulin through an increase in intracellular calcium concentration through Ca channels or by mediating β-cell calcium-dependent activation to facilitate conversion of pro-insulin to insulin [86, 87].

The role of vitamin D in the function of pancreatic cells can be mediated by the union of 1,25-dihydroxyvitamin D to its receptors in the beta cell. Alternatively, vitamin D can work through the activation of 25 hydroxyvitamin D (25OHD) by 1-alpha- hydroxylase expressed in pancreatic beta cells, directly improving insulin sensitivity by stimulating insulin receptor expression and the activation of PPAR-δ (peroxisome proliferator activated receptor delta), which has been associated to the regulation of fatty acid metabolism in skeletal muscle and adipose tissue [88-91].

The expression of calbindin-D28K (vitamin D dependent on the union of proteins and calcium) has demonstrated a protective effect on beta cells from cytokine mediated cell death, reducing the risk of T2DM [86]. There are few studies in humans associating vitamin D and chronic inflammatory status of T2DM patients, however, the evidence suggests that vitamin D can improve insulin sensitivity and promote pancreatic β-cell survival by modulating the effects of cytokines and nuclear transcription factors such as NF-κB [92].

On the other hand vitamin D deficiency has been associated with obesity, although the mechanism is already unclear, it supposed that due to vitamin D accumulation in the adipose tissue, an increment in the proportion of the body fat percentage could decrease its bioavailability [93].

Some cohort studies in multi-ethnic populations have reported an association between low vitamin D status and the risk of T2DM [94-99]. Additional studies have found associations between serum vitamin D levels, insulin resistance and β-cell dysfunction. Even though this association has been specifically observed in females, probably more studies are necessary in order to establish a relation between sex hormones, vitamin D, adipose tissue and β-cell function [100-104].

There is no consensus about vitamin D supplementation; clinical studies have examined the effect of this vitamin and related indicators in different T2DM populations. These studies were carried-out from 2 months to 7 years, while vitamin D doses were between 400 to 200,000 IU/day; some have reported improvements in clinical parameters like central glycaemia [105], insulin sensitivity and even lipid profile, others have shown improvement of risk factors for complications such as endothelial function [104-106]. But some interventional trials have demonstrated that vitamin D supplementation might improve the inflammatory status in diabetic patients by modifying adipokine concentrations and diminish pro-inflammatory cytokines like TNF-α, some other parameters like natriuretic peptide concentrations and blood pressure, but the supplementation does not improve metabolic parameters [107-109]. Other studies showed no effect on reduction of diabetes incidence even after years of follow-up [110-118].

Vitamin D deficiency is a risk factor for cardiovascular disease in diabetes [119-123]. Elderly patiens with type two diabetes are prone to develop vitamin D deficiency, which is very common in European countries [124], associated to inadequate intake, low sun-exposure and age-related alterations in absortion, synthesis and metabolism of the vitamin [125]. There is a positive association between 25-hydroxy vitamin D and 1,25-dihydroxyvitamin D and the development of type 2 diabetes in this group of patients [126]. While the deficiency also represents a high risk for cardiovascular mortality, as well as some autoimmune diseases, Alzheimer's disease and even colorectal and breast cancers [127].

Vitamin E

Tocopherols and tocotrienols form the vitamin E complex, however, only α-tocopherol is present in human plasma and as all the other forms are not exchangeable, they are not considered for human health. Vitamin E has a very important antioxidant role in the organism although it can be substituted by other antioxidants. It also participates in additional processes such as activity of microsomial enzymes and protein kinase C; induction of apoptosis in tumoral cells; inhibition of platelet aggregation; modulating the immune system; gene expression; cell-membrane stability, and erythrocyte formation [128].

Among other vitamins, vitamin E has been found decreased in patients with type 2 diabetes mellitus [74]. High concentrations of α-tocopherol have been associated with decreased risk of diabetes in the general population, but not in middle-aged smokers [6, 129].

The effect of vitamin E on risk of diabetes and its complications is most probably due to its role as antioxidant; a decrease in plasma tocopherol has been observed in diabetic subjects with longer duration of the disease [4, 47] related to lipid peroxidation and cardiovascular complications [130]; as well as with total cholesterol and central type obesity [131]. However, plasma tocopherol was not associated with mortality in hemodyalisis diabetic patients [132].

Some supplementation studies with vitamin E as well as other vitamins have shown positive effects on hypertension, blood glucose and antioxidant status, HDL function in haptoglobin 2-2 genotype carriers, but not with those with the haptoglobin 2-1 gene [80, 133-136]. However, other studies have shown no effect on lipid profile or insulin sensitivity [137-139].

