Reversible coagulopathy associated with vitamin E excess

Summary

Vitamin E refers to a group of compounds that are essential to the diet of animals, where its primary function is an antioxidant. Excessive vitamin E supplementation can cause a reversible coagulopathy in the setting of compromised vitamin K absorption or function. We describe the case of a female in her mid-eighties treated for micronutrient deficiencies following a biliopancreatic diversion as a bariatric procedure 14 years previously. Her coagulation tests were normal until she commenced vitamin E and accidentally over-administered the prescribed dose. This resulted in a coagulopathy, characterised by a prolonged international normalised ratio (INR) and activated partial thromboplastin time (APTT). The patient never had any signs of active bleeding. Both coagulation parameters normalised after stopping the vitamin E and with vitamin K supplementation. This case signifies the importance of careful instruction and monitoring of vitamin replacement, in particular vitamin E supplementation, which in excess leads to coagulopathy.

Background

Obesity represents a growing burden on both the individual and healthcare systems, with an estimated 1 billion people living with obesity worldwide (1). Bariatric surgery remains an effective treatment option, and within England 6500-7000 procedures are performed annually (2-3). Postoperatively bariatric surgery patients are at increased risk of nutrient deficiencies, especially following malabsorptive procedures such as a biliopancreatic diversion (BPD). This mainly occurs due to the bypass of small intestine and subsequent absorptive surface area of the gut, but in addition decreased food intake and reduction of gastric secretions may also contribute. This risk is related to the length of small intestine bypassed (4). Such deficiencies include vitamins A, D, E, K, B12 and folic acid along with deficiencies of iron, copper, selenium, zinc and magnesium (4). Post operatively, guidelines recommend lifelong routine monitoring for these deficiencies with specific nutritional supplementation and further treatment to avoid deficiencies and over supplementation (4). We could find no publications examining physician and patient awareness of over replacement with vitamins, in particular the effects of vitamin E excess.

Case Presentation

A female in her mid-eighties was reviewed by the diabetes and endocrinology team following a BPD at the same hospital 14 years previously. Post-operatively, she had been under regular review for management of micronutrient deficiencies. Urgent review was arranged after tests demonstrated severely deranged coagulation parameters. Her current medical history included dry macular degeneration and osteoarthritis. She previously had type 2 diabetes and hypertension which were in remission.

Two months previously she was newly diagnosed with vitamin E deficiency. Vitamin E level measured as tocopherol and tocopherol/cholesterol ratio were 3.8 µmol/L (normal range-NR:11.0-47.0) and 1.4 (NR:>2.2) respectively. She commenced oral replacement in the form of alpha-tocopherol acetate (500

mg/5mL, 100mL bottle) at a dose of 2.5 mL/day equivalent to 550 units or 250 mg/day**.** She was already receiving vitamin A, vitamin D, calcium, folic acid and iron supplementation, and her medications at this time are shown in Table 1. Faecal elastase was also found to be low at this time, and she was commenced on creon, a pancreatic enzyme supplementation. Coagulation screen testing had previously been normal. The patient did not have any symptoms of vitamin E deficiency.

Table 1: Patient's medications at the time of clinic review prior to commencing vitamin E supplementation

Name of medication	Dose
Forceval (Ascorbic acid 60 mg, Biotin 100 microgram, Calcium 100 mg, Chromium 200 microgram, Copper 2 mg, Cyanocobalamin 3 microgram, Ergocalciferol 400 unit, Folic acid 400 microgram, Iodine 140 microgram, Iron 12 mg, Magnesium 30 mg, Manganese 3 mg, Molybdenum 250 microgram, Nicotinamide 18 mg, Pantothenic acid 4 mg, Phosphorus 77 mg, Potassium 4 mg, Pyridoxine 2 mg, Riboflavin 1.6 mg, Selenium 50 microgram, Thiamine 1.2 mg, Tocopheryl acetate 10 mg, Vitamin A 2500 unit, Zinc 15 mg)	One capsule twice daily
Vitamin A and D capsules (Vitamin A 4000 units, Vitamin D 400 units)	Two capsules four times a day (Total dose: vitamin A 32000 units, vitamin D 3200 units)
Vitamin B12 (hydroxocobalamin) 1 mg intramuscular injection	Every 3 months
Folic acid 5mg	One tablet daily
Ferrous Sulphate 200mg	One tablet twice per day
Cholecalciferol (vitamin D)/Calcium carbonate tablets (cholecalciferol 400 units, 1.5 g calcium carbonate)	Two tablets three times a day (Total dose: vitamin D 2400 units, calcium carbonate 9mg)
Vitamin D (Cholecalciferol) 300,000 units intramuscular injection	Every 3 months
Vitamin A 100,000 units intramuscular injection	Every 3 months.

