Vitamin K Status in Women of Childbearing Years Before or After Bariatric Surgery

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ABSTRACT

Background: Vitamin K adequacy has not been widely studied before or after bariatric surgery. Reports of babies born with intracranial bleeds to women after bariatric surgery make this an important vitamin to study in women of childbearing years.

Objectives: The aim of this study was to assess the functional vitamin K status in 2 groups of women of childbearing age, 1 group seeking bariatric surgery and 1 group post Roux-en-Y gastric bypass (RYGB).

Methods: In a cross-sectional design, 40 women [19 presurgical and 21 post-RYGB (6–18 mo following surgery)], aged 18–40 y, completed the study. Participants provided a 3-d food intake record and a list of dietary supplements routinely taken. Participants then underwent a commercially available test to measure des-γ-carboxyprothrombin (DCP) concentration as a measure of functional vitamin K status.

Results: Independent-samples *t* tests ($P < 0.05$) indicated that there was no significant difference [Sig (2-tailed) 0.821] between the DCP concentrations of the presurgical group and those of the post-RYGB group (mean ± SD DCP: 0.3 ± 0.1 and 0.4 ± 0.2 ng/mL, respectively). Vitamin K intake from food (248 ± 227 and 210 ± 239 μg) and supplements (13 ± 31 and 750 ± 271 μg) showed no linear correlation to DCP (presurgical group: 0.25 and –0.15, respectively; post-RYGB group: 0.13 and 0.05, respectively). Vitamin K intakes for both groups were above the current Institute of Medicine's recommended 90 μg/d for women. Bivariate correlation was conducted on other independent variables with only current BMI for the post-RYGB group having a moderate negative correlation to DCP (–0.54, $P < 0.05$). No correlation with statistical significance was found between other variables and DCP.

Conclusions: Although the American Society for Metabolic and Bariatric Surgery recommends DCP as a test to determine vitamin K adequacy, no published studies in pre- or post-RYGB patients have been performed with the current commercially available test, which is not FDA approved as a vitamin K biomarker. Previous studies reporting vitamin K inadequacies based on DCP utilized a different assay than the one currently available. Due to the importance of ensuring adequate maternal concentrations of vitamin K after bariatric surgery in order to prevent intracranial bleeding in babies, more research is needed to determine suitable vitamin K measures. *Curr Dev Nutr* 2019;3:nzz056.

Introduction

Bariatric surgery is recognized as an effective treatment for obesity and obesity-related conditions, such as type 2 diabetes, hypertension, and hyperlipidemia (1). The American Society for Metabolic and Bariatric Surgery (ASMBS) reported that ~899,000 weight-loss surgeries were performed in the United States between 2011 and 2015, with the majority of these being either Roux-en-Y gastric bypass (RYGB) or gastric sleeve (2).

However, decreased caloric intake and malabsorption after weight-loss surgery increases the risk for vitamin and mineral deficiencies (3–5), and screening for deficiencies preoperatively is

Keywords: bariatric, weight-loss surgery, vitamin K, osteoporosis, bone health, Roux-en-Y, vitamin deficiencies, vitamin K deficiency, intracranial hemorrhage, des-γ-carboxyprothrombin

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Abbreviations: ASMBS, American Society for Metabolic and Bariatric Surgery; DCP, des-γ-carboxyprothrombin; IOM, Institute of Medicine; PI, principal investigator; PIVKA-II, protein induced by vitamin K absence-II; RYGB, Roux-en-Y gastric bypass; uc-OC, undercarboxylated osteocalcin.

now advised because these are widespread in the population as a whole (6, 7). Deficiencies of nutrients can result in osteoporosis, anemias, neuropathies, bleeding issues, and other sequelae (7).

Vitamin K has not been widely studied in recipients of bariatric surgery, with the exception of the less common, but most severely malabsorptive, procedure known as biliopancreatic diversion with or without duodenal switch. Examination of nutrient concentrations after this procedure found low serum phylloquinone (vitamin K) in 60% of those studied (8).

