Eur J Nutr (2013) 52:1099–1105
DOI 10.1007/s00394-012-0419-0

ORIGINAL CONTRIBUTION

Long-term dietary intake of selenium, calcium, and dairy products is associated with improved capillary recruitment in healthy young men

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Received: 6 November 2011 / Accepted: 2 July 2012 / Published online: 22 July 2012

Abstract

Purpose To identify associations between long-term (1 year) food intake and skin nutritive microvascular function in healthy subjects.

Methods This was a cross-sectional study. A validated 88-item food-frequency questionnaire was administered to 39 healthy men aged 23.4 ± 0.5 years and body mass index 23.3 ± 2.3 kg/m^2, who reported food intake during the last year and underwent videocapillaroscopy exams. The main outcome was the increase in functional capillary recruitment, that is, peak capillary density after post-occlusive reactive hyperemia subtracted from basal capillary density (caps/mm^2). Associations between reported food intake and functional capillary recruitment were investigated.

Results Daily average estimates of intake were: total energy (3,745 ± 1,365 kcal), carbohydrates (60.1 ± 5.9 %), lipids (22.1 ± 4.4 %), proteins (17.8 ± 4.1 %), fibers (33.9 ± 18.5 g), and cholesterol (492.8 ± 209.6 mg). Positive significant correlations with capillary recruitment were found for selenium (as μg/day/1,000 kcal; rho = 0.3412, $p = 0.038$,) calcium (as mg/day/1,000 kcal; rho = 0.3390, $p = 0.043$), and percentage of total energy from dairy products (rho = 0.3660, $p = 0.023$).

Conclusions Long-term intakes of selenium, calcium, and dairy products were positively associated with capillary recruitment in skin nutritive microcirculation in healthy young men. The role of such dietary components is discussed and possible mechanisms for their effects should be further investigated. This evidence adds one more possible functional property of these nutrients and food items.

Keywords Food intake · Capillary recruitment · Functional foods · Functional capillary density

Introduction

The function of blood circulation is to service the needs of body tissues—to deliver nutrients, to transport waste products away, to conduct hormones from one part to another, and, in general, to maintain an appropriate environment for optimal survival and function of cells. It is in the microcirculation where the most purposeful function of the circulation occurs: diffusion of substances back and forth between blood and tissues [1]. The physiological ability to regulate its local flow to meet metabolic needs is a key feature of the microcirculation, achieved through modulation of tissue perfusion.

At rest, as little as one-third of capillaries may be continuously perfused [2]. Intermittently perfused capillaries serve as a functional reserve for conditions that would demand increased metabolic turnover. Capillary density affects the spatial pattern of flow in the microvascular bed, modulating the distribution of blood flow among exchange

Electronic supplementary material The online version of this article (doi:10.1007/s00394-012-0419-0) contains supplementary material, which is available to authorized users.

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vessels. Due to local metabolic needs, it is able to regulate pressure and perfusion at pre-capillary level. Functional capillary recruitment (FCR) is a result of vasodilatory action and might act to match flow capillary transport and tissue oxygenation [3]. It has been suggested that FCR is involved in insulin sensitivity and blood pressure regulation by modulating, respectively, the availability of insulin and glucose to muscle cells and total peripheral vascular resistance [4].

The endothelium acts as a biological sensor responding to changes in the blood stream (shear stress, changes in lipid or hormone concentrations) by secreting vasodilators (e.g. nitric oxide, prostacyclin) and vasoconstrictors (e.g. endothelin-1) to regulate vascular tone and flow. A healthy endothelium is crucial for preventing early steps in the development of diseases such as atherosclerosis and diabetes [5, 6]. Dietary factors regularly ingested by healthy subjects have been associated with endothelial function, suggesting that some antioxidant-rich foods would highly influence endothelium homeostasis [7]. Healthy eating patterns such as the Mediterranean diet represent a therapeutic strategy to reduce inflammation and associated metabolic and cardiovascular risks [8].

