

Effects of vitamins C and D in type 2 diabetes mellitus

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Abstract: Scurvy and rickets are largely considered historical diseases in developed countries. However, deficiencies in vitamins C and D are re-emerging due to increased consumption of processed foods and reduced fresh foods in the Western diet, as well as to an indoor sedentary lifestyle away from sun exposure. These dietary and lifestyle factors also predispose one to diabetes and metabolic syndrome. Our understanding of the potential roles of vitamin C (an antioxidant) and vitamin D (a biologically active hormone) in disease is increasing. In this review, we present observational, interventional, and mechanistic studies that examine the potential links between vitamins C and D in reversing defects in glucose homeostasis and the prevention of type 2 diabetes. Studies suggest an association between vitamin C deficiency and diabetes. An association between vitamin D and insulin resistance has been well described; however, the role of vitamin C and D supplementation in diabetes and its prevention requires further controlled trials.

Keywords: glucose homeostasis, diabetes, insulin resistance, vitamin C, vitamin D

Introduction

Nutrients play essential roles in health and the prevention of disease. Nutrients, including vitamins, are vital to cardiovascular health (ie, vitamin B1), nerve function (ie, vitamins B6 and B12), the production of red blood cells (ie, folate and vitamin B12), and coagulation (ie, vitamin K), among many other functions.¹ Scurvy and rickets were largely thought to be conditions of historical interest in developed countries; however, deficiency in vitamins C and D are re-emerging due to increasingly inadequate carbohydrate- and fat-based Western diets and sedentary, indoor living.¹ These same phenomena are contributing to the surging prevalence of obesity, metabolic syndrome, and diabetes. Early evidence suggests that vitamin D deficiency may contribute to diabetes, and that vitamin D repletion may ameliorate abnormal glucose homeostasis. Low vitamin C is associated with an increased risk of the future development of diabetes. It is likely that low vitamin C is a marker of a less healthy lifestyle, a well-known risk factor for diabetes.

Vitamin C is an antioxidant, and the structural similarity between vitamin C and glucose makes it of interest in diabetes.² Oxidative stress can lead to disturbed glucose metabolism and hyperglycemia.³ Therefore, a benefit of antioxidants to prevent diabetes or to achieve positive outcomes in type 2 diabetes mellitus (T2DM) is biologically plausible.

Vitamin D plays a vital role in whole-body calcium homeostasis by exerting classic effects on the duodenum, bone, and kidney.^{4,5} Vitamin D may also alter intracellular

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calcium signals and thus plays a role in pancreatic insulin secretion and insulin sensitivity, both of which relate to calcium levels. It therefore has potential in the prevention of T2DM. The role of vitamin D in insulin resistance has been studied extensively, and vitamin C is another vitamin for which studies have demonstrated significant associations with diabetes.^{6,7} This review explores the observational, interventional, and mechanistic studies that address the effects of vitamins C and D in T2DM.

Effects of vitamin C in diabetes Physiology and vitamin C deficiency

Vitamin C, also known as ascorbic acid, is a cofactor in multiple enzymatic reactions including collagen synthesis.⁸ Humans are unable to produce vitamin C due to the absence of the enzyme, L-gulonolactone oxidase, which catalyzes the final step in the synthesis of ascorbic acid;⁹ therefore, it is an essential nutrient in humans. Vitamin C acts as a reducing agent in free radical-mediated oxidation processes; therefore, it can act as an antioxidant.⁹ Deficiency of vitamin C results in the defective formation of collagen and connective tissues in the skin, cartilage, dentine, bone, and blood vessels.

In its most severe form, vitamin C deficiency results in scurvy, which is uncommon in developed nations due to the inclusion of fresh fruits and vegetables in the diet.¹ Nevertheless, lesser degrees of vitamin C deficiency were found to be common among healthy adults in the United States (National Health and Nutrition Examination Survey [NHANES] 2003–2004: 7.1%).¹⁰ Smokers and people in lower-income groups were at increased risk of deficiency. Other classic risk factors include alcoholism and renal failure.

Though diabetes is not traditionally considered a risk factor for vitamin C deficiency, patients with diabetes should all receive dietary advice about healthy eating and vitamin C dietary sources, including fresh fruits and vegetables. The recommended dietary intake of vitamin C is 45 mg per day for adults.¹ There are some data suggesting that people with diabetes may have increased cellular uptake and turnover of vitamin C that would necessitate increased intake, and they also have an increased risk of deficiency.¹¹

Observational studies

The effects of vitamin C in diabetes have been an area of interest for over 50 years. A review of 23 observational studies looking at the vitamin C status of people with diabetes published between 1935 and 1996 found that people with diabetes have at least 30% lower vitamin C concentrations than do people without diabetes.¹¹ However, there was heterogeneity

among the studies in terms of the methods used to measure vitamin C status, and subjects were unmatched on important covariates such as dietary intake of vitamin C, sex, smoking status, and acute illness.

