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Is the dietary intake of vitamin K associated with obesity parameters among adolescents?

A ingestão dietética de vitamina K está associada a parâmetros de obesidade entre adolescentes?

Abstract

Background: Adolescence is a phase with many changes in body composition, so the investigation of the ingestion of micronutrients like vitamin K becomes important, as it may be indirectly related to obesity among these individuals. Thus, this study aimed to investigate the relationship between vitamin K intake, nutritional status and serum levels of osteocalcin, leptin and adiponectin among adolescents. ***Methodology:*** Cross-sectional study conducted with 129 adolescents of both sexes, aged 14 to 18 years, participants in the São Paulo Municipal Health Survey 2008 (ISA-Capital 2008). Peripheral venous blood was collected to determine: serum intact total osteocalcin (tOC), undercarboxylated osteocalcin (ucOC), leptin and adiponectin. Spearman's correlation and multiple linear regression were performed to evaluate the associations between vitamin K intake and anthropometric and biochemical variables. ***Results:*** In normal weight subjects, vitamin K intake had a positive correlation with age (r= 0.2489; p= 0.0174) and a negative correlation with weight (r= -0.2335; p= 0.0259). In the total sample, vitamin K intake did not correlate with weight (r = -0.0856, p= 0.3442), BMI (r = 0.0669, p = 0.4621), leptin (r=

0.1291, p = 0.1530), adiponectin (r = -0.0682, p = 0.4517), tOC (r = 0.0442, p = 0.6256) and ucOC (r = -0.1136, p = 0.2110). ***Conclusions:*** A negative correlation between vitamin K intake and body weight was observed in normal weight subjects. The metabolic pathways involved in the relation between vitamin K intake and body composition remain unclear.

Keywords: Vitamin K intake. Phylloquinone. Obesity. Adolescents.

Resumo

Introdução: Na adolescência, fase em que ocorrem muitas mudanças na composição corporal, torna-se útil investigar a ingestão de micronutrientes como a vitamina K, que podem estar indiretamente relacionados à obesidade nesses indivíduos. Assim, o objetivo deste estudo foi investigar a relação entre a ingestão de vitamina K, o estado nutricional e as concentrações séricas de osteocalcina, leptina e adiponectina em adolescentes. ***Metodologia:*** Estudo transversal realizado com 129 adolescentes de ambos os sexos, com idade entre 14 e 18 anos, participantes do Inquérito de Saúde no Município de São Paulo 2008 (ISA-Capital 2008). Amostras de sangue venoso periférico foram coletadas para determinar as concentrações séricas de osteocalcina total (tOC), osteocalcina não carboxilada (ucOC), leptina e adiponectina. Foram realizadas correlação de Spearman e regressão linear múltipla para avaliar as associações entre o consumo de vitamina K e as variáveis antropométricas e bioquímicas. ***Resultados:*** Em indivíduos com peso normal, a ingestão de vitamina K apresentou correlação positiva com a idade (r = 0,2489; p = 0,0174) e correlação negativa com o peso (r = -0,2335; p = 0,0259). Na amostra total, a ingestão de vitamina K não se correlacionou com peso (r = -0,0856; p = 0,3442), IMC (r = 0,0669; p = 0,4621), leptina (r = 0,1291; p = 0,1530), adiponectina (r = - 0,0682; p = 0,4517), tOC (r = 0,0442; p = 0,6256) e ucOC (r = -0,1136; p = 0,2110). ***Conclusões:*** Em indivíduos com peso normal, observou-se correlação negativa entre a ingestão de vitamina K e peso corporal. Ainda não está bem elucidado quais as vias metabólicas envolvidas na relação entre a ingestão de vitamina K e a composição corporal.

Palavras-chave: Ingestão de vitamina K. Filoquinona. Obesidade. Adolescentes.