Vitamin K

Phylloquinone and menaquinone form the vitamin K complex, and are present in many animal and vegetable foods. Seven coagulation proteins, as well as γ-glutamil-carboxilase, γ- carboxyl-glutamate acid and the protein in the matrix of γ-glutamic acid, present in bone metabolism, are dependent on vitamin K [140].

Various studies have associated vitamin K intake with insulin sensitivity, glucose metabolism and thus with diabetes. For instance, the PREDIMED study in Spain evaluated dietary vitamin K intake and markers related to diabetes; baseline values showed no associations, however, after one year of follow-up, those subjects with the highest intakes had lower ghrelin, glucose-dependent insulinotropic peptide, glucagon-like peptide-1, IL-6, leptin, TNF and visfatin plasma concentrations. In this same study, a lower risk for diabetes mellitus was observed with increased vitamin K intakes [141, 142]. A retrospective Dutch database analysis of vitamin K intake and incidence of type 2 diabetes mellitus after approximately 10 years of follow-up found that phylloquinone and menaquinone intakes were inversely associated with risk of developing diabetes [143].

Rees *et al.* [144] in a systematic review of studies that evaluated associations of vitamin K deficiency or intake with cardiovascular disease, type 2 diabetes mellitus and the metabolic syndrome, concluded that there is no evidence of an effect of phylloquinone, but menaquinones may have a role in decreasing risk.

Multivitamins

Most of the studies we have reviewed until this point refer to individual vitamins; however, there has also been research on the use of multivitamin supplements and their effect on different outcomes in type 2 diabetes patients. We believe that this type of research should be analyzed separately, due to the possible interactions between nutrients.

The 2010 Dietary Guidelines Advisory Committee did not recommend the use of multivitamins for the general healthy population, but they indicated that some specific diseases might benefit from supplementation [145]. This is the case with type 2 diabetes mellitus and several studies have been undertaken to evaluate the effect of multivitamin and mineral supplementation. For instance, the use of a daily vitamin-B group and antioxidant vitamins in diabetic patients resulted in an increase in folic acid and α-tocopherol concentrations, with a reduction of homocysteine. Supplemented patients also reported having a non-significant decrease in number of infections, when compared to the placebo group [146]. A single-blind randomized study of diabetic patients supplemented with zinc sulfate plus a multivitamin/mineral preparation, only multivitamin/minerals or placebo during 4 months, showed a significant reduction in blood glucose, glycosylated hemoglobin and improvement of lipid profile [147]. Long-term use of dietary supplements, including multivitamin/mineral, B-complex, vitamin C, carotenoids, vitamin E, calcium with vitamin D, omega-3 fatty acids, flavonoids, lecithin, alfalfa, coenzyme Q10 with resveratrol, glucosamine, and a herbal immune supplement from the NHANES and NHANES III, showed better conditions for C-reactive protein, HDL cholesterol, triacylglycerides, serum homocystein, blood pressure and incidence of diabetes [116]. Diabetic patients who had been using multivitamins for six months had lower C-reactive protein concentrations, and an inverse association with vitamins B_6 and C [148].

On the other hand, there are also studies that show opposing results. A prospective evaluation of the multivitamin supplement use from the National Institutes of Health-American Association of Retired Persons Diet and Health Study, found no association with risk of developing diabetes [149].

One-year supplementation with multivitamins and minerals reduced the incidence of infections in type 2 diabetes patients with subclinical micronutrient deficiency [150]. Martini *et al*. [151] concluded that the use of vitamin B complex, antioxidants (vitamin A, C, E and carotenoids), calcium, vitamin D, vitamin K, magnesium, sodium, and potassium is not strongly associated to glucose metabolism so as to recommend multivitamin or mineral supplementation above the normal recommendations for these nutrients. The current evidence does not support the use of high doses of antioxidants on the prevention and treatment of diabetes and its complications [152].

CONCLUSIONS

Even though vitamins exert important effects on risk of diabetes mellitus as well as its progression and complications, there is not enough evidence in most cases to suggest individual or multivitamin supplementation in the general diabetic population. The best recommendation should be to consume adequate quantities of those foods that contain vitamins in sufficient amounts in order to guarantee an appropriate nutritional status. In this sense, it is necessary to undertake dietary evaluations so as to identify specific intake deficiencies and establish recommendations. The use of supplements carries the risk of excess or toxicity with respect to some vitamins; these negative effects are practically non-existent when whole diet is considered. However, there is enough scientific evidence to recommend the supplementation of vitamin B12 in those patients with type 2 diabetes mellitus, who are being treated with metformin, to reduce the risk of developing neuropathy and its consequences.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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