Portion-controlled spinach for improved vitamin K antagonist anticoagulant control

Stable therapeutic anticoagulation protects patients with a predisposition to thrombosis while limiting the risk of bleeding. Therapeutic anticoagulation using vitamin K antagonists (VKAs) is most readily achieved in patients with consistent dietary vitamin K intake (Shearer, 1995). Poor dietary vitamin K intake enhances the pharmacodynamic effect of VKAs and confers increased risk of bleeding (Sconce et al., 2007; Rombouts et al., 2010), estimated to occur in 3–4% of patients taking warfarin (Hansen et al., 2018).

Vitamin K supplementation has been proposed to improve control for patients on VKAs in whom conventional dosing algorithms have failed (Udall, 1968). This approach is not yet widely adopted in clinical practice, largely because patient studies have been unable to demonstrate any consistent benefit (Mahtani et al., 2014; Violi et al., 2016). The current dietary advice given to patients is to maintain a consistent vitamin K intake by avoiding changes in dietary habits and abstaining from foods perceived as being rich in vitamin K (Violi et al., 2016). The British Journal of Haematology guidelines on oral anticoagulation with warfarin (Keeling et al., 2011) state that fluctuations in international normalised ratio (INR) can be reduced for patients with unstable INRs by supplementing the diet with 100–150 µg vitamin K or altering the dietary intake of vitamin K.

A 2017 survey by the UK NEQAS for Blood Coagulation found that the use of vitamin K supplementation in anticoagulation centres in the UK is uncommon. Of the 4438 centres surveyed in the UK, Ireland and New Zealand, 577 responded. One percent of respondents indicated that they use vitamin K supplementation routinely in all patients on VKAs and 11% indicated it is used in select patient groups (patients with low serum transthyretin concentrations/concern over dietary intake).

To understand the reasons for the disparity between the guidelines and routine clinical practice we must consider the barriers to the use of supplements or dietary modifications. For supplements, there is insufficient regulation for clinical use (they are classed as a food rather than a drug). With no certified formulation designed for use in anticoagulation, clinicians are limited to advising the use of over-the-counter supplements. The vitamin K content of these supplements varies, and in the UK is typically 75 µg/tablet (UK RDI), although some do not include any vitamin K. There is also limited assurance in the accuracy of the stated vitamin K content (Bartle et al., 2013). Moreover, supplements often simply state ‘vitamin K’ on their nutritional information and, although most are likely to contain phylloquinone (vitamin K₁), some are also available containing menaquinone-4 or menaquinone-7 (both from the vitamin K₂ series), which have different pharmacological properties to vitamin K₁. Some tablet formulations may have stability issues (depending on the excipient used), as vitamin K is known to be unstable in alkaline conditions. Multi-vitamin supplements often also contain vitamin E, and there is a known interaction between vitamins E and K, resulting in lowered vitamin K stores (Traber, 2008).

When considering the challenges associated with modifying dietary habits, problems are related to the consistency of the intake of foods rich in vitamin K₁ (kale, cabbage, spinach, etc.). Clinical trials of dietary modifications in anticoagulated patients showed that by increasing intake by ≥150 µg/day, the quality of anticoagulation was improved in patients with a history of instability (Sorano et al., 1993; Ferland et al., 2019). Here we provide the rationale for a simplified approach to dietary modification, with the objective of helping anticoagulation centres to trial this approach. Supermarkets in the UK commonly stock frozen spinach in pre-prepared portions, which makes it possible to maintain portion-control and ensure a consistent vitamin K₁ intake. Spinach only contains vitamin K₁ (rather than other forms of vitamin K) and very little vitamin E. The vitamin K₁ content has been reliably estimated for raw spinach (498 µg/100 g, SD = 155), and boiled spinach (525 µg/100 g, SD = 72) (Kamao et al., 2007). A 750 g bag of frozen chopped spinach portions, costing £1.20, contained 25 individual portions weighing on average of 30 g each (range = 26–32 g). After boiling for five minutes, the drained spinach weighed on average 26 g per portion. Applying published data on the vitamin K₁ content of spinach, this equates to 110 µg/portion of frozen spinach. Vitamin K₁ is heat stable, surviving the cooking process intact, and is insoluble in water used for cooking – hence the higher content in boiled spinach (per weight) compared to raw.

The bioavailability of vitamin K₁ in spinach differs from that in supplements. The vitamin K₁ absorption profiles are shown following dietary supplementation and an equivalent IV dose (Fig 1) (Garber et al., 1999) and (Fig 2) (Gijsbers et al., 1996). Oral supplementation and intravenous vitamin K₁ result in highly elevated serum vitamin K₁ concentrations, remaining above the upper limit of the reference range for...
many hours post-administration. In comparison, the equivalent dietary vitamin K₁ intake results in a lowered peak serum concentration but is more constantly within the reference range. It is therefore likely that this regime is better suited for achieving consistent anticoagulation. It is also worth noting that dietary vitamin K₁ absorption is improved by consuming it with oil to stimulate bile secretion.

We suggest that a controlled daily portion of spinach is a feasible approach to enhanced anticoagulant control. One daily portion costs <5 pence per patient and provides a consistent dose of vitamin K₁, giving stable serum vitamin K₁ concentrations. No weighing or special preparation is required, which makes it suitable for integration into any dietary routine. We suggest that one or two portions should be consumed daily (depending on body mass) with an oil, or combined with other foods containing fat. In addition to the possibility of improved anticoagulation control, benefits for patients may include the concomitant increased intake of potassium, vitamin C and folate. Clinicians should also consider that the relatively high oxalate content of spinach may make this approach unsuitable for those at risk of developing kidney stones and there may also be a requirement to monitor iron stores since oxalate inhibits iron absorption.

Fig 1. Adapted from (Garber et al., 1999). Subjects ingested either a supplement containing 500 µg of vitamin K₁ or 495 µg vitamin K₁ in the form of raw spinach. The grey area represents the reference range for vitamin K₁ in human serum (0–34–3–60 nmol/l) (Shearer et al., 1988) and the dotted line is baseline serum vitamin K₁ concentrations.

Fig 2. Adapted from (Gijsbers et al., 1996). Absorption of vitamin K₁ from spinach compared to IV vitamin K₁ (where the absorption can be assumed to be close to 100%). The grey area represents the reference range for vitamin K₁ in human serum (0–34–3–60 nmol/l) (Shearer et al., 1988).


