Original Communication

Higher intakes of dietary caffeine are associated with 25-hydroxyvitamin D deficiency

A cross-sectional study from the NHANES

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Abstract: Low serum 25-hydroxyvitamin D [25(OH)D] levels remain a challenge worldwide. While some *in vitro* studies show a caffeine-induced decrease in vitamin D receptor expression, there is a paucity of research to define the extent of caffeine intake and effects on 25(OH)D levels. Therefore, we aimed to associate dietary caffeine intake with 25(OH)D deficiency through a recognized dataset. Using data collected from the 2005–2006 National Health and Nutrition Examination Survey (NHANES), 25(OH)D levels and dietary caffeine intake were extracted from 13134 individuals (30–47 years, interquartile range). We used one-way ANOVA and chi-square tests for quantitative and qualitative variables, respectively, and performed multivariate logistic regression for four models to assess the odds ratio (OR) of 25(OH)D deficiency (<20 ng/ml or <50 nmol/L) based on quartiles of dietary caffeine intake. Both crude and multivariable models detected higher OR for 25(OH)D deficiency according to the highest intakes of caffeine (15.8±9.5, 51.9±11.9, and 177±156 mg/d) when compared to the reference category (2.19±1.04 mg/d), in which the OR in the highest category of caffeine intake was 1.24 (95% CI: 1.12 to 1.37) and 1.48 (95% CI: 1.16 to 1.78) for the crude model and the most complete multivariable analysis (adjustment for age, sex, race, body mass index, smoking, physical activity, occupation, energy intake, protein intake, and fat intake), respectively. In conclusion, higher dietary intakes of caffeine were associated with 25(OH)D deficiency in a representative sample of the American population, but further investigation is warranted to determine causation.

Keywords: Caffeine, coffee, vitamin D, 25-hydroxyvitamin D

Introduction

Coffee is one of the most consumed beverages worldwide. Particularly, coffee is the second most consumed drink in the world, behind only water [1, 2]. Coffee drinking has been extensively investigated for its possible health benefits since the first observations between the 1960s and 1970s mainly related to glucose homeostasis [3, 4]. Currently, according to meta-analyses, adequate coffee consumption is related to benefits on the liver [5], kidney [6], cardiac [7], and metabolic health [8]. These effects are primarily attributed to coffee as a drink rich in phenolic compounds with antioxidant actions (e.g., chlorogenic acids), minerals (e.g., potassium and magnesium), vitamins (e.g., niacin), soluble fiber, and caffeine [9].

Caffeine, also known as 1,3,7-trimethylxanthine, is a psychoactive substance with antagonistic action to adenosine receptors (mainly A_1 and A_{2A}) whereby central fatigue is reduced and consequently increasing alertness and sports performance [10, 11]. Notwithstanding these benefits, caution should be required because caffeine may be considered a drug with side effects in some clinical situations, such as during pregnancy [12], in children [13], psychiatric patients [14, 15], as well as in gastrointestinal and cardiovascular diseases [16, 17]. Sleep disturbances are another side effect of caffeine, as consumption close to bedtime can affect sleep quality and is associated with daytime sleepiness [18, 19]. Caffeine consumption can also impact the absorption of some nutrients (e.g., non-heme iron, magnesium, and calcium). Concerning calcium homeostasis, despite

the lack of consensus, data are proposing a biological interaction between coffee/caffeine consumption with negative changes in calcium excretion and bone biomarkers, as well as an association with increased risk for falls, osteoporosis, and bone fractures [20–22].

Interestingly, Rapuri et al. (2001) observed that women with a higher intake of caffeine (>300 mg/d) and a genetic variant at the vitamin D receptor (VDR) were at a higher risk for bone loss [23]. In addition, previous *in vitro* studies have shown harmful effects of caffeine on the VDR by reducing its protein expression [24, 25]. Conversely, the association between caffeine intake and serum 25-hydroxyvitamin D [25(OH)D] levels is still poorly understood, whereas 25(OH)D deficiency remains a global challenge linked to many diseases and disorders, e.g., bone metabolic disorders, cardiovascular diseases, and many cancer types [26–30]. Thus, in an attempt to provide further clinical understanding in this landscape, we aimed to investigate the relationship between dietary intake of caffeine and 25(OH)D deficiency (i.e., <20 ng/ml or <50 nmol/L) using the database of the National Health and Nutrition Examination Survey (NHANES).

