

The role of vitamins in the prevention and treatment of type 2 diabetes and its complications

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Article points

1. A healthy diet that includes fruit and vegetables will provide the vitamins required for good health, which can help reduce the development of complications in people with diabetes.
2. There is evidence that targeted supplementation of some vitamins, such as niacin and thiamine, can be useful for people with type 2 diabetes to prevent complications; however, more research is needed into safety and efficacy.
3. There is strong evidence of a link between vitamin D deficiency and insulin resistance, and serum levels should be checked in all people with diabetes.

Key words

- Antioxidants
- Diabetes
- Niacin
- Thiamine
- Vitamin D

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The benefit of isolated vitamins and their role in the prevention and treatment of type 2 diabetes continues to be a focus for research. Evidence suggests that vitamin D deficiency, which is widespread in the UK, is linked to insulin resistance and vitamin D deficiency appears to be particularly prevalent in population groups who are already at high risk of type 2 diabetes. Pharmaceutical doses of vitamins thiamine (B₁) and niacin (B₃) may be useful to prevent renal and cardiovascular complications in people with type 2 diabetes. A balanced and varied diet containing fruit and vegetables can contribute towards reducing the progression of diabetic complications by providing an adequate intake of antioxidant vitamins.

Type 2 diabetes is often attributed to an unhealthy lifestyle. The current recommendation for the prevention and management of type 2 diabetes is a healthy, balanced diet, with particular focus on maintaining a healthy weight and physical activity (Deakin et al, 2011). This article will explore the role of vitamins in diet, as well as vitamins taken as supplements in pharmaceutical doses in relation to the prevention of type 2 diabetes and its complications.

Vitamins

A vitamin is an organic compound required by an organism as a vital nutrient in limited amounts. It cannot be synthesised and must be obtained in the diet, with vitamin D being an exception, as it can also be obtained through exposure to sunlight. Minerals and other micronutrients are not discussed in this article. There are 13 known vitamins. *Table 1* shows the recommended daily intake and major food sources of the 13 vitamins.

Vitamin A, C and E are antioxidants, along with many other minerals and compounds. Antioxidants are not usually implicated in the aetiology of type 2 diabetes but may help to prevent

the complications associated with the condition. Damage to the blood vessels and organs can occur through oxidative stress and damage by free radicals. There is evidence that the antioxidant effect of vitamins C, E and A can reduce this damage.

Vitamin C

Tanaka et al (2013) found a 50% reduced incidence of retinopathy in subjects with a high fruit and vitamin C intake. Hegde et al (2013) also reported that diets rich in fruit can improve dietary antioxidant intake, which in turn, is likely to reduce oxidative stress in people with type 2 diabetes. The antioxidants in foods give protection against the damage that occurs in any inflammatory condition and from exacerbating factors caused by obesity, smoking and physical inactivity.

Harding et al (2008) looked at plasma vitamin C and fruit and vegetable consumption in association with the prevention of type 2 diabetes. They found that higher plasma vitamin C levels and, to a lesser degree, fruit and vegetable intake were associated with a substantially decreased risk of developing diabetes. Their findings highlight a

Table 1. Recommended daily intake and sources of vitamins.

Vitamin	Reference nutrient intake (RNI/day)	Source
A	Men 0.7 mg Women 0.6 mg	Liver, milk and dairy, eggs, fortified fat spreads, carrots.
B ₁ (Thiamine)	Men 1.0 mg Women 0.8 mg	Yeast and yeast products, pork, nuts, pulses, wholegrain cereals.
B ₂ (Riboflavin)	Men 1.3 mg Women 1.1 mg	Milk and dairy, meat and products, cereal products, beer.
B ₃ (Niacin)	Men 17 mg Women 13 mg	Meat, fish, wheat flour, maize flour, yeast extract, coffee
B ₅ (Pantothenic acid)	No RNI Safe level: 3–7 mg	Chicken, beef, potatoes, porridge, tomatoes, kidneys, eggs, broccoli, wholegrain bread
B ₆ (Pyridoxine)	Men 1.4 mg Women 1.2 mg	Meat, wholegrain and fortified cereal products, bananas, nuts, pulses
B ₇ (Biotin)	No RNI Safe level: 10–200 µg	Cereal products, beer, coffee, milk and dairy, eggs, meat
B ₁₂	1.5 µg (men and women)	Meat, fish, dairy, eggs
C	Men 40 mg Women 40 mg	Citrus fruits, berries, kiwi and other fruits; vegetables
D	Over 65 years 10 µg (for men and women) (No RNI for people 5–65 years)	Oily fish, eggs, fortified spreads
E	No RNI Safe level: Men 4 mg Women 3 mg	Nuts and seeds, wheat germ
Folic acid	Men 0.2 mg Women 0.2 mg	Broccoli, Brussels sprouts, asparagus, spinach, cereal products
K	No RNI Safe level: 1 µg/kg	Green leafy vegetables, vegetable oils, cereals

