

Patients on Warfarin Can Consume Soyfoods

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The connection between the blood thinner warfarin and the consumption of soyfoods is by no means an obvious one. But from time to time, questions about this relationship arise, as was the case when a vegan recently expressed concern about consuming soyfoods because he is on warfarin. For the most part, this concern is without foundation. Interest in this relationship is mostly related to the vitamin K content of soy, but not entirely. So, let us look at the data, starting with some basic background information about warfarin and vitamin K.

Warfarin has been used for nearly 70 years for its anticoagulant effects.¹ Indications for its use include the prevention and treatment of thromboembolism (obstruction of a blood vessel by a blood clot that has become dislodged from another site in the circulation) and various cardiovascular conditions such as atrial fibrillation (irregular heartbeat that can lead to blood clots, stroke, heart failure). Warfarin works by competitively inhibiting the vitamin K epoxide reductase complex 1, which is an essential enzyme for activating vitamin K in the body.

Vitamin K is a fat soluble vitamin that functions as a coenzyme during the synthesis of the biologically active form of a number of proteins involved in blood coagulation and bone metabolism.² Research of the proposed benefits of vitamin K include among others, areas such as osteoarthritis,³ diabetes,⁴ vascular disease,⁵ cognitive function,⁶ and fractures.⁷ There are two forms of vitamin K, phylloquinone (vitamin K1) and a series of menaquinones (vitamin K2). The former predominates in plants, especially green leafy vegetables; the latter are predominantly of bacterial origin and are present in modest amounts in various animal-based and fermented foods.

Since warfarin works by inhibiting the activity of vitamin K, patients using this drug need to be mindful of the amount of vitamin K they consume. Consuming too much can inhibit the efficacy of the drug, thereby raising risk of developing blood clots. Too little vitamin K could result in excessive bleeding. In general, the goal is to maintain a consistent vitamin K intake so blood levels can be titrated accordingly. In the U.S., men and women over the age of 20 consume on average 118 and 123.5 ug/d of vitamin K, respectively,⁸ which just about matches the adequate intake for men and exceeds the adequate intake for women by about one-third (table 1). So, with that background in mind, how does soy enter the picture?

Table 1. Adequate Intakes (AIs) for Vitamin K

Age	Micrograms (ug)			
	Male	Female	Pregnancy	Lactation
Birth to 6 months	2.0	2.0		

7–12 months	2.5	2.5	
1–3 years	30	30	
4–8 years	55	55	
9–13 years	60	60	
14–18 years	75	75	No increase required
19+ years	120	90	No increase required

The report that raised most concern about the consumption of soy by patients on warfarin was published in 2002. It describes a 70 year-old Caucasian male taking warfarin who developed subtherapeutic international normalized ratio (INR) values allegedly as a result of his soymilk consumption.⁹ A subtherapeutic INR indicates the drug warfarin was not performing as required. The author of this report concluded that “healthcare professionals should be alerted to the potential implications of this food/drug interaction.” However, this was not the first time an interaction between soy and warfarin had been published in the literature.

Perhaps the first mention of this interaction was in 1978, when it was suggested that the fermented soybean product natto could antagonize the effects of warfarin.¹⁰ Since this article was published in Japanese and involved a food rarely consumed outside of Japan, it isn’t surprising that it didn’t receive much attention. A decade later, research by Kudo¹¹ confirmed the initial report. So, what accounts for this interaction? The answer is --vitamin K.

As shown in table 2, natto has an incredibly high vitamin K content as one serving provides many times the daily value. Furthermore, most of the vitamin K in natto is in the form of MK-7. Menaquinones are designated as MK-4 through MK-13, based on the length of their side chain. MK-4, MK-7, and MK-9 are the most well-studied menaquinones. Few data are available on the relative bioavailability of the various forms of vitamin K supplements, but Schurgers et al.¹² found that MK-7 is well absorbed and has a relatively long half-life resulting in stable and high serum levels. Consequently, these authors recommended that hematologists should be aware that preparations supplying 50 ug/d or more of MK-7 may interfere with oral anticoagulant treatment in a clinically relevant way.

Table 2. Vitamin K content of Selected Foods¹³

Food	ug/100 g		
	PK	MK-4	MK-7
Natto	45	2	939
Chopped natto	23	ND	827
Black (soybean) bean natto	50	ND	796
Tofu (firm)	12	0.04	ND
Tofu (silken)	12	0.01	ND
Tofu (deep fried)	62	ND	ND
Cabbage (boiled)	180	0.4	ND

Broccoli (boiled)	280	ND	ND
Spinach (boiled)	525	ND	ND
Lettuce (raw)	78	ND	ND
Red leaf lettuce (raw)	166	ND	ND

The high concentration of vitamin K in natto is the result of fermentation by *Bacillus subtilis*, which produces vitamin K. In fact, this bacterium continues to synthesize vitamin K in the intestine for several days after natto has been eaten.¹⁴ The high vitamin K content of natto may be why this food was recently found to be associated with a reduction in the risk of osteoporotic fractures among Japanese women.¹⁵ Vitamin K participates in the gamma-carboxylation of osteocalcin, a protein involved in bone mineralization.¹⁶ However, the high vitamin K content of natto is also why it is recommended that patients on warfarin avoid this food.¹⁷ But what about other soyfoods?

As can be seen from table 2, two types of tofu provide about 12 ug/100 g, although another type contained much higher values, but nothing like natto or broccoli, cabbage, and spinach. And most soymilks provide fewer than 10 ug/cup, although again, there is a range.¹⁸ A cup of boiled soybeans provides 33 ug but that cup also provides more than 30 grams of protein.¹⁸ Soybean oil is much higher in vitamin K than are other oils, but a tablespoon provides only about 21% and 28% of the adequate intake for adult men and women, respectively.¹⁸ So, there is no reason to avoid most soyfoods based on their vitamin K content.

Finally, what might have been responsible for the interaction between soymilk and warfarin mentioned previously, when the soymilk consumed by the patient provided less than 1 ug vitamin K? The answer is not known, but the author of this case report speculated that the isoflavones in soy may have altered warfarin absorption and metabolism. However, the soymilk consumed likely contributed no more than 25 mg of isoflavones, which is a relatively small amount considering average intake among older Japanese men is 25 to 50 mg/day.¹⁹ One might reasonably wonder why more cases of soy interfering with warfarin have not been reported, if in fact, isoflavones affect the efficacy of this drug.

In conclusion, except for natto, there appears to be little evidence that warfarin patients need to avoid soyfoods.

Table 3. Vitamin K Content of Selected Oils per Tablespoon (~14 g) according to USDA National Nutrient Database for Standard Reference Release 28¹⁸

Type of Oil	USDA Nutrient Database Number
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