Observational data from NHANES 1988–1994 identified that people with newly diagnosed diabetes had significantly lower serum vitamin C concentrations than did people without diabetes; however, no difference was seen after adjusting for the dietary intake of vitamin C.⁶ On the other hand, among those with a similar dietary intake of vitamin C, those with diabetes of 2 months to 25 years' duration did have lower levels of vitamin C when compared to controls.^{6,12,13} In the Finnish Mobile Clinic Health Examination Survey conducted during 1966–1972, the association between low vitamin C levels and diabetes was also not demonstrated to be due to low dietary vitamin C.¹⁴ This prospective study estimated total habitual food consumption in the previous year, and it examined the incidence of diabetes during a 23-year follow-up period. About 380 cases of diabetes were identified, but vitamin C intake was not associated with the risk of T2DM.

In a cross-sectional study where dietary vitamin C intake was the same, lower vitamin C levels in people with diabetes were seen as a consequence of diabetes itself and not due to the inadequate dietary intake of vitamin C.¹⁵ In a nested case-control study in Korea,¹⁶ there was no difference in dietary vitamin C intake between those with diabetes and controls matched for age, sex, drinking status, and smoking status. Interestingly, however, nonsmoking individuals with a new diagnosis of T2DM had lower serum vitamin C levels ($22.3 \pm 16.8 \mu\text{mol/L}$) than did controls ($26.3 \pm 17.0 \mu\text{mol/L}$) ($P < 0.01$).¹⁶ Among smokers, there was no difference between serum vitamin C levels in those with diabetes and controls. Therefore, smoking – a known trigger of vitamin C deficiency – appears to modify the association between vitamin C and diabetes incidence.

An English population-based prospective cohort study of 25,639 volunteer participants demonstrated a strong inverse association between plasma vitamin C levels and incident diabetes after 8–12 years with a dose–response effect.¹⁷ A 29% reduction was found in diabetes risk per $19.87 \mu\text{mol/L}$ (0.35 mg/dL) change in vitamin C level, which was adjusted for important covariates including the use of vitamin supplements. However, vitamin C may actually be a marker of other protective factors found in fruits and vegetables that may decrease the risk of T2DM.¹⁸

An association between vitamin C levels and glycaemic control was assessed in a cross-sectional study of people

with diabetes, which identified a weak, negative correlation between hemoglobin A_{1c} (HbA_{1c}) and vitamin C levels.¹⁹ The relationship between vitamin C and glucose levels was also demonstrated in a large sample of US adults without a history of diabetes from NHANES 2003–2006, in which serum vitamin C concentrations were inversely associated with HbA_{1c} levels.²⁰ An observational study on the use of vitamin C supplements demonstrated that a significantly lower risk of diabetes was associated with the use of daily vitamin C supplements when compared to nonusage.²¹ The potential benefit of a vitamin C supplement was limited to those who did not take a multivitamin or those who had a lower dietary intake of vitamin C. However, the observational nature could not demonstrate a cause-and-effect relation, nor could confounding be excluded, such as health-conscious users of supplements being less likely to develop disease. To rectify this, a post hoc analysis from the SU.VI.MAX study,²² a randomized trial to assess the effects of a combination of vitamins and minerals including vitamin C, was performed. Plasma concentrations of vitamin C were inversely ($P=0.046$) associated with fasting plasma glucose levels; however, over the follow-up period of 7.5 years, supplementation had no effect on age-adjusted fasting plasma glucose levels.

Observational studies have suggested that people with T2DM have lower vitamin C levels, and this was not explained by differences in dietary vitamin C intake when compared to people without diabetes. There may be an association between lower vitamin C levels and the subsequent development of diabetes, as well as higher glucose levels.