There are evidences that endothelial function may be altered within a few hours after certain food items intake, suggesting that dietary factors are involved in the prevention and progression of cardiovascular disease [5]. It has been shown that pharmacological [9, 10] and also non-pharmacological [11, 12] strategies are able to improve endothelial and microcirculatory function. Non-pharmacological interventions such as physical activity, smoking cessation, and nutritional factors have been associated with enhanced vascular function [13]. Among the latter, fatty acids, antioxidants, L-arginine, folic acid, and soy protein have been the most studied components of diet [11, 14].

The aim of this study was to assess, in healthy subjects, which nutrients regularly ingested might exert some influence on microvascular function. In the absence of disease, the study of such associations may add knowledge to prevention strategies regarding nutritional counseling, in order to avoid early disturbances which might lead to microvascular dysfunction.

Materials and methods

This was a cross-sectional study of baseline data belonging to a recently published randomized trial [15]. The study was carried out at the Clinical and Experimental Laboratory on Vascular Biology at the State University of Rio de Janeiro. Before being enrolled, subjects went through a screening phase which consisted of clinical, biochemical, and anthropometrical assessment as described below. All participants gave their written informed consent. The study was approved by the institutional ethics committee.

During the screening clinical consultation subjects were asked about their medical history, family history of diseases, and eating habits. A validated [16] 88-item food-frequency questionnaire (FFQ) was administered by a trained dietitian to assess eating habits during the last year. The anthropometrical assessment included weight, height and estimated the percentage of body fat through Jackson and Pollock's skin-fold thickness protocol [17]. Subjects who smoked or had high blood pressure ($\geq$130 × 85 mmHg) [18] were not included in the study, and ones with BMI beyond the limits of 18.5–24.9 kg/m^2 were excluded except if classified as overweight (25.0–29.9 kg/m^2) with a body fat below 15 % (the average for male adults [17]). Biochemical tests assessed fasting glucose, total cholesterol, triglycerides, LDL-c and HDL-c (enzymatic–colorimetric); hemogram (automated digital morphological analysis); insulin (eletrochemiluminescence); alanine and aspartate transaminases (uv-kinetic); and creatinine (kinetic–colorimetric). A 75-g oral glucose tolerance test was also performed. Subjects with any altered biochemical result (standards presented in Table 1) were not included in the study. All laboratory measurements were performed in duplicate by automated methods (Modular Analytics E 170 and P, Roche, Basel, Switzerland and CellaVision^{TM} Sysmex do Brasil, PR, Brasil).

On the day of the videocapillaroscopy exams, volunteers arrived at the laboratory after a 12-h overnight fast. They were accommodated in a temperature-controlled room

Table 1 Anthropometrical and biochemical variables of 39 healthy men

	Mean	(SD)	Reference values for age and gender [33, 34]
Age (y)	23.4	0.5	(18–30)
BMI (kg/m^2)	23.3	2.3	18.5–24.9
Body fat (%)	13.6	5.2	15
Waist circumference (cm)	82.9	5.9	<94
SBP (mmHg)	113.7	9.0	<130
DBP (mmHg)	71.1	6.7	<85
Fasting glucose (mg/dl)	83.7	5.5	75–99
OGTT (mg/dl)	77.4	18.8	<140
Insulin (mU/dl)	6.3	2.1	2–13
Total cholesterol (mg/dl)	146.7	27.9	<200
HDL-c (mg/dl)	49.0	7.1	≥40
LDL-c (mg/dl)	83.9	24.9	<100
TG (mg/dl)	67.6	24.3	<150

SBP systolic blood pressure, *DBP* diastolic blood pressure, *OGTT* oral glucose tolerance test; *TG* triglycerides