potentially important public health message for the benefits of a diet rich in fruit and vegetables in the prevention of diabetes. High dose vitamin C has been used in some trials (Wang et al, 2013) to examine a possible link with reducing inflammation, although results have been inconclusive.

Vitamin E

Vitamin E is one of the most important lipid-soluble antioxidants. Its function is to protect the integrity of membranes by inhibiting lipid peroxidation. Although evidence suggests no beneficial effect of vitamin E supplementation in improving glycaemic control in all people with type 2 diabetes, it may decrease HbA_{1c} levels in people with inadequate glycaemic control or low serum levels of vitamin E (Suksomboon et al, 2010). This shows the importance of targeting therapy. It must be noted that high dosage vitamin E supplements (more than 400 international units [IU] per day) may increase all-cause mortality and should be avoided (Miller et al, 2005). Clinical assessment of vitamin E levels would be useful in people where deficiency is suspected, due to either poor diet or malabsorption.

Vitamin B₁ (Thiamine)

Thiamine is an essential co-factor in carbohydrate metabolism. Therefore, low levels are thought to have an impact on glucose homeostasis. Page et al (2011) noted that individuals with diabetes are often deficient in thiamine. Thornalley et al (2007) showed that blood levels of thiamine were 75% less in people with type 2 diabetes than in controls. These low levels are thought to be a result of increased renal clearance. Page et al (2011) suggest that thiamine deficiency may augment hyperglycaemia-induced tissue damage. They suggest there is a beneficial effect of thiamine supplementation on progression of vascular disease, endothelial function and oxidative stress. There may also be long-term benefits on cardiovascular (CV) risks and angiopathic complications. A small randomised controlled trial (González-Ortiz et al, 2011) found that administering 150 mg of thiamine daily (a pharmaceutical dose) for 1 month, decreased glucose and leptin concentrations significantly in people with type 2 diabetes.

Rabbani and Thornalley (2011) state that thiamine supplementation may prevent and reverse early stage nephropathy. In an earlier randomised controlled trial (Rabbani et al, 2009), 300 mg of thiamine was given daily for 3 months, with a 2-month wash-out period for people with microalbuminuria. This resulted in a regression of urinary albumin excretion. Thus, it has been proposed that a high dose of thiamine could be used as a therapy for early stage nephropathy. This was confirmed in a subsequent study from Pakistan, again using 300 mg of thiamine each day for 3 months (Alam et al, 2012). In this study, low thiamine status did not appear to be related to dietary intake, rather to enhanced renal

clearance. Alam et al (2012) recommended that people with type 2 diabetes take 300 mg of thiamine daily to prevent depreciation of thiamine levels. The study did not find adverse effects from this therapy. Although the reasons for increased renal clearance of thiamine are not fully understood, a recent *in vitro* study found that a high glucose concentration inhibited the renal uptake of thiamine (Larkin et al, 2012).

Vitamin B₃ (Niacin)

According to the *British National Formulary* (BNF, 2013), nicotinic acid can be used in doses 1.5–3 g daily to lower cholesterol and triglycerides by inhibiting synthesis, while raising high-density lipoprotein cholesterol. It is often used in combination with a statin.