Vitamin K is known for its role in blood clotting and it is necessary to prevent abnormal bleeding during pregnancy. A number of reports have been published regarding infants with intracranial bleeds resulting from vitamin K inadequacy born to women who have had bariatric surgery (9, 10). One prospective cohort measured serum phylloquinone in pregnant women (age range 18–38 y) after bariatric surgery and compared the concentrations with those found in a control group of pregnant women of similar age without a history of bariatric surgery. Low serum phylloquinone concentrations were found in the first trimester in most women; however, the concentrations were lower in the surgical group (11).

Another study used 2 different vitamin K measures—a direct serum concentration and a functional vitamin K marker. Serum phylloquinone was below the reference range in 40% of study participants. Des-γ-carboxyprothrombin (DCP), a functional marker of vitamin K, was elevated (indicating deficiency) in 19% of those studied (12).

In 2015, Shea and Booth (13) published a review of methods to determine vitamin K adequacy. They noted "there is no single biomarker that is considered a gold standard measure of vitamin K status." In recent guidelines, the ASMBS recommends the use of DCP to determine vitamin K status, if signs and symptoms are suggestive of deficiency (6). These early signs include easy bruising, delayed blood, heavy menstrual or nose bleeds, or, later on, osteoporosis. DCP is a measure of uncarboxylated prothrombin (i.e., factor II) that is induced in the absence or antagonism of vitamin K. DCP is also known as protein induced by vitamin K absence-II (PIVKA-II). A concentration of 2.0 ng/mL is considered the threshold; ≥2.0 ng/mL indicates vitamin K inadequacy (14). To date, there are no published studies reporting DCP in post–bariatric surgery patients.

Due to the risk of intracranial bleeds in infants born to women after bariatric surgery, this study examined functional vitamin K in women of childbearing years, 1 group seeking weight-loss surgery and 1 group post-RYGB. The hypotheses for this study are the following: *1*) DCP concentrations will be elevated in some women prior to surgery; and *2*) after surgery, DCP concentrations will be elevated in some women, with more significant elevations when compared with the presurgical group.

Methods

Forty women aged 18–41 y completed the study: 18 women prior to surgery and 21 women post-RYGB. Participants were recruited from the Sanford Health Eating Disorders and Weight Management Center, Fargo, ND, from January to October 2017. Based on previous DCP (PIVKAII) results (12), 19% of study participants were found to have vitamin K inadequacy. A sample size of 40 participants was selected, which provided a power of 0.80 to detect a large standardized effect ($d = 0.91$) for group differences assessed by independent t test, and large standardized effects ($r = 0.57$–0.59) for bivariate correlations.

The study was designed to enroll 2 groups of women of childbearing age (18–40 y): 1 group of women before surgery, and 1 group who had undergone RYGB surgery in the past 6–18 mo. Exclusion criteria included those who were pregnant at the time of the study or those who were aged <18 y or >40 y at the time of contact for participation.

Potential participants were mailed a study notice. Prior to scheduled appointments, participants were contacted by telephone to ascertain their interest in participating. If interested, each participant was mailed a form asking them to record all food and beverage intake for 3 d and provide a list of any vitamin/mineral supplements routinely taken. Consent was obtained by the principal investigator (PI) when participants presented for a prescheduled surgery consult or follow-up visit. After consent was obtained, an order was placed per study protocol for a DCP test to be performed at one of Sanford's available clinic laboratory sites.

Of the 48 participants who initially consented, 40 underwent the DCP test within the timeframe of the study as displayed in **Figure 1**. Participants who completed the study were sent a $25 internet gift card as a measure of appreciation.

The food and supplement record was collected and reviewed with each participant by the PI at the time consent was obtained. If there were questions on foods, beverages, portions, or vitamin/mineral supplement intake, the PI asked for clarification (including brand names, where possible) at that time. Patient-reported phylloquinone intake was analyzed with Foodworks software for the 3 days recorded. Food data contained in this software utilizes the USDA National Nutrient Database for Standard Reference and the Food and Nutrition Database for Dietary Studies, derived from NHANES. If food items were not in the software, the PI sought vitamin K content information from brand name nutrition facts labels or product nutrient analysis where available from brand manufacturers.

The electronic patient record for each participant was reviewed for independent variables, including presurgical BMI, age, number of pregnancies, and number of live births. For post-RYGB participants, current BMI and number of months since surgery was also obtained. Patients were asked about pregnancy and birth information if unavailable from chart review.