INTRODUCTION

Vitamin K is a fat-soluble micronutrient, originally recognized for its essential function in blood clotting.[1,2] In addition to its classical role, a number of clinical trials with various populations have examined its possible beneficial effects on bone mineral density (BMD).[3] It is assumed that vitamin K may act in the modulation of some cytokines that are related to bone remodeling, such as interleukin-6 and osteoprotegerin, which interfere in bone turnover.[4] The possible mechanism by which vitamin K could be related to bone metabolism is through osteocalcin, although findings in literature are still controversial.[3,5]

Osteocalcin (OC) or bone GLA protein is synthesized by osteoblasts during bone matrix formation and contains three residues of GLA. However, the binding capacity of minerals to osteocalcin depends on its gamma-carboxylation, a vitamin K dependent process, which in turn acts as a cofactor for the action of the carboxylase enzyme.[6-8]

In the bloodstream, OC is found in the carboxylated (cOC) and undercarboxylated (ucOC) forms.[9] In its carboxylated form, it binds to hydroxyapatite in the bone, whereas the percentage of undercarboxylated OC, which is not incorporated into the bone matrix, is known to act on glucose metabolism.[10,11] Evidence has shown that bone tissue also acts as an endocrine organ, affecting energy metabolism through osteocalcin. In this case, ucOC would act as a hormone, increasing the production of adiponectin (a peptidic hormone produced primarily by white adipose tissue, but also found in other tissues such as muscle and bone)[12,13] and then facilitating pancreatic beta cell proliferation, insulin secretion and peripheral insulin sensitivity.[9,14,15]

It is also suggested that osteocalcin concentrations could be modulated by leptin, a hormone produced by adipocytes that regulates body weight, fat mass, food intake and energy expenditure.[16,17] Although leptin controls food intake, obese individuals present high levels of this adipokine, leading to the development of resistance to leptin (hyperleptinemia). Thus, in these individuals leptin does not properly control intake and sensation of satiety.[18,19]

Other metabolic actions of leptin were shown by in vitro studies: it exerts an important action inhibiting the generation of osteoclasts and improving osteoblast differentiation.[20,21] According to Ducy et al.,[22] leptin exerts a negative control on the accumulation of bone mass, demonstrating that mice with leptin deficiency had a higher amount of bone mass.

Adolescence is a phase with many changes in body composition, which are related to increased body mass and physical development, also involving the maturation of organs and systems for the acquisition of new and specific abilities.[23] Results from the last Family Budget Survey (POF 2008-2009)[24] showed that 20.5% of Brazilian adolescents are overweight and 4.9% are obese. It is estimated that approximately 10% of individuals between 5 and 17 years

old have weight excess, and 2 to 3 % are obese.[25] Some studies have shown a possible association between vitamin K intake and body weight, especially with body fat, but the results are still controversial.[9,26,27]

Investigation of factors that may be indirectly related to obesity in adolescence becomes useful in order to complement nutritional care among these individuals. Thus, this study aimed to investigate the relationship between vitamin K intake, nutritional status and serum levels of osteocalcin, leptin and adiponectin among adolescents.

METHODOLOGY

Study population

This is a cross-sectional study conducted with participants from the São Paulo Municipal Health Survey 2008 (ISA-Capital 2008), a population-based household survey, in which general information and blood samples were collected from 129 adolescents of both sexes, aged 14 to 18 years, living in municipality of Sao Paulo. Study participants were part of a sample containing 437 adolescents who met the eligibility criteria, of which 241 agreed to participate, but only 129 individuals attended the scheduled day and had the blood sample collected.

Exclusion criteria were: individuals with growth disturbance or non-communicable chronic diseases besides obesity (such as diabetes mellitus or systemic arterial hypertension); individuals on medication that affect glucose metabolism, bone metabolism and/or food intake; pregnant or lactating women; and use of nutritional supplements. In addition, all female adolescents declared to be postmenarcheal. All participants and their legal guardians (in the case of adolescents under 18 years) signed an Informed Consent Term. The study was approved by the Research Ethics Committee of the School of Public Health of the University of São Paulo (FSP / USP) under protocol number 2307/2011.

