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ORIGINAL CONTRIBUTION

Relationship between diet and anticoagulant response to warfarin

A factor analysis

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Abstract *Background* Diet composition is one of the factors that may contribute to intraindividual variability in the anticoagulant response to warfarin. *Aim of the study* To determine the associations between food pattern and anticoagulant response to warfarin in a group of Brazilian patients with vascular disease. *Methods* Recent and usual food intakes were assessed in 115 patients receiving warfarin; and corresponding plasma phylloquinone (vitamin K_1), serum triglyceride concentrations, prothrombin time (PT), and International Normalized Ratio (INR) were determined. A factor analysis was used to examine the association of specific foods and biochemical variables with anticoagulant data. *Results* Mean age was 59 ± 15 years. Inadequate anticoagulation, defined as values of INR 2 or 3, was found in 48% of the patients. Soybean oil and kidney beans were the primary food sources of phylloquinone intake. Factor analysis yielded four separate factors, explaining 56.4% of the total variance in the data set. The factor analysis revealed that intakes of kidney beans and soybean oil, 24-h recall of phylloquinone intake, PT and INR loaded significantly on factor 1. Triglycerides, PT, INR, plasma phylloquinone, and duration of anticoagulation therapy loaded on factor 3. *Conclusions* Fluctuations in phylloquinone intake, particularly from kidney beans, and plasma phylloquinone concentrations were associated with variation in measures of anticoagulation (PT and INR) in a Brazilian group of patients with vascular disease.

Key words phylloquinone – warfarin – oral anticoagulant response – kidney beans – diet

Introduction

Treatment of vascular obstructive diseases with warfarin, a coumarin-based oral anticoagulant, needs a careful monitoring of anticoagulation in order to maintain a stable response.

Intra-individual variability in response to warfarin has been attributed to genetic polymorphisms in the vitamin K epoxide reductase gene and the CYP2C9 [1], and may also be due in part to variations of the dietary intake of vitamin K [2, 3]. Two main forms of interaction between diet and oral anticoagulation have been described: high dietary vitamin K intake and insufficient anticoagulation; and low dietary vitamin K and excessive anticoagulation, with consequent hemorrhage risks [4, 5].

Case studies have historically focused on single foods as the dietary source responsible for the interaction with warfarin in anticoagulation therapy, without any evaluation of other potential dietary sources. The primary dietary source of vitamin K is phylloquinone (vitamin K_1). Vegetable oils and green leafy vegetables have the highest phylloquinone content, but foods that contain lower amounts may become important dietary sources of phylloquinone when ingested in large quantities [6, 7].

The International Normalized Ratio (INR) has been used for analysis of the relationship of phylloquinone intake levels with anticoagulation response [8]. Although INR fluctuations are sometimes attributed to variations in the dietary phylloquinone intake, particularly fluctuations in green, leafy vegetables, the evidences of this putative relationship is limited [9]. A few studies showed the influence of diet on anticoagulation instability [3, 8, 10], but the dose of phylloquinone intake relative to the warfarin dose required to create an unstable anticoagulant response is not known [9]. Further, diversity in food patterns and food choices may also be important in evaluating phylloquinone–warfarin interactions. With regard to patients being followed in Brazilian anticoagulant clinics, food habits, cultural, and social characteristics are different from those of the USA, making it possible that food sources other than green, leafy vegetables, may make a greater contribution to the phylloquinone content of the diet, and hence may contribute to potential dietary fluctuations in intake. Therefore, the objective of the present study is to determine the associations between recent and usual intake of common foods consumed by patients with vascular diseases and participating in a Brazilian anticoagulant clinic and their anticoagulant response to warfarin.

A factor analysis was carried out to examine the association of specific foods and biochemical variables with anticoagulation data. Factor analysis is a common statistical method used to identify patterns of food intake in reliable and reasonably way [11–13]. This multivariate statistical technique, also, allows categorization of various functional variables and diet features without a priori assumptions.