(24 ± 1 °C), on the exam chair, and their blood pressure was checked using the standard auscultatory method. After a 30-min acclimatization period, the experiment began. The subjects underwent videocapillaroscopy exams, by two different approaches, in order to collect data on the study outcome by the most used and validated methods applied in the literature: the dynamic nailfold videocapillaroscopy and the dorsal finger videocapillaroscopy. The former records the capillaries according to a standardized, validated methodology on the fourth finger of the left hand [10, 19] and assesses the functional capillary density [(FCD), number of capillaries/unit of tissue area (mm^2) with flowing red blood cells], using 250× magnification and an area of 3 mm of the distal row of capillaries into the central portion of the nailfold. The same field is recorded before and after 1-min arterial occlusion of the finger to evaluate FCR during the post-occlusive reactive hyperemia response. The latter assesses FCD at the dorsal portion of the fourth finger and has been validated and well-described elsewhere [4, 20]. Briefly, it estimates baseline capillary density by counting the number of continuously erythrocyte-perfused capillaries during a 15-s period. Post-occlusive reactive hyperemia is also used to assess FCR after 4-min ischemia. Median FCR was not different between the employed methods ($p = 0.09$), which allowed us to present pooled results.

Forty-eight subjects were recruited and nine of them were excluded from the main trial due to loss of data related to its outcomes during the videocapillaroscopy. Nevertheless, comparisons have been made and no significant differences between excluded and included subjects were noticed [15].

Daily intake of macro and micronutrients was calculated as reported in the FFQ [21], using AvaNutri® software (AvaNutri, Brazil), which uses Brazilian Food Composition Table Database [22]. The subjects were asked about their eating habits during the last 12 months. For the analyses of correlations among food intake and microvascular parameters, the relative intake of nutrients per 1,000 kcal was calculated. Proportion of intake of different food groups (as percentage of total energy intake—TEI) was also calculated, grouping food items in the FFQ into one of the groups belonging to the Brazilian food pyramid: carbohydrates; fruits; vegetables; dairy; meat; legumes; sugars; and fats.

The main outcome variable was the increase in functional capillary recruitment (FCR), that is, peak capillary density during the post-occlusive reactive hyperemia (PORH) response subtracted from its basal value (caps/mm^2). All variables were checked for normality. Most outcomes had nonparametrical distribution. Correlations between variables were tested by Spearman's rho test. Stata v 9.2 (StataCorp, TX, USA) was used for statistical analyses. Results are presented as mean ± SD unless otherwise noted, as median (1st–3rd quartiles). The level of significance adopted was 0.05.

Results

Thirty-nine subjects were included in the analyses. Their age was 23.4 ± 0.5 years, BMI 23.3 ± 2.3 kg/m^2, and body fat 13.6 ± 5.2 %. All clinical and anthropometrical characteristics fell into expected ranges for healthy men (Table 1). Assessment of food intake revealed an energy intake of 3,745 ± 1,365 kcal/day. Carbohydrates, proteins, and lipids intakes were within the recommended proportions of total energy intake (TEI), respectively, 60.1 ± 5.9 %, 17.8 ± 4.1 %, and 22.1 ± 4.4 % (Table 2). On the counterpart, the proportion of different types of fat, cholesterol, and fiber intake did not meet recommended values. Cholesterol intake was 492.8 ± 209.6 mg/day, almost 2.5 times higher than the recommended 200 mg/day.

The assessment of micronutrients intake revealed some nutritional discrepancies (Table 3). Vitamin K, complex-B vitamins, calcium, magnesium, and zinc intakes met the dietary recommended values (DRIs), with median (1st–3rd quartiles) daily intake of 414.6 (305.6–539.7) μg/day; 2.2 (1.6–3.2) mg/day—thiamin, 2.6 (2.1–3.6) mg/day—riboflavin, 1.4 (1.1–1.8) mg/day—vitamin B_6; 1,063.9 (714.1–1,538.8) mg/day; 660.0 (476.6–785.2) mg/day and 15.8 (13.5–22.1) mg/day. Antioxidant vitamins, such as C and E, did not meet the DRIs, as well as minerals such as iron, copper, and selenium. Sodium daily intake was estimated in 3.2 g/day, twice as high as the recommended 1.5 g/day.