A small number of studies have shown the beneficial effects of niacin on CV events in people with type 2 diabetes. Sazonov et al (2013), in a post-study analysis from the Coronary Drug Project, looked at the effects of niacin compared with a placebo on the incidence of new-onset type 2 diabetes and on CV event rates in people with normal glycaemia and impaired fasting glucose (IFG). Niacin supplementation produced a modest increase in the risk of new-onset type 2 diabetes, with a potential reduction in CV risk. Phan et al (2012) reported that the use of niacin for 3 years in people with normal baseline glucose was associated with increased glycaemia and a risk of developing IFG, but not diabetes. However, niacin was associated with a significantly decreased incidence of coronary stenosis progression and major CV events. Again, as in thiamine therapy, pharmaceutical doses were used in the trials (2–4 mg per day).

The effects on CV disease are noteworthy, but its use may be difficult to justify in some people with type 2 diabetes, because of the detrimental impact on glycaemia.

Vitamin B₁₂

Data from the US National Health and Nutrition Survey 1999–2006 found metformin therapy was associated with a 5.8% biochemical deficiency of B₁₂ in people over 50 years with type 2 diabetes; this was compared with an incidence in the general population of over 50 years of 3.3% (Reinstatler et al, 2012). The authors quote that other studies show a much higher incidence. Classic symptoms of B₁₂ deficiency are anaemia, neuropathy and cognitive decline, although these are not always seen in a biochemical deficiency.

Although Obeid et al (2013) also found low serum levels of B₁₂ in people with diabetes who were being treated with metformin, intracellular B₁₂ metabolism appeared improved when using metformin.

B₁₂ deficiency can be caused by having a diet that does not include animal products. It can also be due to a lack of intrinsic factor, which is required for the absorption of B₁₂ in the stomach.

B₁₂ is the only water-soluble vitamin that can be stored in the liver for up to 3 years, although many people, including older people and those who have had bariatric surgery, have only a 1-year store. These groups would require injections of B₁₂ every 3 months to address a deficiency. It is good practice to measure B₁₂ routinely, especially in at-risk groups, such as older people.

Vitamin D

Vitamin D has attracted much attention over recent years in relation to its possible role in chronic disease. It is a fat-soluble vitamin with a half-life of about 15 days. Vitamin D can be sourced from food, but is mainly produced in the body by the action of ultraviolet beta rays from sunlight on skin. Deficiency is very common (Pearce, 2010), particularly in the housebound and those who cover their skin for religious reasons. Obese people are at risk of vitamin D deficiency because body fat binds to vitamin D and prevents it from being absorbed into the blood. Dark skin is less efficient at making vitamin D. There is currently no recommendation for the daily allowance of this vitamin, apart from in pregnant and breastfeeding women and older people (10 µg per day) and infants and children under 5 (7–8.5 µg per day). It must be noted that in the UK, vitamin D cannot be synthesised from sunlight between October–April because of the angle of the sun. Even in summer, cloudy days limit our exposure to sunlight, as does the use of sunblock. Sunblock that is higher than 15 SPF will preclude most vitamin D synthesis. Vitamin D insufficiency is thought to affect glucose metabolism, lower beta cell function, increase insulin resistance and glucose intolerance.

A recent meta-analysis (Song et al, 2013) considered 21 studies and found that the association between type 2 diabetes and low serum vitamin D levels was strong. The data revealed a significant linear association between 25-hydroxyvitamin D (25[OH]D; of which vitamin D is a precursor) and diabetes in the range of serum levels 20–160 nmol/L. The relative risk for diabetes decreased by 4% for every 10 nmol/L increase in serum 25[OH]D. A notable reduction in diabetes risk at levels of 50 nmol/L and above was apparent. The authors note that the majority of participants had vitamin D levels <100 nmol/L, so could not comment on a positive effect of high levels of 25[OH]D.

Talaei et al (2013) conducted a small study on 100 people with type 2 diabetes. He supplemented participants with 50 000 IU of oral vitamin D₃ a week for 8 weeks. Reduced fasting plasma glucose levels and insulin resistance were significant at the end of the study. Belenchia et al (2013) corrected vitamin D deficiency in obese adolescents by supplementing 4000 IU (80 µg per day for 6 months). Mean serum levels increased to 49 nmol/L, compared with a placebo group of 7 nmol/L. In the supplemented group there was no change in BMI, serum inflammatory markers or plasma glucose concentrations. However, fasting insulin levels

Page points

1. Vitamin D should be measured routinely in practice and any deficiency should be corrected.
2. NICE guidance states that women with pre-existing diabetes contemplating a pregnancy should take 5 mg folic acid (a high dose supplement, only available on prescription), before conception and for the first 12 weeks of pregnancy during the period of organogenesis.
3. Antioxidants in the diet, primarily derived from fruit and vegetables, are essential to protect the body from free radical damage to blood vessels and organs. Unchecked, this damage will further contribute to future complications of diabetes.

and insulin resistance decreased significantly. A study in older people has shown that high levels of serum 25[OH]D may reduce type 2 diabetes by up to 55% (Parker et al, 2010). Vitamin D should be measured routinely in practice and any deficiency should be corrected.

