Original Article

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Could Vitamin K1 Deficiency be the Problem in Iron Deficiency and/or Anemia in Premenopausal Women?

Premenopozal Kadınlarda, Demir Eksikliği ve/veya Anemisinde Sorun Vitamin K1 Yetersizliği Olabilir Mi?

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ABSTRACT

Objective: The etiology of iron deficiency anemia, which develops as a result of menstrual bleeding in the premenopausal period, is unknown. Vitamin K1 has an important role in the coagulation cascade and is not a well known vitamin. The aim of this study was to investigate whether or not Vitamin K1 had a role in anemia developing in the premenopausal period, for which no additional reason could be found.

Methods: This study included a patient group of women aged 18-50 years, who had a regular menstrual cycle. Patients who were found to have iron deficiency, who were evaluated hematologically, gastrointestinally and gynecologically, and who did not have a pathology that would lead to iron deficiency were included in the study group.The control group comprised volunteers with regular menstrual cycles who had not been previously determined with iron deficiency. In the study, Vitamin K1, Hemogram, ferritin, iron, total iron binding capacity were examined. The Vitamin K1 level was measured by two different methods both using ELISA and liquid chromatography-mass spectrometry (LC-MS/MS) methods. In addition, a record was made for all participants including demographic characteristics, lifestyle habits, and number of menstruating days. The obtained data were then compared between the groups.

Results: A total of 88 voluntary participants were included in the study as 45 patients with iron deficiency anemia (IDA) and

ÖZ

Amaç: Premenopozal dönemdeki menstrüasyon kanamaları sonucu gelişen demir eksikliği anemisinin önemli bir kısmında etiyoloji bilinmemektedir. Vitamin K1 ise koagülasyon kaskatında önemli görevleri olan ve az bilinen bir vitamindir. Amacımız premenapozal dönemde anemi gelişen ve araştırmalara rağmen ek bir neden saptanmayan gönüllülerde Vitamin K1'in rolünün olup olmadığını araştırmaktır.

Yöntemler: Çalışmaya menapoza girmemiş, düzenli adet gören, 18-50 yaş arası kadınlar alınmıştır. Çalışma grubuna demir eksikliği saptanan, hematolojik, gastrointestinal ve jinekolojik olarak değerlendirilmiş ve demir eksikliğine yol açacak bir patoloji saptanmamış hastalar alınmıştır. Kontrol grubuna ise daha önce demir eksikliği saptanmamış ve düzenli adet gören, gönüllü kadınlar alınmıştır. Çalışmada Vitamin K1, hemogram, ferritin, demir, total demir bağlama kapasitesi bakılmıştır. Vitamin K1 düzeyi ELISA ve sıvı kromatografisi-kütle spektrometresi (LC-MS/MS) kitleri kullanılarak iki farklı yöntemle çalışılmıştır. Ayrıca hastaların demografik özellikleri, alışkanlıkları ve menstrüasyon gün sayısı sorgulanarak kaydedilmiştir. Toplanan veriler karşılaştırılmıştır.

Bulgular: Çalışmaya 45'i demir eksikliği anemisi (DEA) olan, 43'ü de kontrol olmak üzere toplam 88 katılımcı alındı. Çalışmaya katılan her iki grupta yaş, beden kitle indeksi, protrombin zamanı, Uluslararası düzeltme oranı, aktif parsiyel tromboplastin zamanı, folik asit ve Vitamin B12 ortalamaları benzer bulundu. Çalışmada

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a control group of 43 subjects. The age, body mass index, partial thromboplastin, International normalized ratio, active partial thromboplastin time, folic acid, and Vitamin B12 values were similar in both groups. In both methods, no significant difference was determined between the groups in respect of the Vitamin K1 level (p=0.9 in ELISA method and p=0.3 in LC-MS/MS method). The number of menstruation days was determined to be significantly higher in the anemic group than in the control group (p=0.002).

Conclusion: From the results of this study, it was considered that IDA developed in premenopausal women with a longer period of menstrual bleeding. However, Vitamin K1 deficiency was not considered to be one of the underlying reasons for longer menstrual bleeding.