Patients and methods

Patients

One hundred fifteen (115) patients of both genders, aged 20–89 years, were randomly recruited from the Outpatient Clinic of Vascular Obstructive Diseases of the Botucatu Medical School, São Paulo, Brazil. All participants of the study were using sodium warfarin anticoagulant medication (Marevan®). The sample size was calculated taking in consideration the total number of ambulatory patients and keeping the proportion of patients with recent or long use of warfarin. The study protocol was approved by the Human Research Ethics Committee of the Medical School of Botucatu (UNESP) and the Tufts-NEMC Institutional Review Board, and the patients signed a written consent.

Demographic and clinical profiles

Demographic and clinical data were obtained from a medical history and physical examination conducted at the baseline visit. A summary of patient characteristics is presented in Table 1.

Assessment of dietary intake

Recent dietary intake and usual dietary pattern were assessed by 24-h recall (24 hR) and food frequency questionnaire (FFQ), respectively. The dietary intake information was collected with the use of a two-dimensional food portion visual aid [14]; the amounts of food were expressed in kitchenware measures and later converted in grams (g) or milliliters (ml), according to Pinheiro et al. [15]. The FFQ included 97 items of foods, preparations and drinks, from which usual daily intakes were estimated, during periods when patients were under treatment with warfarin; therefore, the period of dietary analyses ranged from 30 days to 1 year. The period evaluated with the FFQ was related to the time the patients were in use of warfarin. The list of items was based on foods frequently consumed by a representative sample of the Brazilian population, according the database of "Estudo Nacional de Despesa Familiar (ENDEF)" [16]. Nutrient calculations were performed using the software program, "Programa de apoio à nutrição"

Table 1 Patients characteristics, indication for anticoagulation, plasma phylloquinone and serum triglycerides

Characteristics	Number (%) or median (lower quartile–upper quartile)
Age (*Y*)	59 ± 15
Sex (male/female)	62/53 (54/46)
Caucasian/no-Caucasian	105/10 (91/9)
Income	
Poverty/no poverty	86/29 (75/25)
Education	
Illiterate/elementary school	99 (86)
Educated	16 (14)
Smoking/no smoking/past smoking	21/39/55 (18/34/48)
Alcohol: yes/no	22/93 (19/81)
Indication for anticoagulation	
Venous disease/arterial disease	44/66 (38/58)
Duration of anticoagulant therapy	
Short/long period[a]	48/67 (42/58)
Plasma phylloquinone (nmol/l)	2.21 (1.48–3.34)
Serum triglycerides (mg/100 ml)	142 (100.2–230)

Number (%), mean ± SD or median (lower quartile–upper quartile)
[a] Short period = <6 months; long period = ≥6 months

(Centro de Informática em Saúde da Escola Paulista de Medicina, São Paulo Brazil, 1996). Phylloquinone food composition data were provided by the Vitamin K Laboratory at Tufts University, Boston, USA [17, 18] and unpublished data).

Laboratory methods

For the laboratory measurements venous blood sample was taken at the same day that the dietary assessment and the coagulation measurements were done.

Plasma samples for phylloquinone analysis were shipped in a frozen state to Vitamin K Laboratory at Tufts University, Boston, USA, where they were frozen at −70°C until analysis. Phylloquinone was determined in plasma with EDTA by reverse-phase HPLC using post column solid-phase chemical reduction of phylloquinone to its hydroquinone, followed by fluorometric detection [19].

All other laboratory analyses were conducted at the Central Laboratory of the Clinical Hospital-Botucatu, SP, Brazil. Serum triglyceride concentration was determined by enzymatic reaction kit and measured photometrically (automatic analyzer Technicon RAXT, USA).