In terms of capillary density results, median (1st–3rd quartiles) basal FCD and peak FCD were 15 (9–26) caps/mm^2 and 18 (11–26) caps/mm^2, respectively. Median FCR

Table 2 Daily food intake of macronutrients and fiber as reported in the FFQ, 39 healthy men

	Mean	(SD)	Reference values for age and gender [34, 35]
Energy (kcal/day)	3,745	1,365	2,880–3,200
Carbohydrates (% TEI)	60.1	5.9	45–65
Protein (% TEI)	17.8	4.1	10–35
Fat (% TEI)	22.1	4.4	20–35
Saturated fat (% TEI)	14.6	3.6	<7
Polyunsaturated fat (% TEI)	2.7	0.9	Up to 10
Monounsaturated fat (% TEI)	6.3	1.5	Up to 20
Cholesterol (mg/day)	492.8	209.6	<200
Fiber (g/day)	33.9	18.5	38

TEI total energy intake

Table 3 Daily food intake of vitamins and elements as reported in the FFQ, 39 healthy men

	Median	(p25–p75)	Reference values for age and gender [35, 36]
Vitamin A (μg/day)	731.0	(242.3–1,276.5)	900
Vitamin C (mg/day)	77.5	(35.6–190.9)	90
Vitamin D (μg/day)	1.7	(0.8–3.4)	15
Vitamin E (mg/day)	3.5	(2.5–5.6)	15
Vitamin K (μg/day)	414.6	(305.6–539.7)	120
Thiamin (mg/day)	2.2	(1.6–3.2)	1.2
Riboflavin (mg/day)	2.6	(2.1–3.6)	1.3
Vitamin B6 (mg/day)	1.4	(1.1–1.8)	1.3
Calcium (mg/day)	1,063.9	(714.1–1,538.8)	1,000
Copper (μg/day)	770	(450–920)	900
Iron (mg/day)	6.9	(4.1–9.5)	8
Magnesium (mg/day)	660.0	(476.6–785.2)	400
Selenium (μg/day)	19.1	(13.4–24.6)	55
Zinc (mg/day)	15.8	(13.5–22.1)	11
Folic acid (μg/day)	139.3	(110.3–233.4)	400
Sodium (g/day)	3.2	(2.3–4.5)	1.5

was 1 (0–3) caps/mm^2. When correlations with the increase in FCR were assessed, no macronutrients (as percentage of TEI) showed statistically significant associations with it. On the other hand, two minerals showed positive significant correlations with capillary recruitment, namely selenium (as μg/day/1,000 kcal; rho = 0.3412, $p = 0.038$,) and calcium (as mg/day/1,000 kcal; rho = 0.3390, $p = 0.043$). When proportion of intake of different food groups (as percentage of TEI) was assessed, the only group presenting statistically significant association with capillary recruitment was dairy products (rho = 0.3660, $p = 0.023$—Fig. 1).

