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Vitamin K – an understated dairy nutrient

THIS ISSUE PAGES

EDITORIAL

Interest in vitamin K has seen a resurgence in recent years, with a new focus on the previously overlooked isomer - vitamin K2. In this edition of *DN Forum*, we examine the existing knowledge on vitamin K, highlighting opportunities and some research gaps. We also look at the important role that fermented dairy products, such as cheese, can play in supporting health and vitamin K status.

Also on page 4, we feature our new consumer resource on 'Eating Sustainably'. We hope you enjoy this edition and look forward to any feedback or comments you wish to share: nutrition@ndc.ie

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Summary points

- Vitamin K exists in two natural forms, phylloquinone (vitamin K1) and menaquinone (vitamin K2). Phylloquinone is mainly found in dark green, leafy vegetables, whereas menaquinone (a family of isomers) are produced by bacteria, such as those involved in food fermentation and some colonic microbiota. Menaquinone occurs naturally in meat, dairy and eggs.
- Differences in bioavailability and tissue distribution indicate that while vitamin K1 is more plentiful in the diet, vitamin K2 has higher efficacy and functional capacity. Vitamin K1 forms 90% of the total vitamin K intake but only 10-15% of this is absorbed in the digestive tract. Vitamin K2 intake is much lower and often more difficult to quantify but its absorption is almost complete. Therefore, it is now acknowledged that the relative contribution of vitamin K2 to human vitamin K status is at least equal to that of vitamin K1.
- Originally recognised for its role in blood coagulation, evolving research now indicates that vitamin K also plays important roles in bone mineralisation and vascular health. Vitamin K2 in particular has been shown to promote the calcification of bones and prevent calcification in blood vessels. It is now recognised that vitamin K2 may be an important missing link between diet and some chronic diseases, including osteoporosis and cardiovascular disease.
- A recommended intake for vitamin K has not been established but an adequate intake of 1 µg/kg body weight per day or 70 µg/day is suggested for all European adults. This value does not include vitamin K2 due to insufficient data for compiling suggested intakes. In Ireland, 55% of adults have vitamin K1 intakes below the suggested value. Furthermore, those who avoid animal products may be lacking important dietary sources of vitamin K2. More work is needed to determine how insufficient intakes can be identified.
- Fermented dairy products such as cheese are among the most abundant sources of vitamin K2 in the western diet. Novel research by Food for Health Ireland is setting out to assess the vitamin K content of Irish dairy products and to determine the impact of grass-feeding on nutrient concentrations.

Importance of vitamin K in the diet

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Introduction

First reported in the 1930s, vitamin K was discovered by chance during a cholesterol experiment in chickens. In this experiment, chickens that were deprived of dietary fat began to display haemorrhages, which led to further investigation and the discovery of a fat-soluble compound needed for blood coagulation. The compound was coined '*koagulation vitamin*', or simply vitamin K. Consequently, most of us are first introduced to vitamin K as infants and today it is standard practice to give all newborn babies an intramuscular injection of vitamin K, for the prevention of haemorrhagic disease[1]. Infants are at higher risk of low vitamin K status as it is poorly transferred across the placenta during pregnancy[2].

As knowledge on vitamin K has deepened, research now indicates that its functionality extends beyond blood coagulation and that the nutrient also plays important roles in bone mineralisation and vascular health[3]. Vitamin K acts as an exclusive cofactor for the enzyme, gamma-glutamyl carboxylase. As its name suggests, this enzyme is involved in carboxylation reactions, which are required to convert specific proteins into their active form. These specific proteins, known as 'gla-proteins' include blood clotting factors such as prothrombin; bone and tooth factors such as osteocalcin; and vascular factors such as the matrix-gla protein[1,3]. When gla-proteins are activated, they have the capacity to bind calcium and this is central to their biological activity in both clotting and mineralisation.

In the European Union, there are two authorised health claims relating to vitamin K, indicating that it "contributes to the maintenance of normal bone" and "contributes to normal blood coagulation"[3]. At the time the European Food Safety Authority (EFSA) Opinion was published in 2009, the evidence relating to vitamin K's contribution to the normal function of the heart and blood vessels was considered insufficient[3]. However, since then, research has been building to support a role for vitamin K in vascular health and the reduction of cardiovascular disease risk[4-7]. Given that vitamin K's role in both bone and cardiovascular health is seldom highlighted, its potential in reducing the risks of osteoporosis and cardiovascular disease is perhaps understated. As dairy is an important provider of vitamin K, the purpose of this publication is to examine dairy's potential and explore novel Irish research in the area.