Anthropometric measurements

Weight was measured in portable digital scale (Filizola®), with a maximum capacity of 150 kg and an accuracy of 0.1 kg. Measurements were performed in duplicate, in a non-consecutive way and their mean values were used. To measure height, a stadiometer of the brand Seca bodymeter 208® was used, with a maximum capacity of 2.0m and accuracy of 1 mm. Then the body mass index (BMI) was calculated according to the equation: BMI = Weight (kg) / Stature² (m²), and the classification of the nutritional status followed the cutoff points established by the World Health Organization's BMI-for-age curves28: BMI below the 3rd percentile (equivalent to the Z-score <-2): undernutrition; BMI equal to or greater than the

3rd percentile to the 85th percentile (equivalent to the Z-scores between -2 and 1): normal weight; BMI between 85th and 97th percentiles (equivalent to Z-scores between 1 and 2): overweight; and BMI with values greater than or equal to the 97th percentile (equivalent to the Z-score - 2): obesity.

Blood analyses

After a 12-hour fast, approximately 20 ml of peripheral venous blood was collected at the adolescent's residence using disposable materials to determine: serum intact total osteocalcin (tOC), ucOC, leptin and adiponectin. Serum concentrations for tOC (IBL America, Minneapolis, MN, USA), ucOC (Cusabio, China), leptin (Enzo Life Sciences, Farmingdale, NY, USA) and adiponectin (Enzo Life Sciences, Farmingdale, NY, USA) were determined by Enzyme-Linked Immunosorbent Assay (ELISA).

Food intake

Food intake data for vitamin K was obtained through the 24-hour food recall (R24h), a method consisting of records on all foods and beverages consumed by the individual the day before the interview. Data collection was performed in two moments: at home and through telephone interviews. The second collection occurred on a non-consecutive day, and allowed adjustment of the distribution of energy consumption, macro and micronutrients through the removal of intrapersonal variance. The conversion of the home measurements into units of weight (g) and volume (mL) was performed according to standardizations described by Pinheiro et al.[29] and Fisberg and Villar.[30] Food and regional preparations had the estimated nutritional value based on the Brazilian Food Composition Table (TACO).[31] Nutrient conversion was assessed with the Nutrition Data System for Research (NDS-R) software (version 2007, Nutrition Coordinating Center, University of Minnesota, Minneapolis, USA).

Statistical analysis

Vitamin K had its intrapersonal variability adjusted by the Multiple Source Method (MSM) program, an online software developed by the Department of Epidemiology of the German Institute of Human Nutrition Postdam-Rehbrucke (DIfE), which, through a statistical modeling technique, uses the R24h (among other types of food surveys) to estimate habitual intake from repeated measurements of this instrument.[32] In addition, for all statistical analyzes, energy-adjusted vitamin K was used according to the formula: vitamin K / calories x 1,000 and to minimize errors due to over-reporting or sub-reporting of intake, R24h with energy values higher than 4,000 kilocalories or lower than 500 kilocalories were excluded.

All continuous variables had their distribution evaluated using the Shapiro-Wilk test. As the variables did not present normal distribution, tests of differences between medians

for two groups were performed using Mann-Whitney-Wilcoxon (Ranksum) test. Differences according to quartiles of vitamin K intake was tested by Pearson's Chi-Square test.

For purposes of comparison, individuals were classified according to their nutritional status into two categories: normal weight and weight excess (comprising overweight or obesity). Correlations between intake of vitamin K (energy adjusted) and all variables were evaluated using Spearman's Linear Correlation. To evaluate the associations between vitamin K intake and the variables of the study, Multiple Linear Regression was performed using all the variables into their log version since did not present normal distribution. Leptin, adiponectin, ucOC and tOC concentrations were used as dependent variables in each model. Vitamin K was used as independent variable, as BMI and gender (adjustment variables).