The dependent variable in this cross-sectional research is the DCP (aka PIVKA-II) value, a functional measure of vitamin K adequacy. Concentrations <2.0 ng/mL are considered representative of vitamin K adequacy (13, 14). Blood samples obtained were sent to a reference laboratory, Quest Diagnostics, where a kit from Wako Diagnostics, Richmond, VA, was used to perform the analysis.

Approval for study design and participant consent was obtained from the institutional review boards of both Sanford Health and Indiana State University (Terra Haute, IN).

Statistical analysis

IBM SPSS Statistics version 24 was used to perform an independent-sample t test comparing the DCP values of the presurgery and post-surgery groups at a 95% CI. Bivariate correlation was conducted between the DCP concentrations of each group and the phylloquinone intake (food and supplements), age, presurgery BMI, previous pregnancies, and previous miscarriages, and for post-RYGB

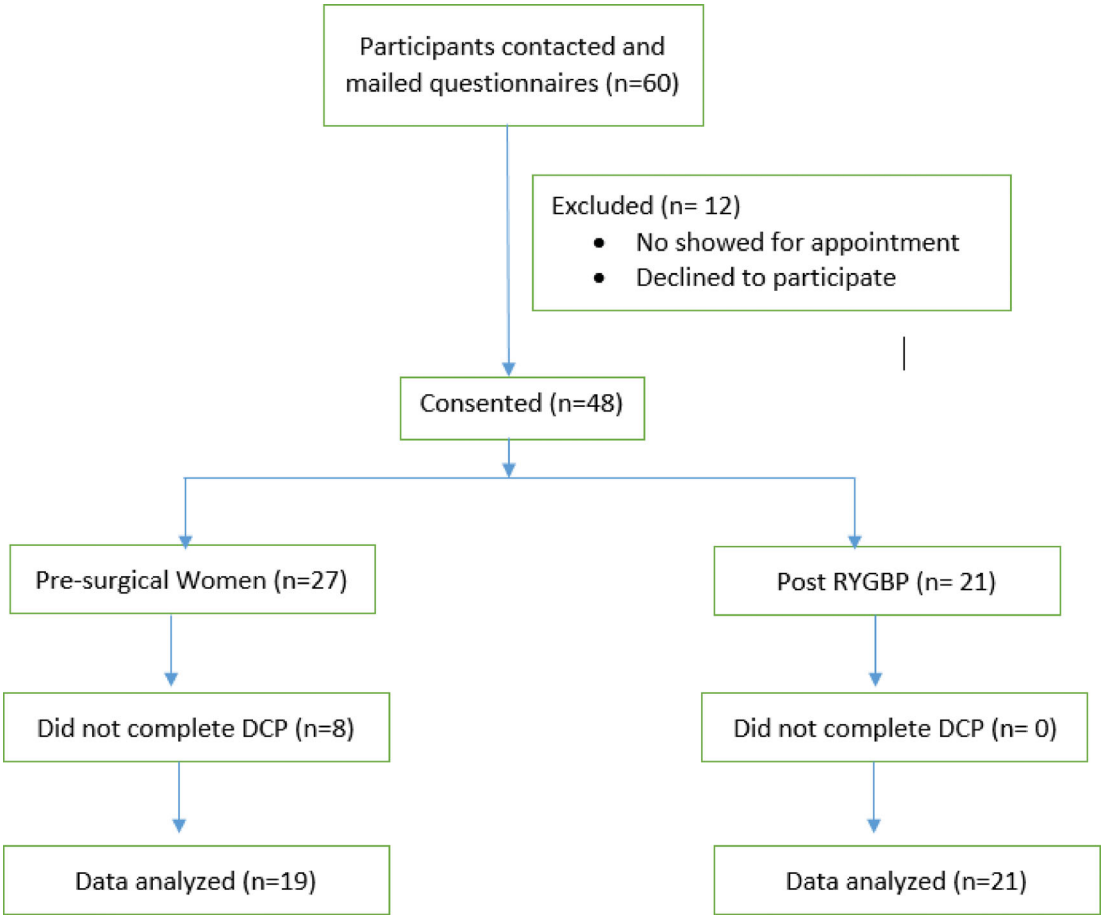

FIGURE 1 Flow diagram showing the number of presurgical and post-RYGB participants recruited ($n = 60$), excluded ($n = 12$), consented ($n = 48$), and the number people who completed the study ($n = 19$ presurgery; $n = 21$ postsurgery). DCP, des-γ-carboxyprothrombin; RYGB, Roux-en-Y gastric bypass.

participants, current BMI, number of months since surgery, and change in BMI.