Interventional studies

In three intervention studies of vitamin C supplementation in T2DM, an improvement was seen in fasting glucose and HbA_{1c} levels, but only with a higher dose supplementation of 2,000 mg of vitamin C per day for 90 days, with no improvement observed after 2 months of 500 mg daily vitamin C supplementation, nor with short-term supplementation over 2 weeks.^{23–25} This finding may be due to an inadequate increase in vitamin C levels in diabetes with standard supplementation doses or of brief duration. The difficulty with interpreting the vitamin C intervention studies is the use of study populations with adequate vitamin C levels, which significantly decreases the likelihood of observing any effects of the intervention.^{26,27} Another randomized controlled trial²⁸ demonstrated that supplementation with 800 mg per day for 4 weeks in people with T2DM and low plasma vitamin C levels ($<40 \mu\text{mol/L}$) at baseline was insufficient for replenishing serum levels to what is seen in healthy

subjects ($>80 \mu\text{mol/L}$). The lower vitamin C levels achieved could have explained the lack of improvement in measures of insulin resistance in the supplemented group.

The addition of vitamin C supplementation to standard therapy was assessed in 70 patients treated with metformin for T2DM who were randomized to 500 mg twice daily of vitamin C or placebo for 12 weeks.²⁹ Those given vitamin C were identified to have lower HbA_{1c}, fasting, and postmeal blood glucose levels when compared to the placebo group, despite all being treated with metformin.

Apart from the impact on glycemic control, antioxidant supplementation has been studied for the prevention of complications of diabetes. An improvement in neuropathic symptoms (but not in objective signs of neuropathy) and decreased odds of retinopathy were seen with the use of a combination of vitamin supplements including vitamin C.^{30,31} The impact of high dietary vitamin C and supplementation has been demonstrated to have variable effects on cardiovascular complications in diabetes.^{32,33}

Interventional studies with vitamin C supplements have not consistently demonstrated improvements in glycemic control in T2DM. Vitamin C as an antioxidant could reduce the risk of complications of T2DM; however, excess supplementation may increase the risk of cardiovascular disease.³²

Potential mechanisms

The significance of vitamin C in T2DM has been suggested by the hypothesis that hyperglycemia inhibits the cellular uptake of dehydroascorbic acid (DHA), which is the oxidized transportable form of vitamin C.^{34,35} In the red blood cell, glucose strongly inhibits the uptake of DHA; therefore, hyperglycemia in diabetes would be expected to cause vitamin C deficiency within the cell.³⁵ DHA uptake into the cells is accomplished through glucose transporters, GLUT1 and GLUT3, which transport DHA in competition with glucose,^{36,37} and this effect may be overcome by a large intake of vitamin C.³⁸

The mechanisms for reduced vitamin C levels in diabetes are suggested by animal studies. A study of rats with streptozotocin-induced diabetes³⁹ demonstrated a decrease in serum levels of vitamin C and the increased urinary excretion of vitamin C when compared to the levels obtained prior to the induction of diabetes in the same rats, suggesting that the renal reabsorption of vitamin C is reduced in diabetes. Another study of diabetic rats¹² demonstrated an increased turnover of vitamin C, and this finding was most likely due to the increased oxidation of ascorbate to DHA in tissue

mitochondria. Furthermore, a human study of vitamin C turnover, measured by the rate of reduction of DHA to ascorbic acid, indicated that this turnover was higher in a group of people with diabetes than in volunteers without diabetes.¹² This higher turnover of vitamin C in diabetes may underlie the need for higher dietary vitamin C requirements in diabetes.

Significant benefits of vitamin C supplementation have been demonstrated in an animal model of T2DM. Vitamin C supplementation in ob/ob mice caused significant reductions in food intake, plasma glucose, HbA_{1c} levels, plasma glucose levels, and insulin concentrations when compared with untreated control ob/ob mice.⁴⁰ The total insulin content and the extent of insulin glycation in the pancreas of ob/ob mice also decreased after vitamin C supplementation. These parameters did not change with vitamin C supplementation in lean mice.

The biological mechanisms underlying lower vitamin C levels in people with diabetes includes decreased cellular uptake, increased urinary losses, and increased metabolic turnover of vitamin C in diabetes. These mechanisms suggest higher dietary vitamin C requirements in diabetes, along with the benefits of supplementation, as seen in a mouse model of T2DM.

Effects of vitamin D in diabetes

Vitamin D physiology

The name “vitamin D” is a historical misnomer because a vitamin, by definition, is something that we cannot synthesize ourselves. The active form of vitamin D, calcitriol, is synthesized in humans, and is a hormone that undergoes autocrine regulation. Vitamin D is synthesized from cholesterol precursors. Moreover, 7-dehydrocholesterol is converted to vitamin D in the skin following exposure to ultraviolet radiation. This molecule binds to vitamin D-binding protein (DBP) and undergoes hydroxylation in two stages: firstly, in the liver to form 25-OH vitamin D (25OHD); and secondly, in the kidney to form 1,25(OH)₂ vitamin D (1,25[OH]₂D). In its active form, vitamin D (1,25[OH]₂D) has predominant effects in calcium and mineral homeostasis by interacting with the vitamin D receptor (VDR).⁴ The VDR is present in tissues involved in calcium/phosphate homeostasis (ie, the intestine, bone, kidney), and it is present at lower levels in other tissues, suggesting the nonclassical roles of vitamin D (eg, in glucose homeostasis).