Oral anticoagulant therapy and control

The median dose of sodium warfarin used by study patients was calculated over a period ranging from 30 days to 1 year. The anticoagulation status was assessed by INR, using prothrombin time (PT). PT was determined in citrated plasma, by Quick's one step method [20], employing thromboplastin from rabbit brain tissue Simplastin® Excel S (Organon Teknika Company, Durham, North Carolina, USA). The value for normal PT (normal standard) was obtained from a plasma pool of volunteer donators. The INR therapeutic level was defined in this study as 2.0–3.0 [21].

Statistical analysis

The results were expressed by mean ± SD, median and 25 and 75 percentile values or percentages. The Spearman rank correlation coefficient was calculated to examine the association between variables. The level of significance was considered to be 5% for all tests. The statistical tests were performed with a SigmaStat for Windows v2.03 (SPSS; Chicago, IL).

A factor analysis was conducted to explore whether 14 variables (PT, INR, plasma phylloquinone, serum triglycerides, warfarin dose, duration of anticoagulation therapy, phylloquinone contents of foods estimated by the 24-h recalls and amounts of food estimated by FFQ: soybean oil, collards, lettuce, soup, cabbage, kidney beans, and margarine) were made up of distinctive groupings, and describe the interaction among these variables. The individual food items included in the analysis represented the major dietary contributors of phylloquinone in this clinic population, as determined by dietary assessment using 24-h recall. Factor analysis is a statistical technique that consists of clustering of variables into independent subgroups of variables called "factors", and then simplifying the factor structure by Varimax rotation [22].

Factor analysis is a statistical technique useful for identifying and summarizing inter-relationship in studies where a great number of variables are measured. The end product of the statistical procedure is the "factor matrix", showing the input variables, the "factors" and the "factor loading". The procedure leads to the clustering of variables in separate groupings; in each group, the variables are highly correlated with one another and represent a common underlying variable called "factor". The "factor loading" represents the degree to which each of the variables correlates in the factor. The variables with the high loadings on the factor are those that provide meaning and interpretation of the factor and those with low values do not contribute to the interpretation of the factor. Factor loading can vary, in value, from −1.00 to 1.00. We adopted one common and conventional rule to consider factor loadings of 0.40 or larger do be "high". Also is show that is little or no correlation between factor, that is, they are independent of one another.

As far as the number of factors to be extracted, the procedures that can be used are the determination of the eigenvalues, the plot of the incremental variance accounted for by the successive factors (the "scree test") and the total variance explained by the factors. It is referred that the first extracted factor typically accounts for the largest part of the total variance in the available data. The last stage of the technique is the rotation of factors; there are many types of rotation possible; "varimax" is one of them. This technique redefines factors making more clear the relationship between variables and factors, that is redefines how the variables correlate in the factor.

The factor analysis was performed using Systat 10.0 (SPSS, Chicago, IL).

Results

Patient characteristics are shown in Table 1. The mean age was 59 ± 15 years, 54% were men and 91% white. The income per capita was less than US$ 150.00 per month in 75% of the subjects. The main indication for anticoagulant therapy was arterial disease (58%), followed by deep venous thrombosis (38%). The most frequent reported illnesses were cardiovascular diseases (67 patients, 58%), diabetes mellitus (21 patients, 18%) and cancer (10 patients, 9%). The majority of patients (67 patients, 58%) were under anticoagulant treatment for more than 6 months (median = 25 months); 80 patients (70%) received other therapeutic drugs: diuretics (33%), digoxin (19%), and insulin or antidiabetic oral drugs (10%). Daily warfarin dose was 5 mg in 86 patients (75%). Inadequate anticoagulation (2.0 < INR > 3.0) was found in 55 (48%) of the 115 patients. Self-reported intakes and primary food sources of phylloquinone are presented in Table 2. The median recent phylloquinone intake was 76 μg/day (47–120 μg/day), as determined by the 24-h recall, and habitual intake was 120 μg/day (77–177 μg/day), as determined by the FFQ. Soybean oil and kidney beans were identified as the primary food sources of phylloquinone when recent intake was assessed by the 24-h recall. With respect to usual intake, as assessed by FFQ, kidney beans were ingested more than other foods (median of 90 g). The relative contribution of primary food sources of phylloquinone, referred to as the total phylloquinone intake is shown in Fig. 1, as estimated by 24 hR and by FFQ. Soybean oil and collards were the main contributors of usual phylloquinone intake, as estimated by the FFQ; together with lettuce, kidney beans, and cabbage, they supplied approximately 51% of the phylloquinone intake; the green leafy vegetables alone contributed with 28%. Based on recent intake, as estimated by 24 diet recall, soybean oil and kidney beans accounted for approximately 40% of the phylloquinone intake.