Results

The independent-sample *t* tests comparing both groups did not indicate a statistically significant difference between the mean ± SD DCP concentrations for each group [presurgical: 0.3 ± 0.1 ng/mL; post-RYGB: 0.4 ± 0.2 ng/mL; 95% CI: −0.132, 0.106; t (36) = −0.228; $P = 0.821$]. The results are listed in **Table 1** and **Figure 2**. Additionally, neither group showed any values ≥2.0 ng/mL, which would have indicated vitamin K inadequacy. Neither of the proposed hypotheses were supported by the results obtained.

Although mean ± SD self-reported intake of phylloquinone from foods (presurgical: 248 ± 227 μg; post-RYGB: 210 ± 239 μg) and supplements (presurgical: 13 ± 31 μg; post-RYGB: 750 ± 271 μg) was, in total, much lower for the presurgical group than for the post-RYGB participants, the functional vitamin K measure (DCP) did not vary significantly between groups.

Bivariate correlation with DCP for each independent variable showed no linear association for all variables with the exception of current BMI for post-RYGB participants. Current BMI had a statistically significant inverse association with DCP with a Pearson correlation of −0.54 ($P < 0.05$). The relevant statistics are listed in **Tables 2** and **3**. Initial DCP results received were reported as generalized

TABLE 1 Descriptive analysis of DCP and independent variables for presurgical and post-RYGB; the resulting means show little difference between groups[1]

	Presurgical ($n = 19$)	Post-RYGB ($n = 21$)
DCP, ng/mL	0.3 ± 0.1	0.4 ± 0.21
Age, y	34.1 ± 4.7	32.9 ± 3.5
Vitamin K intake, μg		
Food	248 ± 227	210 ± 239
Supplements	13 ± 31	750 ± 271
Presurgical BMI, kg/m^2	45.8 ± 7.8	46.0 ± 5.0
Number of pregnancies	2.0 ± 1.6	1.8 ± 1.4
Number of miscarriages	0.7 ± 0.9	0.2 ± 0.4
Current BMI	—	31.0 ± 5.2
Time since surgery, mo	—	10.4 ± 4.3
Change in BMI	—	14.8 ± 3.6

[1]DCP, des-γ-carboxyprothrombin; RYGB, Roux-en-Y gastric bypass.

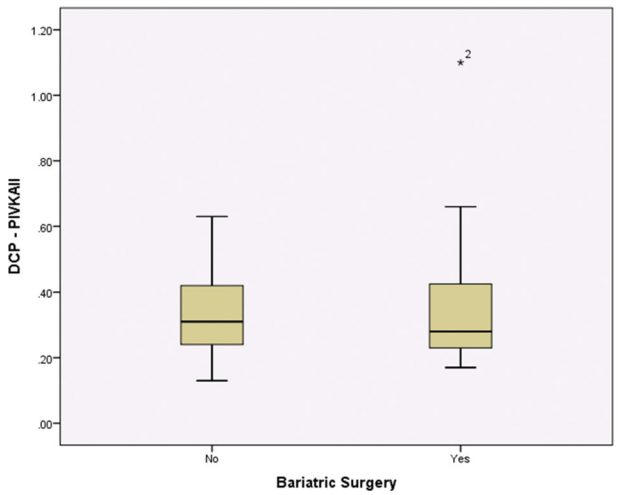

FIGURE 2 Box plot of DCP concentration results for presurgery participants (No) and post-RYGB participants (Yes). Both groups had results in the normal range (<2.0 ng/mL). *Two values were not included in the analysis as a specific DCP concentration could not be determined below the generalized <1.0 mg/dL value. DCP, des-γ-carboxyprothrombin.

values of <1.0 ng/mL. After making inquiries to Wako Diagnostics, the PI was informed that values with an accuracy of down to 0.1 ng/mL should be achievable. The PI contacted the reporting laboratory, which was able to resend all DCP values with the proper accuracy, with the exception of 2 results, which were excluded from the analysis. Vitamin K intake information was not completed by 1 participant, and this value was therefore missing from the analysis.