Keywords: Vitamin K1, menstruation, iron deficiency anemia

Vitamin K1 düzeyi ELISA yöntemi ile değerlendirildi ve gruplar arasında anlamlı fark saptanmadı (p=0,9). LC-MS/MS yöntemi kullanılarak ölçülen Vitamin K1 sonuçları karşılaştırıldığında da gruplar arasında fark olmadığı görüldü (p=0,3). Çalışmada menstrüasyon gün sayısı anemik grupta anlamlı olarak daha uzun saptandı (p=0,002).

Sonuç: Premenapozal dönemdeki kadınların menstrüasyon kanamaları daha uzun sürdüğü için DEA geliştiğini düşünmekteyiz. Ancak daha uzun menstrüasyon kanaması nedenlerinden birinin Vitamin K1 yetersizliği veya eksikliği olduğu gösterilemedi.

Anahtar Sözcükler: Vitamin K1, menstrüasyon, demir eksikliği anemisi

Introduction

Iron deficiency anemia (IDA) is seen in one third of women in the menstrual period (1). Excessive menstrual bleeding and menstrual irregularities developing associated with gynaecological problems in the premenopausal period, absorption problems or losses originating from the gastrointestinal system, and hematological problems such as factor or vitamin deficiencies are thought to be the most common causes of iron deficiency or IDA. However, despite similar nutrition and lifestyles, it is not known why IDA develops in some menstruating women (2). A significant proportion of this anemia of unknown cause is seen to improve with menopause (3).

When the causes of excessive menstrual bleeding have been investigated, no organic pathology can be determined in at least 50% of patients (4). Although many studies have been conducted on the etiology in this subject, the effect of Vitamin K1 level on menstrual bleeding has not been researched. Vitamin K has an important role in the activation of Factors II, VII, IX and X, protein C and protein S (5). As the body does not synthesize this vitamin, it cannot be stored in large amounts, and acquired Vitamin K1 deficiency can develop in adults and excessive menstrual bleeding may be seen (5). When Vitamin K1 deficiency develops, first Factor VII decreases, prolonging the prothrombin time/international normalized ratio (PT/INR). When Vitamin K deficiency continues, the active partial thromboblastin time (aPTT) can prolong as other factors decrease. However, when Vitamin K1 deficiency develops and significant reductions in factor levels are not seen, it is not known whether or not bleeding increases without a longer PT/INR. In previous observations in our clinic, it was determined that in patients with iron deficiency continuously taking iron supplementation, when the Vitamin K level was at the lower limits, the PT/INR level was within the normal range.

The aim of this study was to investigate whether or not there was a difference in terms of Vitamin K1 level between a control group and patients with IDA, for which no additional reason could be determined, and which was thought to develop associated with menstrual bleeding.

Methods

This cross-sectional study included a patient group of women aged 18-50 years, who had not entered the menopause and had a regular menstrual cycle, and who had been determined with iron deficiency, for which no pathology could be determined from hematological, gastrointestinal and gynaecological evaluations. The control group comprised volunteers with regular menstrual cycles who had not entered the menopause and who had not been previously diagnosed with iron deficiency and had therefore never received any treatment. Patients or control group subjects were excluded from the study if they had any known disease or were taking any drugs, if they had prolonged PT/INR anda PTT tests, von Willebrand's disease, low thrombocyte count or function impairment, or had any abnormality in terms of Vitamin B12, folic acid, celiac antibody tests, stool occult blood test or full urine analysis. In addition, those using any method of birth control, who were pregnant or breastfeeding, were vegetarian or vegan, or who did not wish to participate in the study, were excluded. Vitamin K1, hemogram, ferritin, iron, and total iron-binding capacity were examined in all participants. To obtain more reliable results, Vitamin K1 levels were examined separately with two different methods. In addition, a record was made for all participants including demographic characteristics, lifestyle habits, and number of menstruating days. To determine the response to oral iron treatment, the hemoglobin and ferritin levels of the anemia group were evaluated after 3 months. The obtained data were then compared between the groups.