Study design

Using data from the National Health and Nutrition Examination Survey (NHANES), we analyzed the effect of dietary caffeine intake on 25(OH)D levels. We used NHANES data from the years 2005 to 2006, by which 13134 participants 16 years and older (18–84 years) were enrolled. The NHANES is a national program designed to assess the health and nutritional status of children and adults in the United States of America (USA) [31]. The survey covers a nationally representative sample of approximately 10,000 people each year situated across the USA. The NHANES survey collects health information from participants through both interviews and physical examinations. The interviews include demographic, socioeconomic, dietary, and health-related questions, whereas the physical examination component consists of medical, dental, and physiological evaluations by trained personnel.

Measures

Baseline demographic characteristics included participants' age, body mass index (BMI), body weight (kg), waist circumference (cm), sex, race/ethnicity (Hispanic, White, Black, other), smoking (nonsmoking, former, and current). Use of dietary supplements (yes vs. no) was also considered, as well as intakes of dietary caffeine, energy, nutrients, and other food components were evaluated by the 24-hour dietary recall –i.e., the 24 hours before the interview (midnight to midnight). Comorbidities at baseline included coronary heart disease and history (yes vs. no) of physician-diagnosed diabetes, angina pectoris, and myocardial infarction, cancer, and stroke.

For baseline laboratory measurements, serum specimens were collected during the corresponding medical examinations and were frozen and stored at below −70 °C until analysis. Serum concentrations of 25(OH)D were analyzed using the DiaSorin radioimmunoassay (DiaSorin Corporation 25-hydroxyvitamin D 125I RIA kit; DiaSorin Corporation, Stillwater, Minnesota, USA), which has previously been described thoroughly according to the laboratory procedures and manuals [32].

Statistical methods

We analyzed the normal distribution and homogeneity of variance using the Kolmogorov-Smirnov and Levene's tests, respectively. The individuals were grouped based on the quartiles of dietary caffeine intake. For comparing general characteristics among the quartiles of dietary caffeine intake, we used one-way ANOVA and Chi-square tests for quantitative and qualitative variables, respectively. We carried out multivariate logistic regression in four models to assess the risk of 25(OH)D deficiency (<20 ng/ml or <50 nmol/L) based on quartiles of dietary caffeine intake. All analyses were performed by using a statistical package for the social sciences software, version 22, and significant P-values less than 0.05 were considered for all the tests.

Results

General characteristics of the subjects based on quartiles of dietary caffeine intakes can be seen in Table 1. The majority of subjects in the high category of dietary caffeine intake were men (56.4%) and Non-Hispanic White (65%). The subjects in the high category of dietary caffeine intake had higher body weight (81.4±22.1 vs. 60.8±29.3 kg), waist circumference (97.7±16.6 vs. 83.9±22.1 cm), BMI (28.3±6.6 vs 24.5±7.48 kg/m^2), and serum C-reactive protein (0.42±0.77 vs. 0.33±0.69 mg/dL) than the low category of dietary caffeine intake. In addition, participants in the high category of dietary caffeine intake had lower 25(OH)D levels (58.8±20.2 nmol/L) compared to the low category (60.8±20.1 nmol/L) of dietary caffeine intake.

Usual intakes of macronutrients and energy within quartiles of dietary caffeine intake are provided in Table 2. Individuals in the highest quartiles of dietary caffeine intake had significantly more intakes of energy, proteins, fats, and dietary fiber than lower quartiles. Multivariable-adjusted

Table 1. Characteristics of NHANES participants in different quartile of dietary caffeine intake