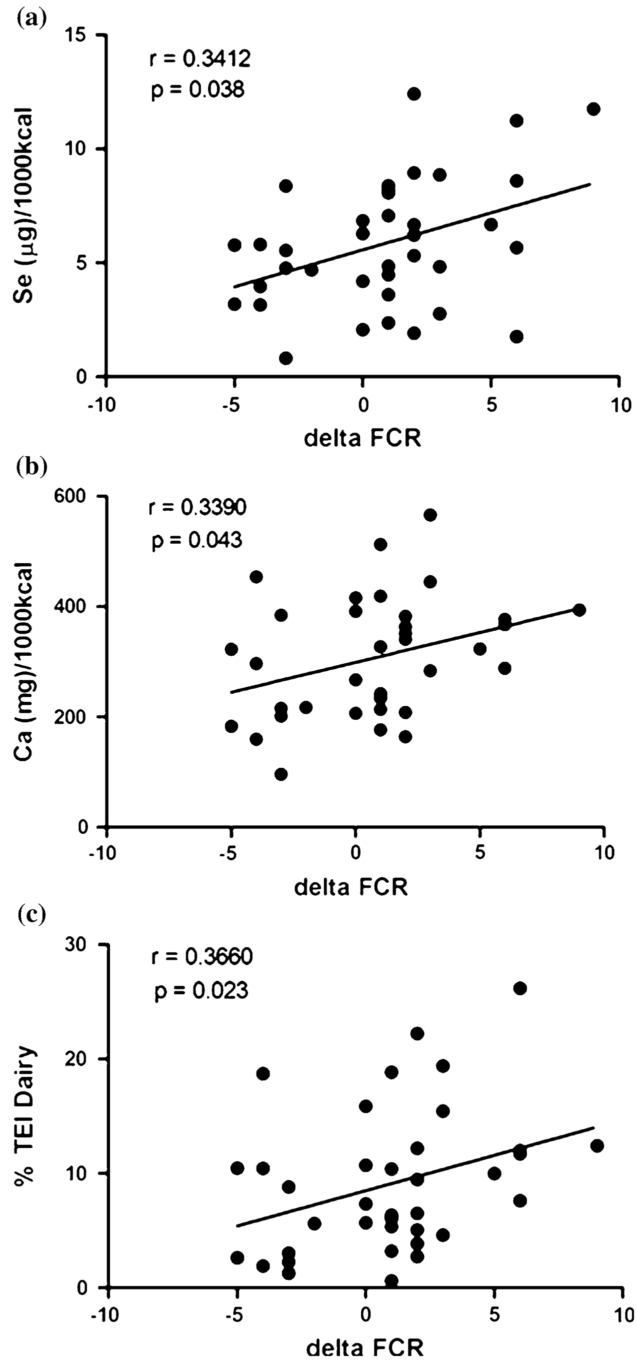

Fig. 1 Correlations between functional capillary recruitment (FCR, caps/mm^2) and daily intake of **a** selenium, **b** calcium, and **c** dairy products [as percentage of total energy intake (TEI)]

Discussion

This study assessed long-term food intake and its associations with microvascular function in a sample of healthy young men. The main novel findings were positive associations between intakes of selenium, calcium and dairy products and functional capillary recruitment (FCR). An overall assessment of intake showed that energy and macronutrients consumption fell into expected ranges, while intakes of different fat types, cholesterol, fiber, and selected micronutrients did not meet recommendations for their age group.

General distribution of macronutrients was in accordance with recommendations. The types of fat consumed, however, showed a poor distribution of polyunsaturated, monounsaturated, and saturated fat, with excessive intake of the latter. This finding most likely reflects the kind of food consumed by the sample, mainly composed by college students. High-frequencies of fast-food and ready-to-eat meals were highly reported in the FFQ, which may also corroborate observed excessive intake of cholesterol and sodium. One might also find the reported energy intake somewhat excessive, but this may not be the case since levels of physical activity varied within the sample, mostly being moderately physically active (data not shown). These trends in energy and fat consumption are in accordance with national surveys [23].

The assessment of micronutrients intake revealed some nutritional deficiencies. Subjects reported intakes of vitamin K, complex-B vitamins, calcium, magnesium, and zinc were satisfactory. These micronutrients main sources in the diet are, respectively, green leafy vegetables, peas, tuna canned in oil; ready-to-eat cereals, sweet potato, rice, wheat flour, beef, chicken, tuna; dairy; nuts, seeds, spinach, soybeans, beans; and meat, seafood, ready-to-eat cereals [24]. However, consumption of antioxidant vitamins, such as C and E, associated with fruits, vegetables, and nuts was below dietary recommended intakes (DRIs), which is also in agreement with national food intake reports in this age group [23]. Also, iron, copper, and selenium reported intakes failed to meet the DRIs. Their main sources in the diet are meat, enriched flour, seafood, nuts, and Brazil nuts, fish, turkey, respectively [24].