Procedure Technique: Vitamin K1: Venous blood samples were taken into 2 separate non-gel vacuum tubes (Becton Dickinson) wrapped in silver foil to prevent any effect from light, and the Vitamin K1 levels were examined with 2 different methods. Within 30 mins, the samples were centrifuged at 1,600 g for 15 mins at 4 ˚C. The serums were separated and stored at -80 ˚C until assay. Hemolytic and lipemic samples were not included in the study analyses. The Human Vitamin K1 levels were measured with an ELISA using commercial kits (Elabscience; Lot no:AK0018MAR21043; PRC) and an ELISA reader (Multiskan FC® Microplate Photometer; Thermo Scientific; USA). The results were expressed in 100-2,100 pg/mL.

The other sample taken from the same patients was examined with the liquid chromatography-mass spectrometry (LC-MS/MS) method to measure the Vitamin K1 level. The normal range was accepted as 0.1-2.1 ng/mL.

Approval for the study was granted by the Ethics Committee of Bezmialem Vakıf University (decision no: 71306642-050.01.04). The costs of the tests applied were met by the Scientific Research Program fund. Informed consent was obtained from all the study participants.

Statistical Analysis

Data obtained in the study were analysed statistically using SPSS for Windows vn 16.0 software (Statistical Package for Social Sciences, SPSS Inc, Chicago, IL, USA). In addition to definitive statistical methods (mean, median, standard deviation), the Student's t-test was used to compare normally distributed parameters, and the Mann-Whitney U test for those not conforming to normal distribution. In the comparison of numerical data, the Pearson correlation coefficient test was used. A two sided p value of <0.05 was considered statistically significant.

Results

A total of 88 voluntary participants were included in the study as 45 patients with IDA and a control group of 43 subjects with a mean age of 34.3±6.7 years (range, 21-49 years). The age, body mass index, PT, INR, aPTT, folic acid, and Vitamin B12 values were similar in both groups, with no statistically significant difference determined (Table 1). The Vitamin K1 level was measured using both the ELISA and the LC-MS/MS methods. In both methods, no significant difference was determined between the groups in respect of the Vitamin K1 level (Table 2).

Using both methods, no correlation was observed between Vitamin K1 and hemoglobin, ferritin, transferrin saturation, INR, and PT (Table 3). The number of menstruation days was determined to be significantly higher in the anemic group than in the control group (p=0.002) (Table 2). A significant correlation was determined between the number of menstruation days and ferritin. As the number of menstruation days increased, the serum ferritin level was found to decrease (r=-0.34, p=0.003). The hemoglobin and ferritin levels of all the patients in the iron deficiency group were determined to increase with oral iron treatment.

Table 1. Demographic data and laboratory test results of the anemic group and the control group

	Anemic group (45)	Control grup (43)	p
Age (years)	35.6±6.5	32.9±6.8	0.07
BMI (kg/m²)	24.3±3.3	23.1±3.3	0.1
PT (sn) (10.8-15.3)	13.7±0.8	13.9±0.8	0.15
INR (0.8-1.2)	1.05±0.08	1.07±0.08	0.3
aPTT (sn) (24-42)	30.4±2.7	31.4±3	0.1
Folic acid (pg/mL)	6.9±2.6	5.9±1.6	0.06
Vitamin B12 (ng/mL)	321.2±110	324±146	0.9

BMI: Body mass index, PT: Prothrombin time, aPTT: Active partial prothrombin time, INR: International normal range

Discussion

Although seen in 30% of women of reproductive age, iron deficiency and/or anemia caused by menorrhagia is not fully understood. This means that the majority of these women have to use various iron preparates until menopause. These drugs have many unwanted effects, and a significant proportion of these women undergo hysterectomy before the age of 60 years (4). The basic underlying cause of this problem that affects a large section of society remains unknown.