What is vitamin K?

Vitamin K exists in various forms and refers to a family of fat-soluble vitamins. There are two natural forms, Phylloquinone (vitamin K1) and Menaquinone (collectively known as vitamin K2 or MK-n, depending on the length of the side chain, e.g. MK-4 to MK-14). Menadione (vitamin K3) is a synthetic, water-soluble form of the vitamin[8,9]. Each of these molecules have a similar structure and are characterised by having a body of quinone rings (2-methyl-1, 4-naphthoquinone). They differ by the length and degree of saturation and the number of repeating isoprene units in their side chain. Phylloquinone is mainly found in dark green leafy vegetables and algae, whereas menaquinone is produced by bacteria, such as those involved in food fermentation and some colonic microbiota. Menaquinone also occurs naturally in meat, cheese and eggs[1,3,8]. **Table 1** shows the vitamin K content of some common food sources[10-12]. The data for vitamin K2 can appear to vary significantly but this is mainly related to the capacity of the analysis protocol to capture all menaquinone isomers. Therefore, in some cases, the true quantity may be underestimated.

Both vitamin K1 and K2 can also be produced by biotechnological processes, such as biosynthesis from cell cultures or algae[13], which can be used for supplementation or food fortification. Generally, the synthetic form, menadione is no longer used as very high doses have been associated with oxidative damage[8].

Food	Vitamin K1 µg/100 g	Vitamin K2 µg/100 g
Kale[10]	73.3	No data
Spinach[10]	96.7	No data
Broccoli[10]	146.7	No data
Sauerkraut[10]	22.4	5.5
Beef[10]	0.02	1.9
Liver (beef)[10]	2.3	11.2
Chicken[10]	Not detected	10.1
Cheddar (UK)[12]	2.2	23.5
Cheddar (US)[11]	2.4	279
Brie[10,12]	4.9	12.5
Feta[12]	1.4	11.7
Stilton[10,12]	3.6	49.4
Blue cheese (US)[11]	3.2	437
Mozzarella[12]	1.5	6.2
Münster[10,12]	2.1	80.1

▲ Table 1: Vitamin K content of common food sources[10-12]

Vitamin K metabolism

Vitamin K is predominantly absorbed in the small intestine in the presence of dietary fat and then transported to the liver by chylomicrons. Vitamin K1 remains in the liver, where it is metabolised rapidly and is mainly associated with coagulation. However, vitamin K2, particularly the longer chain menaquinone has a longer half-life, which means they circulate for longer and thus reach extrahepatic tissues, including the skeletal and circulatory systems[9]. MK-7, MK-8 and MK-9 account for 70% of activity outside the liver, with phylloquinone accounting for just 5%[10]. This gives rise to the variance in function between vitamin K isoforms and why vitamin K2 is more associated with bone and vascular derived protein activity.

Both the food matrix that provides the nutrient and the structural variation between the various vitamin K molecules appear to influence its digestive fate[14]. For example, a study comparing the bioavailability of a vitamin K1 supplement, a vitamin K1-rich food (spinach) and a vitamin K2-rich food (natto), showed faster absorption from the supplement, and the circulating amounts of vitamin K2 were 10 times higher compared to K1[15].

Earlier research focused mainly on vitamin K1 because dietary phylloquinone forms 90% of the total vitamin K intake. However, only 10-15% of this is absorbed in the digestive tract[15]. Although vitamin K2 intakes are much lower and often more difficult to quantify, its absorption is almost complete and therefore, its relevance should not be dismissed[12]. The differences in bioavailability and tissue distribution indicate that while phylloquinone is more plentiful in the diet, menaquinone has a higher efficacy and wider functional capacity[9]. Due to bioavailability differences, it is now acknowledged that the relative contribution of menaquinone to human vitamin K status is at least equal to that of phylloquinone[12]. It is now also recognised that vitamin K2 may be an important missing link between diet and several chronic diseases[4]. While longer chain menaquinone tend to have longer half-lives, MK-7 is understood to have the greatest bioavailability of the vitamin K2 molecules[9,10,16].