STATA version 13 software (StataCorp LP®) was used and for all statistical tests and a significance level of 5% was considered, thus results with p <0.05 were considered statistically significant.

RESULTS

Total sample comprised 129 adolescents with a mean age of 16.3 years (± 1.4), of which 48.1% (n= 62) were female. Overall, 73.4% of the subjects were normal weight. General characteristics of the participants are shown in Table 1.

Table 1. Characteristics and metabolic parameters of participants according to sex, São Paulo -SP, Brazil, 2018.

	Mean Male (n= 67)	Mean Female (n=62)	Mean (SD) Total n=129
Age (years)	16.3 (1.4)	16.3 (1.4)	16.3 (1.4)
Weight (kg)	62.1 (11.6)	60.5 (15.9)	61.3 (13.8)
Height (m)**	1.73 (0.07)	1.62 (0.06)*	1.68 (0.1)
BMI (kg/m²)**	20.8 (3.6)	22.1 (5.97)	21.8 (5.0)
Leptin (ng/mL)	10.4 (11.8)	40.2 (13.6)	24.7 (19.6)

Table 1. Characteristics and metabolic parameters of participants according to sex, São Paulo -SP, Brazil, 2018. (cont.)

	Mean Male (n= 67)	Mean Female (n=62)	Mean (SD) Total n=129
Adiponectin (µg/mL)	31.1 (17.8)	29.3 (16.9)	30.59 (17.33)
tOC (ng/mL)	65.6 (82.8)	50.5 (61.0)	58.3 (73.2)
ucOC (ng/mL)**	1.1 (0.9)	0.9 (1.2)	0.1 (1.1)

BMI, body mass index; tOC, total osteocalcin;ucOC,undercarboxylated osteocalcin; SD: standard deviation. *p< 0.05 (Mann-Whitney Test) **n=128.

Median intake of vitamin K was 89.9 µg (or 45.33 µg/1,000kcal of the diet, being 41.74µg and 48.76 µg for male and female, respectively), with no differences according to sex or nutritional status. There was no statistically significant difference in energy-adjusted vitamin K intake between groups according to nutritional status (p= 0.5995) and sex (p=0.1141). In the total sample, vitamin K intake did not correlate with age (r=0.1308, p = 0.1477), weight (r = -0.0856, p= 0.3442), BMI (r = 0.0669, p = 0.4621), leptin (r= 0.1291, p = 0.1530), adiponectin (r = -0.0682, p = 0.4517), total OC (r = 0.0442, p = 0.6256) and ucOC (r = -0.1136, p = 0.2110). However, in normal weight subjects vitamin K intake had a positive correlation with age (r= 0.2489; p= 0.0174) and a negative correlation with weight (r= -0.2335; p= 0.0259).

In the total sample, BMI presented a positive correlation with leptin (r= 0.5782, p= 0.0000) and negative correlation with tOC (r=-0.1815, p= 0.0404), without correlations with adiponectin (r= 0.0903, p= 0.3105) or with ucOC (r= 0.0970, p= 0.2780).

Evaluating adiposity parameters according to quartiles of vitamin K intake, a significant difference between leptin (p = 0.045), weight (p = 0.022) and ucOC (p = 0.042) was observed, between quartile 1 and 4 (table 2).

Table 2. Characteristics of study participants divided by quartiles of vitamin K intake (ug). São Paulo- SP, Brazil, 2018.