Our main goal in this study was to assess, in a healthy sample, which dietary factors might be related to microvascular function. We found positive correlations demonstrating associations between the variation in intakes and FCR, like for instance the selenium intake was positively associated with FCR. The essential function of selenium in humans is protection against oxidative damage, mediated by 25 selenoproteins that contain this mineral in the form of selenocysteine, including glutathione peroxidise [25]. A recent review [26] points out the anti-inflammatory effects secondary to selenium intake or supplementation. Since oxidative stress plays a causative role in the development of endothelial dysfunction, the study of nutrients directly involved in oxidative protection has emerged in the past decades. However, few studies have evaluated selenium intake effect on microvascular function in healthy subjects. A recent study by Hawkes et al. (2009) [25] on selenium supplementation in healthy men suggests that a suboptimal intake of selenium and antioxidants can impair endothelial function and increase the risk of cardiovascular disease; however, a supranutritional intake confers no additional benefit on microvascular responsiveness. A recently published clinical trial demonstrated the positive effect of Brazil nuts, a natural source of selenium, on microvascular function in obese adolescents [27]. Here, we found that the higher the intake of selenium, the higher was the individual's capacity for FCR, in this healthy group.

Correlations found between calcium intake as well as dairy products consumption and FCR were also positive ones. These are naturally closely related, since dietary calcium main sources are dairy products. Nevertheless, different factors might be involved in these associations. Dietary calcium has been well established as an antihypertensive agent [28], due to calcium involvement in normal muscle contraction and relaxation and, thus, in vascular resistance and blood pressure control. For this function, supplementation of calcium has been shown not to be as effective as dietary calcium intake [29], and this might be related to other bioactive components of milk [30]. Some biological activities of milk proteins and peptides include immunomodulatory (immunopeptides), hypotensive—angiotensin I-converting enzyme inhibition (lactokinins, casokinins), antioxidant (peptides derived from α-lactalbumin and β-lactoglobulin), hypocholesterolemic (peptides derived from β-lactoglobulin) and antithrombotic (casoplatelin) properties [30]. These physiological effects have been observed in vitro or in animal models [31] and human clinical studies are limited, as well as their effect on microvascular response. The correlations found in our analyses might possibly reflect the functional properties of such food items in long-term consumption on healthy subjects.

Although the healthy men tested presented excessive intake of saturated fat, it did not show a detrimental effect on microvascular reactivity. The reason for that remains speculative, and one might suggest that young age and low fat mass of subjects tested would act as protective factors. Another reason could be that the positive correlations found with other nutrients might also be counteracting as protective factors, and thus, their functional properties would be even highlighted.

This study has limitations. Its observational design fails to establish a causative effect of such nutrients on functional capillary recruitment. Notwithstanding, these associations are in accordance with evidence describing selenium, calcium, and dairy intakes positive overall effect on improving markers of cardiovascular risk, such as oxidative stress and hypertension [30, 31]. If they definitely possess actions toward vascular responsiveness remains to be elucidated with further investigations accordingly designed for such goal. The use of a FFQ in a small sample might limit our conclusions. The FFQ provides a better approximation of the habitual diet over a longer period than short-term food records, which might provide a more accurate intake report [32]. Although testing in a small sample size, we aimed to assess the association of long-term food intake with microvascular function and the FFQ was the eligible method. One limitation regarding food intake report is the over-estimation characteristic of FFQs [32]. We did not observe any extremely high intake in this sample, and even high reported energy intakes might be feasible due to age and gender of subjects.

This study observed positive associations between intakes of selenium, calcium and dairy products and functional capillary recruitment on skin nutritive microcirculation in a sample of healthy young men. This evidence adds one more possible functional property of these nutrients and food items and raises some important hypothesis for controlled studies. Future investigations may also clarify mechanisms involved with these specific nutrients and microvascular responsiveness.

Acknowledgments National Council for Scientific and Technological Development (CNPq, 141690/2008-9); State of Rio de Janeiro Carlos Chagas Filho Research Foundation (FAPERJ); Financing Agency of Studies and Projects (FINEP) and Coordination for the Enhancement of Education Personnel (CAPES).

Conflict of interest The authors declare that they have no conflict of interest.

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