Discussion

Assessment of vitamin K adequacy in population studies is complex due to the various forms in which it exists in the diet and in the body (15, 16). Intake adequacy concentrations set by the US Institute of Medicine (IOM) are 90 and 120 μg phylloquinone/d for women and men, respectively. This was based on the amount needed for adequate blood clotting and calculated phylloquinone intakes from NHANES III and other US population studies (17). Neither the presurgical nor the post-RYGB groups reported 3-d intakes (food and supplements) that were deficient according to the 90 μg/d (270 μg/3 d) IOM recommendations for phylloquinone for women. It should, however, be noted that reported vitamin K intake has not been strongly associated with the biomarker DCP (PIVKA-II) (15).

Previous studies have identified vitamin K inadequacy during pregnancy and in persons seeking bariatric surgery (11, 12) by measuring serum phylloquinone or DCP concentrations, or a combination of both. Although the women in our study did not have elevated DCP indicative of vitamin K deficiency, a study of 709 multiethnic men and women followed over 11 y showed that those with increased DCP at the onset of the study had an increased incidence of ischemic cardiovascular disease. In fact, 84% of the cohort had a DCP concentration >2.0 ng/mL (indicating vitamin K inadequacy) (14). The study also found that DCP tended to be higher in individuals who were older, had a higher BMI, were taking cholesterol-lowering medications, had a lower physical activity level, and decreased renal function. The participants were aged between 51 and 73 y, older than the women in our study (14).

The inverse association between DCP concentration and the post-RYGB women's current BMI (Table 2) is rational considering findings from another study that concluded men and women with higher percentage body fat had poorer vitamin K status (18). That study investigated older community-dwelling adults ranging in age from 65 to 80 y, and did not identify any persons post-RYGB (18). The somewhat higher DCP concentrations in our post-RYGB women may be due to weight and fat loss or to malabsorption, common in post-RYGB patients (3–5). However, the DCP concentrations are still not considered deficient or suboptimal.

One factor that may have influenced the results is the difference in clinical laboratory tests utilized for this study compared with other studies reporting DCP values. DCP (PIVKA-II) tests have been commissioned by Sanford to examine functional vitamin K concentrations for a number of years. The current DCP (PIVKA-II) analysis utilizes the μTASWako i30 immunologic test from Wako Diagnostics to provide a DCP concentration. Other studies reporting the use of DCP for vitamin K assessment have utilized the Human Vitamin K ELISA kit which uses a monoclonal anti-VK antibody and a VK-HRP conjugate. This ELISA test is noted to have high sensitivity and specificity for detection of vitamin K inadequacy (12–14, 18–20). This is likely why the ASMBS lists DCP as a desired test for investigating vitamin K inadequacy (6). Although reporting the same DCP protein, the Wako test kit was FDA approved and intended as a biomarker for determination of hepatocellular carcinoma (21). The Wako test kit is, to date, the only commercially available test for determination of DCP, whereas the Human Vitamin K ELISA kit is currently only available for research (20).

Table 2 Bivariate correlations among variables in the presurgical group (n = 19)[1]

	Vitamin K supplements	Vitamin K food	Age	BMI current	Pregnancies	Miscarriages
DCP concentration	0.13	0.25	−0.09	−0.21	0.39	0.47
Vitamin K supplements, mcg		−0.07	0.16	−0.29	0.15	0.26
Vitamin K food, mcg			−0.21	−0.16	−0.09	−0.09
Age, year				−0.11	−0.09	−0.48*
BMI current					0.03	0.14
Pregnancies						0.62**

[1]DCP, des-γ-carboxyprothrombin.
**P < 0.01; *P < 0.05

Table 3 Bivariate correlations among variables in the postsurgical group ($n = 21$)[1]