Vitamin K (ug)	<35,0 1stQuartile (n=33)	≥35,1-44,7 2ndQuartile (n= 32)	≥44,8 – 54,4 3rd Quartile (n= 32)	≥44,8 – 54,4 4th Quartile (n= 32)
Age (years)	16.2 (1.4)	16.3 (1.3)	16.5 (1.4)	16.4 (1.5)
Weight (kg)	64.9 (15.9)	59.9 (12.9)	55.6 (8.1)	64.7 (15.4)*
BMI (kg/m²)	22.5 (5.5)	20.9 (4.5)	19.5 (2.2)	24.3 (5.8)
Leptin (ng/mL)	25.1 (17.5)	18.5 (21.1)	21.1 (17)	34.2 (19.7)*
Adiponectin (µg/mL)	29.4 (15.6)	32.7 (17)	32 (18.5)	28.4 (18.5)
tOC (ng/mL)	61.2 (90.4)	66.8 (79.7)	57.8 (67)	47.4 (51.6)
ucOC*(ng/mL)	1.2 (1.1)	1.1 (1.1)	0.6 (0.5)	1.0 (1.3)*

BMI, body mass index; tOC, total osteocalcin; ucOC, undercarboxylated osteocalcin. *p< 0.05 (Mann-Whitney Test).

According to multiple linear regression analysis adjusted for nutritional status and sex, there were no associations between vitamin K intake and leptin, adiponectin, ucOCand tOC.

DISCUSSION

In this study, which aimed to investigate the relationship between vitamin K intake and serum levels of osteocalcin, leptin, adiponectin and nutritional status of adolescents, vitamin K intake was negatively correlated with weight and positively correlated with age among normal weight subjects. BMI was correlated positively with leptin and had a negative correlation with tOC in the total sample. Garanty-Bogacka et al.,[33] examining the relationship between serum osteocalcin and metabolic risk factors in obese children and adolescents, found that OC was inversely associated with fat mass and BMI-standard deviation score (BMISDS), suggesting that osteocalcin acts as a negative regulator of fat mass and has favorable effects on fat and glucose metabolism. This result is similar to the one found in a study by Reinehr and Roth,[17] in which osteocalcin was negatively correlated with BMI and BMISDS in obese children.

Obesity in childhood and adolescence is related to the development of insulin resistance causing metabolic alterations, such as impaired glucose tolerance and type 2 diabetes,

atherosclerosis and hypertension.[34] Likewise, adolescence is a potentially critical period for body composition alterations and to the development of obesity in adulthood.[35]

Some evidences have shown a possible effect of vitamin K intake on body fat.[26] Knapen et al.[9] using combined data from three vitamin K trials, with ucOC as an indicator of low vitamin K status, found that better vitamin K status was related to maintenance of body weight and fat mass, and that supplementation with menaquinone (MK), one of the forms of vitamin K, for three years, may prevent weight gain in postmenopausal women. In another study, Knapenet al.[36] found that poor status as deduced from low cOC plasma concentrations was associated with higher fat mass at different body sites in adult and elderly women.

In animal studies, rats fed a diet with addition of phylloquinone (PK), another form of vitamin K, and MK showed significant reduction of visceral and subcutaneous fat.[5] Kim et al.[37] showed that mice fed a high-fat diet supplemented with MK for three months gained less weight, less body fat, and presented reduced serum glucose and leptin compared to those fed the high-fat diet without supplementation. However, caution should be taken when comparing these results with those of the present study, since the sample and populations studied differ in age and also in relation to the form (MK or PK), and if the intake of vitamin K was made through diet or supplementation.

It is still unclear which mechanisms may be involved in the performance of vitamin K in body weight, but ***in vitro*** studies suggest that the effect of vitamin K occurs at the cellular level influencing the differentiation and functions of bone marrow cells to inhibit adipogenesis and osteoclastogenesis.[38] In addition to inhibiting adipogenesis, treatment with MK-4 inhibited the expression of the osteoclast differentiation factor (ODF)/receptor activator of nuclear factor-kappa-B-ligand (RANKL) – a membrane surface molecule that is part of the tumor necrosis factor (TNF) receptor family, which is essential for the survival, development and differentiation of osteoclasts[39]– and the formation of osteoclast-like cells induced by 1,25-dihydroxyvitamin D_3.[38]