Observational studies

The potential effects of vitamin D on insulin sensitivity and glucose tolerance have been the subject of a recent review.⁵

In 808 subjects without diabetes, plasma 25OHD correlated inversely with fasting insulin levels and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) scores after adjusting for sex, age, and body mass index (BMI).⁴¹ A similar link between HOMA-IR and 25OHD was found in 712 prediabetic subjects.⁴² HOMA used data from physiological studies to derive equations to assess insulin resistance (HOMA-IR) and insulin sensitivity (HOMA-S) from matched fasting insulin and glucose samples.⁴³ In an elegant study of healthy adults,⁴⁴ there was a significant association between 25OHD and insulin sensitivity assessed by hyperglycemic clamps, after adjusting for BMI and a range of other factors.

Prospective studies have demonstrated that 25OHD levels correlate with the long-term risk of insulin resistance. In a study of 5,200 participants, a 25 nmol/L increment in baseline serum 25OHD levels correlated with a 24% reduced risk of developing diabetes over 5 years, although this was a nonlinear relation.⁴⁵ Furthermore, a meta-analysis of 21 prospective studies identified a linear trend for each 10 nmol/L increment in 25OHD levels to be associated with a 4% lower risk of T2DM (95% confidence interval [CI]: 3–6; *P* for a linear trend, <0.0001).⁴⁶ An independent association with HOMA-S at 5 years was also found ($r=0.16$; $P<0.001$). Furthermore, vitamin D status and T2DM were inversely associated in multiple observational studies.^{46–52}

In the Women’s Health Study,⁵³ dietary vitamin D was inversely associated with metabolic syndrome, but this was related to total calcium intake. The Nurses’ Health Study⁴⁸ showed that there was a decrease in the relative risk of incident diabetes of 0.87 (95% CI: 0.75–1.00; *P* for trend =0.04) among those on high-dose vitamin D supplements (>800 IU daily), as compared to those on low-dose vitamin D supplements (<400 IU daily); this was also seen with calcium intake.

Studies have demonstrated an association between vitamin D and insulin resistance, which is significant for the risk of developing T2DM. Although suggestive, these observational studies do not prove a causal relationship between vitamin D and insulin resistance. A number of factors may confound this link, such as adiposity.⁵⁴ Obese individuals may avoid sun exposure, and vitamin D (a lipophilic compound) may be trapped in adipose tissue, resulting in serum deficiency. Obesity is also a major determinant of insulin resistance. Other confounders include parathyroid hormone levels,⁵⁵ calcium levels, physical activity, and diet. These may influence vitamin D and independently alter insulin sensitivity.

Interventional studies

In the absence of insulin resistance, vitamin D supplementation does not alter insulin sensitivity.^{7,56–58} However, some evidence indicates that subjects with prediabetes may benefit. At-risk subjects receiving various regimens of vitamin D and calcium over 6 weeks to 3 years showed significant improvements in insulin secretion, sensitivity, and/or the disposition index (a marker of insulin secretion/activity).^{7,59–61}

The evidence that vitamin D improves glycemic control in subjects with established diabetes is mixed. In a recent trial,⁶² 90 subjects with diabetes were randomized to daily vitamin D (1,000 IU), taken in fortified yogurt; these subjects showed better glycemic control and reduced insulin resistance (HOMA-IR) when compared to subjects on plain yogurt. Importantly, serum vitamin D levels and HOMA-IR scores correlated inversely in this study. Another three studies of vitamin D supplementation of 3 weeks to 3 months' duration have demonstrated positive effects on HbA_{1c} levels, insulin resistance, and insulin secretion compared to placebo, while other studies have shown no benefit from brief supplementation with low doses of vitamin D, nor with high doses of over 6 months' duration.^{63–67}

Small interventional studies examining different populations with variable vitamin D levels, using different regimens of supplementation, make it difficult to draw definite conclusions. Parameters of insulin sensitivity are variable, ranging from measuring fasting insulin to hyperinsulinemic–euglycemic clamps. While insulin resistance leads to diabetes, a complex interaction between glucose and insulin levels exists. Glycemic outcomes reflect the interplay between insulin resistance and insulin secretion by pancreatic beta-cells.