Table 2. Comparisons of values between the anemic group and the control group

	Anemic group (n=45)	Control group (n=43)	p
Hemoglobin (g/dL)	9.5±1.3	13.3±0.7	0.001
MCV (fL)	70.3±6.5	86.9±3.7	0.001
Thrombocyte (10*³/uL)	288±102	246±49	0.005
Ferritin (ng/mL) (4.63-204)	4.4±3	31.9±19.1	0.001
Iron (ug/dL) (50-170)	19.9±6.2	92.3±30.8	0.001
TIBC (ug/dL) (250-425)	425.9±46.6	324.3±52.1	0.001
Transferrin saturation (%)	4.7±1.4	29.5±11.5	0.001
No of menstrual bleeding days	7.2±2.2	5.9±1.8	0.002
Vitamin K1 (ng/mL) (LC-MS/MS)	0.27±0.16	0.23±0.17	0.3
Vitamin K1 (pg/mL)/ELISA)	104±38	103±39	0.9

MCV: Mean corpusculer volume, TIBC: Totaliron binding capasity, LC-MS/MS: Liquid chromatography-mass spectrometry

Table 3. Correlation analyses related to Vitamin K1

Vitamin K1 ELISA	r	p
Hemoglobin (g/dL)	-0.16	0.17
Ferritin (g/dL)	-0.06	0.65
Transferrin saturation (%)	-0.04	0.73
INR (0.8-1.2)	-0.09	0.45
PT (sn)	0.004	0.97
Vitamin K1 (LC-MS/MS)	r	p
Hemoglobin (g/dL)	-0.08	0.46
Ferritin (g/dL)	0.016	0.9
Transferrin saturation (%)	-0.19	0.1
INR	-0.05	0.64
PT (sn)	-0.06	0.58

PT: Prothrombin time, INR: International normal range, LC-MS/MS: Liquid chromatography-mass spectrometry

Vitamin K is known to be a vitamin that cannot be directly synthesized in the body. Vitamin K1 is synthesized with nutrients and Vitamin K2 more by the bacterial flora in the intestinal system. Vitamin K provides activation of the coagulation cascade with clotting. When this vitamin is insufficient, firstly prolongation of PT (INR) is seen because of the shortened half-life of Factor 7, and in more severe deficiencies, prolongation of aPTT may be seen as Factors II, IX and X are affected (6). Various bleeding disorders may be seen in the neonatal period because of Vitamin K1 deficiency passing from mother to infant and insufficient synthesis as the intestinal flora has not developed (7).

However, these disorders are believed to be rarely seen in adults, as in addition to the wide availability of leafy green vegetables throughout the world, it can be synthesised in the intestines. Nevertheless, it may be seen in adults taking Vitamin K antagonists, those with chronic liver disease, fat absorption disorder, and those with long-term use of drugs similar to antibiotics which disrupt the intestinal flora (8,9). However, when there is subclinical Vitamin K deficiency without factor deficiencies reaching a severe level, the PT (INR) level remains within the normal range. In this situation, Vitamin K deficiency may cause a slight increase in bleeding or subcutaneous bleeding. Thus, more sensitive methods than INR should be used to determine subclinical Vitamin K deficiency (9). To this end, Vitamin K1 and K2 levels have been examined where there is a relationship between osteoporosis and atherosclerosis (8). It is thought that Vitamin K2 corrects bleeding diathesis by supporting Vitamin K1 (10). Deficiency of Vitamin K2 in particular is seen more often in some countries with different nutritional habits and causes more diseases such as osteoporosis (11). The prevalence in Turkey is unknown as to the best of our knowledge there have been no studies conducted on this subject.

To be able to obtain more reliable results in the current study, the Vitamin K levels were examined with the two most frequently used methods with the highest proven reliability. In both methods, when the Vitamin K level was determined below the accepted reference range of 0.1-2.1 ng/mL (100-2,100 pg/mL), the INR (PT) level was determined within the normal reference range. This suggested that subclinical Vitamin K deficiency was widespread and the study hypothesis could be correct. However, when compared with the control group of those with normal menstruation who had never developed iron deficiency, the mean Vitamin K1 values were found to be similar. These results could be explained by 3 different hypotheses.

First, not all Vitamin K was included in the current study as only the Vitamin K1 level was examined. Therefore, a sufficient Vitamin K2 level might be compensated for those with a low Vitamin K1 level. Or when Vitamin K1 was at the lower limit but within the reference range, Vitamin K2 might be insufficient. Due to these types of variations, the results might be misleading. If both Vitamin K1 and Vitamin K2 had been examined in this study, the results would have been more comprehensive, and results might support the hypothesis. Therefore, this study should be considered a preliminary study for further research, and as such, sheds light on future studies.