In humans, high MK intake was related to the lower prevalence of metabolic syndrome (MS), and vitamin K status was associated with its low occurrence. In addition, the highest tertile for vitamin K status was correlated with lower BMI when compared to those in the lowest tertile.[40] Although few studies have evaluated associations between body weight and vitamin K intake, especially among adolescents, it is known that adequate micronutrients intake are essential for the maintenance of various metabolic functions of the organism,[41] while insufficient intake appears among the ten main risk factors for the total global burden of diseases worldwide, and is also considered the third preventable risk factor for non-communicable diseases.[42]

During adolescence, the most prevalent nutritional problems are not only obesity and its comorbidities, but also some micronutrient deficiencies such as vitamin A, iron and iodine, which may affect the health and performance of adolescents.[43] Some evidence suggests that the pattern of food intake among adolescents is not healthy, given that their diet offers few nutrients from foods such as fruits and vegetables (sources of vitamins and minerals such as vitamin K) and includes large amounts of high energy density foods such as snacks and soft drinks, which may contribute to the higher prevalence of obesity.[44]

As in the present study, Campos et al.[45] found a positive correlation between leptin and BMI. Similar results were also found by Van Der Heijden et al.:[46] not only BMI but also body fat was correlated with leptin. Additionally, when vitamin K intake was divided into quartiles, a statistically significant difference was found between the first and the fourth quartile with leptin, weight and ucOC. In a study with mice, in addition to weight loss, intracerebroventricular infusion of leptin also led to bone loss, suggesting that this hormone acts through the central nervous system to inhibit bone formation.[22] This effect of leptin is exerted through a hypothalamic mechanism using two neural mediators:the sympathetic system and the Cocaine-Regulated Transcript and Amphetamine (CART), both acting on osteoblasts.[22,47] This mechanism involves the transport of leptin through the blood-brain barrier and is necessary for specific receptors on serotonergic neurons of the brainstem, inhibiting the synthesis of serotonin (a hormone regulator positive for appetite and an inhibitor of the synthesis of catecholamines of hypothalamic neurons).[22,47-49]

In this study, adiponectin did not show associations with vitamin K intake or BMI. Knapen et al.[9] also did not find associations between vitamin K status (determined by ucOC) and circulating adiponectin, before or after vitamin K supplementation. However, PK supplementation significantly increased serum adiponectin concentration in study performed by Rasekhi et al.,[50] who investigated the possible role of adiponectin as a mediator of glucose homeostasis following PK supplementation in premenopause women with prediabetes. Adiponectin is one of the main adipokines present in adipose tissue and plays an essential role in improving insulin sensitivity and also acting as an anti-inflammatory regulator.[51,52] It is present in the regulation of glucose metabolism and fatty acid degradation, being inversely correlated with leptin. Its plasma levels are increased after weight reduction and are significantly reduced in obese individuals, in insulin resistant individuals, and in type 2 diabetic patients.[51,52]

There are still a limited number of studies that investigate the relationships between vitamin K dietary intake and nutritional status, especially among adolescents. In the present study, in total sample, vitamin K intake was not associated with obesity parameters, but the results suggest a possible relationship between vitamin K intake, weight, BMI, leptin and total OC in adolescents.

As positive points, we can mention the measurement of osteocalcin in its total version and in its undercarboxylated fraction, which is the main form related to glucose homeostasis. There are some limitations that need to be mentioned. First, serum concentrations of vitamin K were not evaluated. Second, although BMI is a good measure of nutritional status in a large number of people, it does not assess body composition, especially fat mass.

CONCLUSIONS

Besides no direct associations was observed between vitamin K intake with nutritional status, osteocalcin and adipokines, a negative correlation with body weight was observed in normal weight subjects, indicating the possible role of this vitamin in weight regulation. Anyway, it is still unclear the metabolic pathways involved in the relation between vitamin K intake and body composition, and future studies on this subject are needed.

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Collaborators

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