During metabolism, vitamin K may interact with other nutrients. For example, excessive intakes of vitamins A or E can inhibit vitamin K action[8,17]. Drug interactions with vitamin K are few but anticoagulant drugs such as warfarin interfere with vitamin K's activation of the coagulation cascade. Therefore, although vitamin K deficiency is

uncommon, those on anti-coagulation therapy are at increased risk of deficiency. Vitamin K can also be used clinically for the reversal of over-anticoagulation caused by taking too much warfarin[17].

Requirements and adequate intakes

Currently, a conclusive recommended intake (Dietary Reference Value) for vitamin K has not been established, due to a lack of sufficient data available at the time of the most recent EFSA review in 2017. As an alternative, EFSA proposed an adequate intake (AI) of 1 µg/kg body weight per day or 70 µg/day for all adults[1]. In the United States, the Institute of Medicine (IOM) set a slightly higher AI for vitamin K at 90 and 120 µg/day for adult females and males respectively[18]. These values are based solely on representative vitamin K1 intake data from healthy individuals following an average diet. Given that representative samples showed no signs of deficiency, it was concluded that this amount would be adequate for the majority of the adult population. It is important to note that both the EFSA and IOM values did not take vitamin K2 intake into account due to considerable uncertainties regarding intakes and metabolism. However, more recently, a review of the metabolic capacity of vitamin K2 suggested that it meets all of the criteria necessary to have a specific dietary recommended intake of its own, which is separate from that of vitamin K1[10]. Regardless of whether the isomers have individual or combined recommended intakes, the expanding evidence suggests that the importance of vitamin K2 should not be overlooked[4].

There are relatively few reports of vitamin K toxicity, with almost no adverse effects associated with high intakes[1,8]. Therefore, a Tolerable Upper Intake Level (UL) has not been established. In the absence of a UL for vitamin K intake, the UK Expert Group on Vitamins and Minerals have established a safe guidance level of 1000 µg/day, on the basis that no adverse effects were observed at doses of 10,000 µg/day (UK EG). In Japan, supplementation of up to 45-90 mg/day of MK-4 has been used for several years for the treatment of osteoporosis, with no adverse effects reported[19].

As vitamin K is available from a wide range of foods and also provided by gut bacteria, deficiency is uncommon. It is generally secondary to conditions such as malabsorption or malfunction of the gut[8]. In addition to newborn babies, exclusively breastfed infants are more susceptible to deficiency, due to the low content in human milk. Consequently, infant formula is often fortified with vitamin K[2]. Without the consumption of fermented foods, those who avoid animal products may have low intakes of vitamin K2. Given the emerging evidence that vitamin K2 has different metabolic activity, more work is necessary to determine how insufficient intakes can be identified.

Vitamin K intake in Ireland

There are key challenges in assessing vitamin K intakes in national dietary surveys. These include the global lack of food composition data and the lack of recognition for vitamin K2's contribution to overall vitamin K status. In Ireland, recent efforts have been made to populate the Irish Food Composition Database with available values for both vitamin K1 and K2[20]. The most recent data on Irish intakes show a mean daily intake of 85.2 µg for vitamin K1 (with a standard deviation of 59 µg)[21]. However, 55% had intakes below the AI value. The main contributors to vitamin K1 intake were vegetables, with smaller amounts coming from fried potatoes, meat and dairy. Another study examined the intake of vitamin K2 and indicated a mean intake of 42-64 µg/day, with key sources including meat, meat products, milk and cheese[22]. With recommendations to choose only low-fat dairy and to reduce meat intake becoming more prevalent, a growing number of individuals may consequently be avoiding important sources of vitamin K2.

Vitamin K and health

As mentioned above, vitamin K has established roles in blood coagulation, bone metabolism and vascular condition. The past decade has seen increasing attention towards the benefits of vitamin K2, particularly in relation to its potential role in the reduction of osteoporosis and cardiovascular disease risk.

Bone health: Calcium, vitamin D and vitamin K act synergistically for bone health. Vitamin D supports calcium absorption, while vitamin K facilitates its mineralisation into bone tissue, through activation of the vitamin K-dependant protein, osteocalcin. Osteocalcin is a key hormone secreted by bone-building osteoblasts during synthesis of bone and dentine. Research shows that MK-7 in particular is associated with increases in both bone quality and strength[16]. A meta-analysis of vitamin K supplementation in adults ranging from 29 – 72 years, concluded that menaquinone was associated with approximately 60% reduction in vertebral fractures, 77% reduction in hip fractures and 81% reduction in all non- vertebral fractures[19].