	Caffeine intake quartiles				
	1st quartile (n=3738)	2nd (n=3453)	3rd (n=2743)	4th (n=3200)	P-Value[1]
Caffeine intake (mg/d)	2.2±1.0	15.8±9.5	51.9±12.0	177.8±156.7	
Age	31.8±26.1	30.7±22.2	38.7±21.4	47.0±19.6	<0.001
Sex (M/F) (%)	45.3/54.7	49.8/50.2	50.7/49.3	56.4/43.6	<0.001
Race/Ethnicity (%)					<0.001
Mexican American	25.3	29.5	22.3	17.3	
Other Hispanic	2.9	3.4	3.2	2.9	
Non-Hispanic White	48.1	42.4	52	65	
Non-Hispanic Black	19.7	20.6	17.1	14	
Other Races – Including Multiracial Americans	3.9	25.1	26.4	21.9	
Body weight (kg)	60.9±29.3	66.7±27.2	76.4±23.7	81.4±22.1	<0.001
Waist circumference (cm)	83.9±22.1	86.9±20.5	93.5±18.0	97.7±16.7	<0.001
Body mass index (kg/m^2)	24.6±7.5	25.4±7.2	27.4±6.9	28.3±6.7	<0.001
Serum 25-hydroxyvitamin D (nmol/L)	60.8±20.2	58.1±20.6	56.9±20.4	58.8±20.2	<0.001
Serum C-reactive protein (mg/dL)	0.33±0.69	0.35±0.73	0.37±0.67	0.42±0.77	<0.001
Calcium intake (mg/day)	1004.3±559.6	1005.7±601.9	893.3±553.5	829.0±567.6	<0.001
Parathyroid hormone (pg/mL)	43.4±25.7	43.1±4.5	44.2±24.3	44.0±25.7	0.209

Values were described as mean and standard deviation.
[1]P-values were calculated by using the one-way ANOVA test for continuous variables and chi-square for categorical variables.

Table 2. Macronutrients and energy intake according to the quartiles of dietary caffeine intake

	Caffeine intake quartiles				
	1st (2.2±1.0 mg/d; n=3738)	2nd (15.8±9.5 mg/d; n=3453)	3rd (51.9±12.0 mg/d; n=2743)	4th (177.8±156.7; mg/d; n=3200)	P-Value[1]
Energy (kcal/day)	1965.25±841.86	2106.81±945.62	2045.02±910.59	2074.71±904.17	<0.001
Protein (g/day)	74.03±34.83	78.98±40.55	78.69±38.89	81.61±39.88	<0.001
Carbohydrate (g/day)	255.07±115.79	271.01±127.40	259.92±124.43	254.65±123.19	<0.001
Total fats (g/day)	73.25±39.35	79.20±44.37	76.99±42.43	79.07±43.23	<0.001
Dietary fiber, total (g/day)	14.97±8.62	15.14±9.49	15.22±9.16	15.83±9.72	<0.001

[1]P-values were calculated by using the one-way ANOVA test.

OR for 25(OH)D deficiency based on quartiles of dietary caffeine intake are presented in Table 3. In the crude model, subjects in the top quartile of dietary caffeine intake had a 24% higher likelihood (OR 1.24; 95% CI: 1.12, 1.37) of having 25(OH)D deficiency compared with subjects in the bottom quartile. After adjustment for potential confounders such as adjusted for age, sex, race, BMI, physical activity, occupation, energy intake, protein intake, and fat intake this association remained significant (OR 1.48; 95% CI: 1.16 to 1.78) (Figure 1).

Discussion

Our study investigated the effect of dietary caffeine intake on serum 25(OH)D levels using NHANES data. In the crude and the more adjusted multivariable (adjustment for age, sex, race, BMI, smoking, energy intake, protein intake, and fat intake) models, subjects in the upper quartile of dietary caffeine intake had 24% (95% CI: 1.12 to 1.37) and 48% (95% CI: 1.16 to 1.78) higher odds of having 25(OH)D deficiency compared to subjects in the lower quartile. Compared with subjects in the lower caffeine quartile, subjects in the upper quartile had higher odds of having 25(OH)D deficiency for the other models (1.17 OR; 95% CI: 1.05 to 1.30, adjusted for age and sex; 1.18 OR; 95% CI: 1.05 to 1.33, adjusted for age, sex, race, and BMI) as well.