Folic Acid (FA)

Metanx[®] (a combination of pharmaceutical doses of folate B₁₂ and B₆) has been found to alleviate symptoms of peripheral neuropathy in the short term (Fonseca et al, 2013) and it is suggested that long-term studies are conducted to look at each of these B vitamins in isolation.

A systematic review and meta-analysis on the effects of folic acid supplementation on plasma homocysteine (a risk factor for cardiovascular disease) and glycaemic control in people with type 2 diabetes was conducted by Sudchada et al (2012). There were four studies, with a total of 183 people included in the review. It was concluded that folic acid supplements may decrease homocysteine levels, and there was a weak link with improved diabetes control.

NICE (2008) guidance states that women with pre-existing diabetes contemplating a pregnancy should take 5 mg folic acid (a high dose supplement, only available on prescription), before conception and for the first 12 weeks of pregnancy during the period of organogenesis. It is particularly associated with protection from neural tube defects, such as spina bifida.

The implication for practice is that women with type 2 diabetes are frequently overlooked in preconception planning. Thus 5 mg folic acid supplements should be prescribed to all women with diabetes of childbearing age who cease to use contraception when sexually active.

Discussion

Although there is currently no evidence to recommend that people with diabetes take vitamin supplements (Deakin et al, 2011), there are certain situations where deficiencies occur and require correction. In most clinical situations, the emphasis is on improving glycaemic control and the importance of a balanced diet is forgotten. Antioxidants in the diet, primarily derived from fruit and vegetables, are essential to protect the

body from free radical damage to blood vessels and organs. Unchecked, this damage will further contribute to future complications of diabetes.

Specific vitamin deficiencies are clearly prevalent in specific groups, such as older people or those who have undergone bariatric surgery. Bariatric surgery is becoming increasingly popular in obese people with type 2 diabetes. This group suffers from malabsorption (especially with bypass and sleeve gastrectomy procedures), as well as poor appetite and poor choice of food. Most of these people find it impossible to manage their “five a day” fruit and vegetables intake, as recommended by the Department of Health. It is generally agreed that people who have undergone bariatric surgery should take a multivitamin and mineral supplement every day for life. They will also require B₁₂ injections every 3 months. Women who have had bariatric surgery are being seen more frequently in the antenatal clinic. They should be told to swap to a pregnancy-specific multivitamin and mineral supplement in the pre-conception period and continue taking throughout pregnancy. Standard supplements should be avoided as they are too high in vitamin A, which is teratogenic to the foetus. In addition, as with other women with diabetes, 5 mg folic acid should be recommended for pre-conception and in the first 12 weeks. Vitamin D supplementation may also be required if serum levels are low.

Healthcare professionals need to be more aware of the importance of vitamin D as many people in the UK continue to have a deficiency. For pale skin, 30 minutes a day sun exposure for the face, neck and forearms with no sun block would give 2000 IU of vitamin D (Pearce, 2010). Exposure for darker skinned or older people may need to be 2–10 times the amount for people with pale skin. Although sufficient in summer, vitamin D intake may be inadequate in winter, even with the consumption of oily fish. The Department of Health recommends daily supplementary vitamin drops containing 400 IU for all infants, pre-school children, pregnant and breastfeeding women (Department of Health, 2012). Since strong evidence of a link between vitamin D deficiency and insulin resistance is emerging, it would seem appropriate to recommend that serum vitamin D levels be checked in all people with diabetes.

Further research is also required to determine the efficacy and safety of pharmaceutical doses of niacin and thiamine in the prevention of cardiovascular and renal complications respectively. In the case of niacin, investigation as to whether the CV benefits outweigh the adverse effects on glucose metabolism may need to be considered. ■

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