Second was that Vitamin K analyses were extremely complex and difficult tests, which might be affected by several factors. As there were no reference tests with proven international reliability, the tests were not well known and were performed in few centres, this could affect the results and made it difficult to reach accurate results (8,12). Although the utmost care was taken to obtain robust results and two different methods were used, the results were not statistically significant. In previous studies conducted on Vitamin K1, the results were found to be conflicting (8,13,14).

Finally, the Vitamin K1 level might not have an effect on longer duration of menstrual bleeding, as found in the current study, but as no similar studies could be found in literature, it was not possible to make comparisons.

In the patients followed up throughout the current study, the iron deficiency was observed to be easily corrected with oral iron treatment. Thus, it was determined that these women were not able to provide sufficient iron in the body as they lost more of the required nutritional iron intake in comparison to the control group. In each menstrual cycle, an extra 10 mg iron is lost, and in those with heavy bleeding this amount can increase to 42 mg (15). Therefore, every month, reserves are used up after a time and this can lead to the development of iron deficiency again. In the current study, the number of menstrual bleeding days was found to be higher in the iron deficiency group than in the control group. Moreover, as the number of menstrual days increased, so the level of serum ferritin was determined to decrease. However, Vitamin K deficiency could not be shown as the reason for an increasing number of menstrual bleeding days leading to iron deficiency. These results suggest that there could be one of two possibilities or the two together.

The first possibility is that when menstrual bleeding increases, the iron absorption capacity does not increase. Iron is absorbed in the duodenum and jejunum in the intestines. While iron absorption increases with ascorbic acid (Vitamin C) and meat, it decreases with the intake of calcium, fibre, tea and coffee (15). This type of effect was not expected in the current study as the patients and control group were of the same culture with the same nutritional conditions.

The other possibility is that as proposed in the current study, there is a disorder causing the longer duration of bleeding. Although no relationship could be shown between Vitamin K level and menstrual bleeding, it could be considered a disorder prolonging menstrual bleeding. This is supported by the fact that iron deficiency seen in the premenopausal period is corrected after menopause (16). It can also be that there is another factor like Vitamin K, which has not yet been determined, which affects the coagulation mechanism and contributes to the longer duration of bleeding.

Study Limitations

There were some limitations to this study, primarily that not all types of Vitamin K (K1, K2) were measured. Another limitation was that the amount of menstrual bleeding of the women in the study was not measured. Although Vitamin K levels were

detected too low to be measured, subjects with non-prolonged PT (INR) were determined in both groups. However, the reason that INR was not prolonged in this situation or why the bleeding of the control group was not prolonged, could not be explained.

Conclusion

In women developing iron deficiency and/or anemia because of menstrual bleeding, there is thought to be a greater loss of iron because of a longer duration of menstrual bleeding. However, no relationship could be determined between Vitamin K1 level and iron deficiency and/or anemia developing in pre-menopausal women. We believe that further research is needed about what is the factor that increases and prolongs menstrual bleeding without changing bleeding tests and Vitamin K1 levels.

Ethics

Ethics Committee Approval: Approval for the study was granted by the Ethics Committee of Bezmialem Vakıf University (decision no: 71306642-050.01.04).

Informed Consent: Informed consent was obtained from all the study participants.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: C.K., A.Ş., T.K., A.O., Ö.F.Ö., Ş.S., F.K., İ.E., Design: C.K., A.Ş., T.K., A.O., Ö.F.Ö., Ş.S., F.K., İ.E., Data Collection or Processing: C.K., A.Ş., T.K., A.O., Ö.F.Ö., Ş.S., F.K., İ.E., Analysis or Interpretation: C.K., A.Ş., T.K., A.O., Ö.F.Ö., Ş.S., F.K., İ.E., Literature Search: C.K., A.Ş., T.K., A.O., Ö.F.Ö., Ş.S., F.K., İ.E., Writing: C.K., A.Ş., T.K., A.O., Ö.F.Ö., Ş.S., F.K., İ.E.

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