While Rapuri et al. (2001) conducted the seminal study in this context, little scientific attention was directed afterward [23]. Working on postmenopausal elderly women, these authors compared only caffeine intake at $\leq$300 mg/d (n=265) *vs* >300 mg/d (n=178) and did not find differences for 25(OH)D levels between groups

Table 3. Odds ratios and confidence intervals for 25(OH)D deficiency based on dietary caffeine intake quartiles

	Caffeine intake quartiles				
	1st (2.2±1.0 mg/d; n=3738)	2nd (15.8±9.5 mg/d; n=3453)	3rd (51.9±12.0 mg/d; n=2743)	4th (177.8±156.7; n=3200)	P-Value
Model[1]	1	1.33 (1.21 to 1.47)	1.45 (1.41 to 1.61)	1.24 (1.12 to 1.37)	<0.001
Model[2]	1	1.36 (1.23 to 1.50)	1.42 (1.27 to 1.57)	1.17 (1.05 to 1.30)	0.001
Model[3]	1	1.25 (1.12 to 1.40)	1.38 (1.23 to 1.56)	1.18 (1.05 to 1.33)	<0.001
Model[4]	1	1.31 (1.17 to 1.47)	1.34 (1.16 to 1.71)	1.48 (1.16 to 1.78)	<0.001

[1]Crude model.
[2]Adjusted for age, sex
[3]Adjusted for age, sex, race, BMI
[4]Adjusted for age, sex, race, BMI, smoking, physical activity, occupation, energy intake, protein intake, fat intake
P-values were calculated by using the one-way ANOVA test.

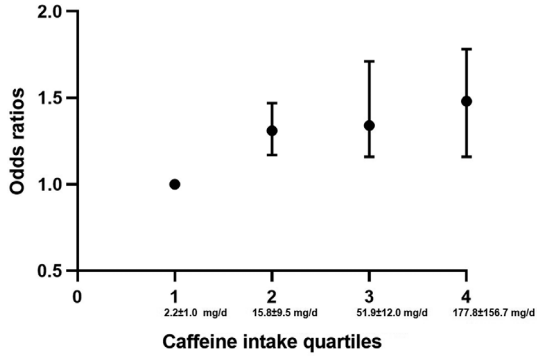

Figure 1. Odds ratios and confidence intervals for 25(OH)D deficiency based on dietary caffeine intake quartiles. 1=Reference category. All odds ratios and confidence intervals were >1, thus expressing a significantly increased risk of 25(OH)D deficiency compared with the reference category (p<0.001). These results were obtained upon the fully adjusted model (adjustment for age, sex, race, BMI, smoking, energy intake, protein intake, and fat intake).

(75.80±2.2 and *vs* 72.5±2.25 for high and low caffeine levels, respectively) [23, 33]. In our study, we included a larger sample size (n=13134) and divided the caffeine intake according to the most usual ranges, by which 2.19±1.04, 15.8±9.50, 51.9±11.9, and 177±156 mg/d were the first, second, third, and fourth quartiles, respectively. Nevertheless, it ought to be highlighted that Rapuri et al. also performed analyses for *VDR* genotypes, observing that patients with *tt* genotype and habitual caffeine intake >300 mg/day had significantly higher rates (−8.14±2.62%) of bone loss at the spine than those with the *TT* genotype (−0.34 ±1.42%) [23]. Additionally, patients who habitually ingested >300 mg/day of caffeine had significantly higher rates (−1.90±0.97% *vs* 1.19±1.08%) of bone loss at the spine than those with a low intake (≤300 mg/day) [23, 34].

Given that we divided caffeine intake into common doses, even the highest quartiles can be easily obtained through popular foods and caffeinated drinks. For instance, approximately 100 mg of caffeine is found in a standard cup (240 mL) of instant coffee, whereas a 237 mL cup of espresso coffee can contain obtain up to 320 mg of caffeine [33]. Moreover, caffeine must also be found in other common foods and drinks, such as dark chocolate bar (31 mg in 41 g), cocoa powder (46 mg in 20 g), coca soft drinks (35 mg in 355 mL), Red Bull® energy drink (80 mg in 245 mL), among others [34, 35]. Despite the complex mixture of functional components (e.g., chlorogenic acid), drinking coffee per se naturally deserves attention since coffee is the main dietary source of caffeine [36–38]. In light of this relevance, in an analysis of the 5th Korea National Health and Nutrition Examination Survey consisting of 2,523 young adults, subjects who habitually consumed more coffee had lower levels of 25(OH)D. In this study, 25(OH)D insufficiency and deficiency were detected in 70.7% for the frequency of coffee drinking less than 1 time/week, 83.8% for 2–6 times/week, 82% for 1 time/day, and 84.5% for more than 2 times/day.