	Vitamin K supplements	Vitamin K food	Age	BMI presurgery	BMI current	Months since surgery	Δ BMI	Pregnancies	Miscarriages
DCP concentration	0.05	−0.15	0.10	−0.40	−0.54*	−0.27	−0.20	0.14	−0.12
Vitamin K supplement, mcg		0.27	−0.04	−0.21	−0.22	−0.31	−0.02	−0.04	0.14
Vitamin K food, mcg			−0.01	0.30	0.16	0.11	−0.19	−0.05	−0.07
Age, year				0.29	0.18	−0.09	−0.15	0.48*	0.31
BMI pre surgery					0.75**	0.35	−0.33	0.01	0.18
BMI current						−0.02	0.39	−0.17	−0.05
Months since surgery							−0.52*	−0.16	0.19
Δ BMI								−0.25	−0.31
Pregnancies									0.52*

[1]DCP, des-γ-carboxyprothrombin.
**$P < 0.01$; *$P < 0.05$

There is no consensus as to the best method for assessing vitamin K status (15). Undercarboxylated prothrombin (DCP) and undercarboxylated osteocalcin (uc-OC) are known to be sensitive measures of vitamin K status. Both plasma phylloquinone and uc-OC are affected by recent dietary vitamin K intake (22–24). A higher uc-OC is associated with a lower vitamin K intake and low serum phylloquinone (24), and low serum phylloquinone also reflects low tissue reserves (22). However, uc-OC is the first indicator of vitamin K inadequacy and the last to respond to supplementation (13). Perhaps the body preferentially uses vitamin K for blood clotting and, if stores are adequate for that purpose, the remaining supply is then used to support other functions. Because the ASMBS lists osteoporosis as a symptom requiring investigation of vitamin K concentration, measurement of uc-OC may be an option because γ-carboxylation of osteocalcin is necessary for osteoblast function in bone matrix metabolism (22, 25). This measure may provide insight into osteopenia and osteoporosis which have previously been reported in persons after bariatric surgery (26).

There are several limitations in this study. First, the study design was cross-sectional and did not provide information on vitamin K status before and after surgery for the same participants. Second, the DCP test in this study involved a different assay than used in previous studies looking at this test for vitamin K adequacy (12, 14). The only DCP test commercially available at this time does not have FDA approval for use as a valid nutritional measure of vitamin K adequacy (21). Lastly 8 presurgical participants did not complete their DCP laboratory test and it is not known whether the missing tests would have significantly affected DCP results.

One additional consideration is the vitamin/mineral protocol that Sanford Health in Fargo recommends for its post–bariatric surgery patients. This protocol may be higher in vitamin K or differ from those employed by other bariatric surgery centers. Many of the post-RYGB participants were following the most recent supplementation protocol, which provides 300 μg vitamin K1/d (about 3 times the IOM's daily recommendation) (15, 17). Only 1 post-RYGB participant was not taking a vitamin supplement that contained vitamin K. Three participants were following the older supplement protocol, which provides ~90 μg vitamin K1/d. The exemplary compliance of our participants may be a contributor to our finding no vitamin K inadequacies.

Due to potential brain bleeds as a significant harm to infants born to women after bariatric surgery, this study limited potential participants to females in their child-bearing years. The assay used in this study was intended to determine whether or not there would be sufficient vitamin K to support carboxylation of prothrombin and blood clotting in babies born to women after bariatric surgery. No participants were pregnant at the time of the study, and therefore adequacy could only be theorized if these women were to become pregnant.

Vitamin K is needed to support blood clotting. The ASMBS notes osteoporosis as an additional reason to investigate its status (6). Thus, it is of interest to monitor vitamin K in the weight-loss surgery population. Ideally, further studies of undercarboxylated vitamin K–dependent proteins would include patients of both genders and all ages with a prospective design, following participants prior to and after bariatric surgery, with a matched control group of patients who have not undergone bariatric surgery during the same time period. Additional research should also control for and compare vitamin/mineral regimens and patient compliance with those regimens.

The ASMBS now recommends measuring DCP concentrations to assess vitamin K status (6). More studies are needed to compare the commercially available test for DCP with the ELISA method used in previous studies that have shown vitamin K inadequacy in a number of populations.

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The authors' responsibilities were as follows—LB (principal investigator): study design, implementation, consents, data collection, data analysis and interpretation; LG: study protocol design, order approval and oversight; KB and MM: study design approval and oversight; and all authors: read and approved the final manuscript.

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