Four weeks later the patient mentioned during a telephone conversation with our department that she had used all her vitamin E supplements despite receiving written instruction and advice and correct prescribing. A coagulation screen was arranged which was grossly deranged, with an international normalised ratio (INR) of 7.8, prothrombin time (PT) of 78.1 (NR: 9.0-12.5 seconds) and activated partial thromboplastin time (APTT) of 44.4 (NR: 22.1-30.9 seconds). On clinical review the patient was asymptomatic without any clinical signs of bleeding. Her haemoglobin level was also stable.

On direct questioning the patient stated she had been taking approximately 12.5 mL daily, equivalent to 1250 mg (2775 IU) vitamin E daily for 6 weeks prior to the blood test, not the 2.5mL prescribed dose. She was advised to stop vitamin E and commenced oral liquid vitamin K (phytomenadione 10 mg daily) for 3 days, when a repeat coagulation screen demonstrated INR 1.2, PT 12.2, APTT 21.7. Of interest, the vitamin E level measured as tocopherol and Tocopherol/Cholesterol ratio were both below the normal

range, 6.3 µmol/L and 2.0 respectively. She was commenced on oral vitamin K tablets (menadiol), initially 10mg three times a week, and then continued on 10mg twice weekly for 1 month and then reduced to 10 mg once a week. The patient remained well with no recurring coagulopathy as shown in figure 1. At present the coagulation screen is normal and the patient remains on menadiol 10mg once weekly. Of note the vitamin E level remains normal. The trend in the coagulation screen and vitamin E level are presented in Figure 1. The patient described that she felt well during this period and acknowledged that she took the vitamin E in excess in error. She did describe that measuring the correct volume may be a challenge for patients. She also commented that perhaps the general public often believe that too much vitamins can't cause any harm, and this should be more widely publicised.

Diagnosis

Reversible coagulopathy secondary to Vitamin E excess.
This diagnosis was reached because the new coagulopathy was found directly after the patient accidentally took vitamin E in excess of her prescription for 6 weeks.

Treatment

- Stop vitamin E supplements immediately
- Commence oral vitamin K 10 mg once daily
- Repeat coagulation in three days' time
- Subsequent titration of oral vitamin K to 10 mg twice weekly

Outcome

- Patient remained well with no signs of bleeding during treatment
- INR and APTT have both stayed in normal range since treatment
- Patient requires ongoing monitoring of micronutrient levels

Discussion

This case provides useful insight into the risks associated with excess vitamin supplementation, in particular vitamin E. This is important from the clinician and patient perspective. One of the challenges is in measuring the correct dose. Whilst this is only a single case, we have subsequently observed another patient who also administered excess vitamin E with a resulting prolonged prothrombin time, which corrected on cessation of the vitamin E and treatment with menadiol. A limitation in our case was an inability to measure vitamin K levels and the coagulation screen was used as an alternative. We understand from colleagues that measuring vitamin K is not routinely available in many clinical settings, and we are addressing this locally. Interactions between vitamin E and K with resultant coagulopathy have been demonstrated in animal studies since 1945 (5). This case provides an opportunity to discuss the role of vitamins E and K, and the effect of bariatric surgery on these fat-soluble vitamins.

Bariatric surgery and micronutrient deficiencies

A range of bariatric procedures exist for the treatment of obesity. Current surgical approaches include sleeve gastrectomy, Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, jejunoileal bypass and previously BPD (6). The type and degree of micronutrient or vitamin deficiency expected depends on the extent to which the small bowel, pancreatic enzymes and bile salts are bypassed. Micronutrient deficiency is one of the key considerations promoting a shift in preference for less malabsorptive procedures. These deficiencies are often found in patients prior to bariatric surgery because of poor diet, and surgery does not necessarily result in a nutritionally improved diet. The British Obesity and Metabolic Surgery Society (BOMSS) guidelines now provide a standard framework for managing patients undergoing metabolic surgery in the perioperative period and managing their micronutrient requirements (4). In our case, the patient had a BPD which is associated with a relatively high risk of micronutrient deficiencies, highlighted by the frequency and breadth of micronutrient supplementation she required. As a consequence, BPD is no longer performed frequently in the UK.

Vitamin E

Vitamin E refers to a group of fat-soluble compounds that are essential to the diet of animals. They are found in high concentrations in fatty nuts, salmon, trout, red pepper, butternut squash, avocado, mango and kiwi. Vitamin E is absorbed by enterocytes in the small intestine sharing common pathways with both vitamin D and K (7). To prevent rapid clearance of vitamin E from the body it must be sequestered inside very low-density lipoproteins. This takes place in the liver and is facilitated by alpha-tocopherol transfer protein. Mutations in the *TTPA* gene coding for this protein prevent sequestration, leading to rapid metabolism and renal clearance of vitamin E and subsequent severe isolated deficiency (8).