Table 2 Phylloquinone intake, and amounts of foods rich in phylloquinone consumed as estimated using 24 h recall (24 hR) and food frequency questionnaire (FFQ)

	24 hR	FFQ
Dietary vitamin K (μg/day)		
Ingestion	76 (47–120)	120 (77–177)
Food (g/day)		
Soybean oil	11.4 (4.8–17.1)	12 (6.6–16.0)
Collards	0 (0–0)	4.6 (1.1–11.6)
Lettuce	0 (0–27.5)	10.7 (4.1–21.4)
Cabbage	0 (0–0)	3.3 (0.4–8.5)
Soup	0 (0–0)	55.7 (8.6–106.4)
Kidney beans	90 (36–180)	90 (0–140)

Median (lower quartile–upper quartile)

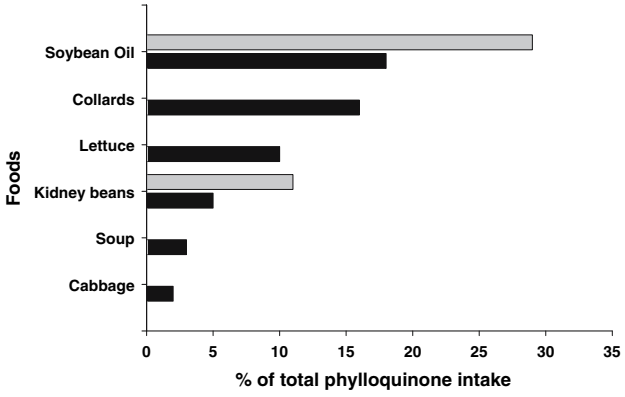

Fig. 1 Percentage contribution of each food source to total vitamin K intake, based on self-reported assessment of recent (24 hR) and usual (FFQ) intake

The median plasma phylloquinone was 2.21 nmol/l (1.48–3.34 nmol/l). Recent phylloquinone intake was inversely correlated with PT ($r = -0.22$, $P = 0.017$) and INR ($r = -0.23$, $P = 0.011$), whereas there was a positive association between habitual vitamin K intake and median warfarin dose ($r = 0.23$, $P = 0.011$). It was also found a negative association between plasma phylloquinone levels and INR ($r = -0.18$, $P = 0.041$). No other significant associations were found between amounts of food and data of anticoagulation measurements.

Factor analysis

Factor analysis yielded four separate factors, explaining 56.4% of the total variance in the data set. The correlations with the original variables for each Varimax-rotate factor and the eigenvalues are displayed in Table 3. The component analysis revealed that kidney beans, soybean oil, 24-h recall of phylloquinone intake, PT and INR loaded significantly on factor 1. Factor 2

Table 3 Results of factor analysis (loading matrix) of phylloquinone intake estimated using 24 h recall (24 hR), foods rich in phylloquinone estimated by food frequency questionnaire and values from laboratory analyses in Brazilian patients with vascular disease