Taking into account the population characterization of our study, despite the statistical difference in 25(OH)D levels between the caffeine intake quartiles, the difference was only ≈2–4 ng/mL between the highest quartile compared to the others. On the other hand, it must be mentioned that both quartiles 2, 3, and 4 for caffeine intake showed 25(OH)D levels below 60 nmol/L and, previously, Jesudason et al. noted that postmenopausal women with 25(OH)D levels <60 nmol/L had higher concentrations of bone reabsorption markers (urinary hydroxyproline/creatinine, pyridinoline/creatinine, and deoxypyridinoline/creatinine) and serum alkaline phosphatase as a marker of bone formation [39]. Hence, due to the fundamental role of 25(OH)D as an associated bone health biomarker, high consumption of caffeine could be an important concern especially in groups at risk for bone diseases and disorders (e.g., elderly and postmenopausal women) [40, 41]. Along these lines, in a meta-analysis including 15 prospective cohort studies with a total of 51239 participants and 3386 cases of hip fracture, 58% (adjusted relative risk) were more likely to have hip fracture when serum 25(OH)D levels were less than 60 nmol/L [42]. In contrast, the vast majority of the populations included were older adults [42], while in our study

the mean age corresponded to an extent of middle-aged people (30–46 years), that is, people with less risk of bone fractures when compared to aged subjects.

Our study has notable strengths, such as the sample size of more than 13000 participants representing the American population. Furthermore, these data are a novelty given the scarcity of a robust study analyzing the association between 25(OH)D levels and caffeine intake. As a limitation of our work, caffeine consumption was estimated using a single 24-hour dietary recall, whereas the food frequency questionnaire or multiple 24-hour dietary recalls could be more reliable measures [43]. In addition to the caffeine consumption, other dietary data were self-reported based on a single 24-hour dietary recall and we did not have access to vitamin D intake. The nature of the cross-sectional design cannot be translated into clinical recommendation and is susceptible to confounding factors; in contrast, we employed adjustments for age, sex, race, BMI, smoking, physical activity, occupation, energy intake, protein intake, and fat intake. Furthermore, we emphasize that this study does not decipher the need to limit caffeine intake in order not to affect 25(OH)D levels.

Bearing bone fractures in mind as a primary clinical event, the association between low 25(OH)D levels and higher caffeine intake could partially underpin the studies in which higher coffee intake was regarded as a risk factor for this outcome. However, the ideal scenario to elucidate the direct impact of caffeine intake on 25(OH)D levels and related biomarkers of bone health and osteoporosis risk, as well as bone fractures, would be through a long-term randomized clinical trial controlling the consumption of caffeine-rich foods along with staggered doses of caffeine supplementation to avoid the effects of functional substances across coffee and tea. Undoubtedly, such a design must be performed among a uniformity of sex, race, physical activity level, body composition, smoking status, pharmacotherapy, and age between caffeine and placebo groups. Given the lack of this study to date, a threshold of caffeine intake for 25(OH)D levels and related outcomes cannot be postulated, but perhaps screening for vitamin D deficiency in heavy coffee drinkers could be conceivable in clinical practice. Lastly, although a couple of *in vitro* studies have shown caffeine-induced reduced expression of VDR [24, 25], further mechanistic research is warranted to expand the biological rationale.

Conclusion

Higher caffeine intakes were associated with greater odds of having 25(OH)D deficiency among a representative sample of the American population (NHANES dataset). It is important to note that this study focused only on an intermediate outcome in which a subsequent event could be bone diseases and disorders, given the pivotal relevance of 25(OH)D in bone health. Ultimately, our data do not postulate an ideal threshold of caffeine intake as a means of preventing 25(OH)D deficiency and its consequences.

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Conflict of interest
The authors declare that there are no conflicts of interest.

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