Vitamin E plays a vital role in the body inhibiting oxidative destruction of cellular membranes. It has also been shown to have an important role in foetal development in animals and humans. Because of its transportation in lipoproteins in the blood, it is difficult to measure vitamin E in a way that accurately reflects either tissue or serum levels or find a useful reference range as the level changes depending on age and plasma lipid levels (9). In our case the serum vitamin E levels measured were low, but this did not reflect the high oral dose the patient had taken, approximately 1250 mg daily for 6 weeks.

Causes of vitamin E deficiency include malnutrition (particularly in children where demands for vitamin E are higher and stores lower) and malabsorption. Malabsorption can be caused by anything that affects the absorption of fats in the small intestine, including short bowel syndrome, pancreatic insufficiency, cystic fibrosis and bariatric surgery (9). These cases may present symptomatically with a progressive neurological disorder, starting with peripheral sensory neuropathy and spinocerebellar syndrome progressing to ataxia. Of course, patients may not report symptoms, particularly in older age such as in the patient presented here, highlighting the importance of screening for vitamin E deficiency in those with risk factors.

Vitamin K

Vitamin K plays a vital role in the coagulation cascade and haemostasis, where it acts as a cofactor for the enzyme gamma-glutamyl carboxylase. This enzyme is responsible for activation of factors II, VII, IX and X (10).

Like vitamin E, vitamin K is solubilised into micelles by bile salts and subsequently absorbed by enterocytes. The two main sources of vitamin K are dietary phylloquinone (vitamin K1) and menaquinone (vitamin K2) which is obtained via symbiosis with the gut microbiome. Patients have been shown to be vitamin K1 deficient post malabsorptive bariatric surgery (11) however this did not lead to any appreciable difference in prothrombin time or INR. There are cases where vitamin K deficiency has also been attributed to broad spectrum antibiotics disrupting the menaquinone producing bacteria (12). Coagulation times do not necessarily change in people with vitamin K deficiency or those receiving supplementation (13) which may explain why Homan and colleagues (11) did not observe appreciable differences in coagulation times associated with Vitamin K deficiency. This suggests vitamin K absorption and metabolism must be severely affected before an appreciable difference in clotting times is observed.

Vitamin E Toxicity

Given vitamin E's *in vivo* function as an antioxidant, significant interest has been shown in its role as a preventer of atherosclerosis and cardiovascular disease (14). Despite this, guidelines for cardiovascular disease do not recommend its use (15) and randomised controlled trials have shown conflicting results (16). More concerning has been studies demonstrating the deleterious effects of too much vitamin E. There is a consensus that bleeding risk is the major adverse effect associated with excess vitamin E, and this defines the safe upper limit for intake (17). High vitamin E levels prevent both platelet aggregation and carboxylation of vitamin K dependent clotting factors. A meta-analysis of studies comparing the effects of vitamin E supplementation found a statistically significant increase in the risk of hemorrhagic stroke, and a smaller reduction in ischemic stroke (18).

Conversely short-term dosing (360 mg for 14 days) showed no effect on coagulation or platelet aggregation in healthy individuals (19). Other studies have made a case for the safety of vitamin E at doses higher than this (20). Currently the European Food Safety Association Panel on Nutrition, Novel Foods and Food Allergens suggests an upper limit of 300 mg/day but says this recommendation does not apply in patients with vitamin K deficiency, on vitamin K antagonists or on anti-platelet medication (21). In most cases of vitamin E induced coagulopathy, a further risk factor was contributing to vitamin K depletion or inactivity (10, 22, 23). Only one previous case report was found where vitamin E appears to have caused a vitamin K dependent coagulopathy without another predisposing factor (23). In this case vitamin E was taken as a non-prescribed supplement without proven pre-existing deficiency, unlike in our case of taking a significantly greater dose than prescribed as part of replacement therapy.

These studies suggest that excess vitamin E as an isolated supplement can increase bleeding risk in susceptible populations. This is likely to include patients with other risk factors for vitamin K deficiency and those already on treatments that affect platelet aggregation. However adequate intake of vitamin E as part of a balanced diet that includes other micronutrients is likely to play a beneficial role in reducing cardiovascular and cerebrovascular disease. In our case the patient's high doses of vitamin E likely led to deranged coagulation because her BPD was already a risk factor for vitamin K deficiency.

Learning Points

- ∉ High doses of vitamin E supplementation can cause a reversible coagulopathy in the setting of compromised vitamin K absorption or function.
- ∉ Treatment with oral vitamin K and cessation of vitamin E was effective in normalizing coagulation in this case.
- ∉ Monitoring for coagulopathy should be considered in patients with risk of vitamin K deficiency or those on vitamin E replacement or supplements

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Figure Captions

- Figure 1: a timeline of the patient's serum INR/APTT values and how they respond to the patient's vitamin E prescription

Patients Perspective

I felt well and took the vitamin E in excess in error. I experienced no symptoms and the abnormity was picked up on the routine blood tests done by the doctor. I understood that the blood tests were important for monitoring and now understand that vitamin E can be harmful in excess. People often think that too much vitamins can't cause any harm, but this is obviously not the case and people should be made aware of this.

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