	Factor 1	Factor 2	Factor 3	Factor 4
Lettuce	0.214	−0.116	0.236	0.230
Collards	0.321	−0.025	−0.013	*0.786*
Kidney beans	*0.643*	0.352	0.133	−0.363
Margarine	0.135	0.072	0.297	0.015
Soybean oil	*0.672*	0.311	0.257	−0.324
Soup	−0.208	−0.282	−0.393	0.120
Cabbage	0.385	−0.116	0.204	0.020
Phylloquinone intake—recent (24 hR)	*0.736*	−0.064	0.159	*0.583*
Serum triglycerides	0.148	*0.636*	*−0.594*	−0.025
Prothrombin time	*−0.556*	*0.638*	*0.421*	0.251
Duration of anticoagulation therapy	−0.075	0.237	*−0.531*	0.047
INR	*−0.560*	*0.632*	*0.425*	0.226
Plasma phylloquinone	0.342	*0.566*	*−0.554*	0.166
Warfarin dose	0.252	0.236	0.350	−0.189
% Total of variance	18.6	14.1	13.4	10.3
% Cumulative total variance	18.6	32.7	46.1	56.4

Factor loading ≥0.40 are in italics

included serum triglycerides, PT, INR, and plasma phylloquinone. Triglycerides, PT, INR, plasma phylloquinone, and duration of anticoagulation therapy loaded on factor 3, whereas collards, and 24-h recall of phylloquinone intake loaded on factor 4.

Discussion

Although warfarin is an effective anticoagulant and is widely prescribed in vascular obstructive diseases, the response associated with this drug shows high variability, requiring frequent anticoagulation monitoring in order to achieve a stable and adequate therapeutic range, and avoiding risks of bleeding or thrombosis. Several factors have been considered as responsible for the variability in the anticoagulant response to warfarin, including age, diet, co-morbidities, drug interactions, compliance with medical recommendations, racial, genetic, and cultural factors. Age is associated with increased individual variable response to treatment [23] and increased risk of bleeding in the elderly [24]. In our study, the mean age of the group was 59 years, and 53% of the subjects were 61 years or more; therefore, age might be one of the determinant factors of the high inadequate anticoagulation rates (48%) present in these patients. Alternatively, the inadequate anticoagulation rates may be associated with low compliance with health professional recommendations. In our patients, low compliance was related to the need of frequent blood tests, expenses for traveling to and from the hospital, and difficulty in understanding and adhering to therapeutic recommendations. Since 86 patients (75%) had an income that was lower than US$ 150, and the state health-care funds were limited, financial constraints may account for the low compliance.

Variability in anticoagulant response to warfarin may also be associated with the amount of dietary phylloquinone consumed. We have found that in 76 patients (66%), recent phylloquinone intake (76 μg/day) was below current dietary recommendations [25]. The median value for the usual phylloquinone intake (120 μg/d) for the patient study group was more consistent with dietary recommendations [25], but must be interpreted with caution because the FFQ over-estimates phylloquinone intake when compared to intakes estimated using the 24-h recall [6]. It has been referred that 24 h recall method is appropriate for studies in large populations of different ethnicity, has a relatively low respondent and interviewer burden and is open-ended and is cost-effective; therefore, it has been considered as the best method to get population mean intakes [26]. However, the FFQ is a useful tool to identify individual foods that are not consumed on a regular basis, so as to detecting a food pattern that might contribute to vitamin K nutriture.

Since vitamin K status is influenced by recent dietary intake [27] and taking into consideration the variability of intakes of phylloquinone-rich foods reported in our study, the interaction between diet and oral anticoagulation warrants investigation. In our study, the negative correlations between recent phylloquinone intake and PT or INR, and the positive correlation between usual phylloquinone intake and the median values of warfarin provide support for the existence of association between dietary phylloquinone and anticoagulation. These findings are consistent with associations between high dietary phylloquinone and insufficient anticoagulation, and associations between low dietary phylloquinone and excessive anticoagulation and consequent hemorrhage risk, as previously described [4, 5].