Heart health: Vascular calcification is a strong predictor of cardiovascular disease[23]. When the vitamin K dependant matrix-gla protein (MGP) is activated, it has a high affinity for calcium and can thereby inhibit vascular calcification. However, due to conflicting reports more research is warranted[24]. The cardioprotective role of vitamin K has been shown by improved vascular elasticity and reduced calcification following supplementation[25]. The Rotterdam study of over 4800 individuals, showed that those with the highest menaquinone intake had a 57% lower risk of dying from heart disease[5]. A more recent study in Norway evaluated vitamin K intake and risk of coronary heart disease, indicating that higher intakes of vitamin K2, but not K1, were associated with lower risk[6]. Given the risk of arterial calcification in the absence of vitamin K, it has been highlighted that calcium supplementation may not be ideal for those with low vitamin K status[23].

Emerging roles: Vitamin K related disease risk reduction has been suggested for diabetes, cancer, liver disease, kidney disease, multiple sclerosis and obesity[9]. In addition, menoquinones have been positively associated with cognitive function in older Irish adults[26].

▲ Figure 1: Total vitamin K content of milk, cheese and yogurt[11]

Dairy and novel Irish research

Dairy is perhaps best recognised for its calcium content but it also contains a rich matrix of other nutrients, including vitamin K[27]. The quantity and isoforms present vary significantly across dairy foods, with fermented dairy products such as cheese being among the most abundant source of menaquinone in the western diet[11-12]. One study assessed the vitamin K content of a wide range of dairy products in the US and found that total vitamin K content in cheese ranged from 40 µg/100g to 850 µg/100g[11]. All forms of cheese contained MK-9, MK-10 and MK-11, with some samples also containing phylloquinone, MK-4, MK-7, MK-8 and MK-12. A range of vitamin K isomers were also found in milk and yogurt samples, with vitamin K1 only detected in full-fat samples. Reduced-fat or fat-free dairy products also contained lower amounts of total vitamin K, shown in **Figure 1**[11]. Another study which assessed the vitamin K content of various European cheeses detected much lower amounts of menaquinone but indicated that more mature cheeses had higher concentrations, due to greater bacterial growth during ripening[12]. In a cheese intervention study, volunteers consuming 57g Jarlsberg cheese daily for five weeks, showed increased serum vitamin K2 and osteocalcin levels, in addition to improved blood lipid and blood pressure profiles[7]. Such emerging data on the vitamin K content of cheese strengthens its role as part of a heart-healthy diet[5,12] (this topic is discussed in volume 7, issue 3 of *DN Forum*).

As the vitamin K content of dairy products can vary across geographical regions, a need for national databases and intake data has been highlighted[12]. In the future, the possibility of fortified milk could offer potential for enhancing vitamin K intakes for individuals

with sub-optimal status. Research by Food for Health Ireland is focused on exploring various health components within dairy foods and one element of this will assess vitamin K in Irish dairy. Given our grass-based production system, it will be important to determine whether this impacts the vitamin K1 content of Irish dairy. In addition, the most commonly consumed cheese, Irish Cheddar as a source of vitamin K2 needs clarification/assessment.

Conclusion

A focus on the unique properties of vitamin K2, and not just vitamin K1, has provoked an exciting evolution in vitamin K research. More work is needed to populate food composition databases, assess population intakes and to further explore vitamin K's potential in disease risk reduction. Such data would support the establishment of recommended intakes and give more clarity around the unique health benefits of this previously understated nutrient.

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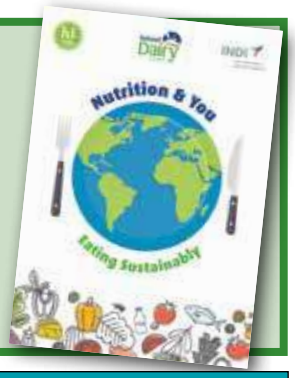
New Resource

With a growing awareness of how the food we eat impacts climate change, consumers are seeking advice on how to follow a healthy, sustainable diet. In response, the National Dairy Council has produced a new booklet on Eating Sustainably. The booklet outlines key principles of a sustainable diet and offers practical tips on lifestyle choices that can make a difference.
It is endorsed by the Irish Nutrition and Dietetic Institute and free copies can be ordered by contacting **publications@ndc.ie**



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