Therefore, whether vitamin D supplementation results in clear improvement in diabetes remains unclear. A randomized controlled trial of two doses of vitamin D supplementation (5,000 IU versus 400 IU daily) did not demonstrate improved glucose levels in pregnancy, despite another study showing a link between vitamin D levels and the subsequent risk of gestational diabetes.^{68,69} Large trials are currently underway in other populations, which may definitively resolve this question (eg, NCT01354964, NCT01315366, NCT00736632, and Pittas et al⁷⁰).

Potential mechanisms

Mouse models of diabetes demonstrate improvements in insulin sensitivity following the administration of 1 α OHD₃.⁴ This vitamin D analog is automatically 25-hydroxylated in the liver, forming calcitriol, and it bypasses normal

endocrine regulation of the activation process. An *in vitro* study has shown that 1,25(OH)₂D increases insulin receptor expression and insulin signaling via Akt and insulin receptor phosphorylation.⁷¹ Nongenomic, rapid effects of vitamin D may also play a role. Apart from calcium regulation, vitamin D leads to the release of arachidonic acid, a polyunsaturated fatty acid, from the cell membrane and into the muscle cell cytoplasm.⁷² This links vitamin D with insulin sensitivity, as does the possibility that vitamin D may modulate caveolin-1,⁷³ a scaffolding protein within the membrane that exerts its effects in metabolism.

Pancreatic beta-cells, responsible for insulin secretion, express components of the vitamin D pathway, including 1 α -hydroxylase enzyme, a vitamin D-dependent calcium-binding protein (calbindin), and the VDR.⁷⁴ Vitamin D treatment increases insulin secretion in vitamin D-deficient rodents and cultured pancreatic cells. This effect occurs via intracellular calcium signals and altered gene expression, but its physiological significance is unclear. Animal models and *in vitro* studies provide potential mechanisms for the associations between vitamin D and insulin resistance.

Summary points

- Observational studies indicate a link between deficiencies in vitamins C and D and the prevalence of type 2 diabetes.
- There is biological plausibility for the effects of vitamins C and D in glucose homeostasis. Vitamin C prevents oxidative stress and is known to interact with glucose transporters, potential mechanisms by which it may also alter glucose homeostasis. Vitamin D may affect calcium handling in pancreatic beta-cells and skeletal muscle, thereby affecting insulin secretion and sensitivity, respectively.
- Randomized controlled trials have not clearly demonstrated the effects of vitamins C and D in the prevention or treatment of diabetes. This is due to a range of factors, including heterogeneity in study design and endpoints, and the lack of standardized supplementation regimens. Further research will address the impact of these nutrients in glucose homeostasis.

Conclusion

The relationship between diabetes and vitamins C and D have been demonstrated by human and animal studies. The limitation of observational studies is that confounders cannot be excluded to explain the relationship between vitamin

deficiency and diabetes outcomes. Interventional studies that are randomized provide the best evidence for a benefit of supplementation, with serum vitamin levels indicating variations in the dietary intake of vitamin C and the levels of sun exposure for vitamin D. Animal models can provide an indication of the mechanisms that underlie these associations; however, metabolic processes in animals are not directly translated in humans.

Vitamin C levels are lower among people with T2DM and not completely explained by a difference in dietary vitamin C intake. A number of mechanisms underlying the decrease in vitamin C levels and increased requirements in T2DM have been proposed.⁷⁵ Consequently, the dietary requirements or the need for supplementation of vitamin C may be greater in people with diabetes. However, studies of vitamin C supplements alone or in combination have not demonstrated sufficient benefit to support a recommendation for routine supplementation, nor higher target serum vitamin C levels, in people with T2DM. Further studies are needed to determine if vitamin C supplementation may play a role in minimizing the risk of complications of diabetes.

While strong links between vitamin D and diabetes have been demonstrated, it remains to be determined whether this is by cause or association. Increasing endogenous levels of vitamins C and D can be achieved by dietary modifications, and in the case of vitamin D, also by judicious sun exposure.⁷⁶ The availability of supplements enables a convenient method of reaching a prespecified serum vitamin C and D level. However, as with many other nutrients, the maximum health benefit is probably obtained by achieving the recommended daily intake of vitamin C as part of a balanced diet, and maintaining vitamin D status by regular sun exposure. Further studies – in particular, randomized controlled trials – are needed to determine if there is a benefit of routine supplementation with these vitamins in diabetes or for its prevention.

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Disclosure

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