We also performed a factor analysis using biochemical and food data, that resulted in a four-factor structure, explaining ~56% of the total variance. These four factors strengthen the interaction between phylloquinone intake and warfarin, and provide evidence that recent phylloquinone intake and intake of specific foods, mainly kidney beans and soybean oil, are positively associated with oral anticoagulation response. Factor analysis has not been applied previously to data obtained from patients on oral anticoagulation; nevertheless our study findings concur with those of Khan et al. [3], which showed a significant inverse association between vitamin K intake and different levels of anticoagulation. Franco et al. also showed that the intake of several vitamin K rich foods was associated with low INR values (<2) and that a decrease of these foods led to high INR values [28].

In our study, the green leafy vegetables contributed with 28% of the total habitual intake of phylloquinone, followed by soybean oil, with a contribution of 18%, findings which are consistent with previous data from a healthy adult population [29]. Dark-green vegetables are assumed to be the greatest contributors of phylloquinone by virtue of their high phylloquinone concentrations. However, they are not food items usually consumed on a daily basis by our patient population; in contrast, kidney beans, which are relatively low in phylloquinone content [29], ranked among the top six contributors to total phylloquinone intake in our patients. This finding is due to the consistently high consumption of kidney beans in the usual Brazilian diet, and also because kidney beans are prepared with soybean oil, a phylloquinone-rich oil. Therefore, foods that contain lower amounts of phylloquinone may be appreciable sources of this vitamin when large amounts are ingested [6, 7], and monitoring of their intake may be critical for stability of the anticoagulant response. According to the statistical method of factor analysis, kidney bean intake represents an important contribution to overall vitamin K status in our patient study group. This factorial approach was useful for the purpose of showing a statistical association between food intake and anticoagulation status, as defined by PT & INR, that could not be shown by univariate analysis.

This finding can be of clinical importance, because the consumption of kidney beans is part of the most traditional foods in the Brazilian diet. Kidney beans are frequently eaten with rice, the mixture being consumed by people of different ages and socioeconomic groups [30–32]. The intake of beans in Europe is low, not exceeding 3.5 kg/capita/year, but in other parts of the world, like in Latin-America, India and Central Africa, the intake is very high [33]. Since the nowadays increase of migratory movement of populations and that people tend to keep their choice of food and food traditions in their new countries, the knowledge of the association of kidney beans with impairment of anticoagulation is useful not only in the Brazilian set, but also for other population groups.

In our study, values for plasma phylloquinone were higher than those found in healthy populations [10, 34–38]. This finding may be due to the fact that 67 patients (58%) were affected by peripheral artery disease, a pathological condition associated with high serum triglycerides [39]. The factor analyses clearly show the association between plasma phylloquinone and serum triglycerides, an association previously reported in healthy individuals [40–43]. This association between circulating levels of phylloquinone and triglycerides, and the anticoagulant response is also consistent with the findings of Kohnke et al. [44], who reported that apolipoprotein E genotype explains some of the variance in warfarin dose response. Phylloquinone concentration in blood is determined by the presence of specific variants of apolipoprotein E (apoE) [40, 45]. ApoE is a component of plasma lipoproteins that transport lipids from the intestine to circulation, and then subsequently participate on the chylomicron clearance from circulation. It has been proposed that patients with the *APOE*E4* allele have greater uptake of vitamin K into the liver, hence a greater requirement of warfarin to maintain stable anticoagulant response [44]. Unfortunately the patient population in this study did not have available genotype data, but future studies examining the diet-gene interaction on warfarin dose and stability of anticoagulant response would be of clinical importance.

Our results showed that values of plasma and dietary phylloquinone were negatively associated with INR and PT. In support of our findings, a negative association of plasma phylloquinone with INR and PT has also been reported by Kamali et al. [46].

In conclusion, this study showed that variations in plasma and dietary phylloquinone were associated with anticoagulant response, as defined by PT and INR in Brazilian patients with vascular disease. Although not classically identified as a major dietary contributor of vitamin K, kidney bean intake was one of the primary dietary contributors of PT and INR, a reflection of its prominence in terms of frequency and volume in the Brazilian diet.

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