Clinical Nutrition 30 (2011) 369–375

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original Article

Inverse association of serum carotenoids with prevalence of metabolic syndrome among Japanese

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ARTICLE INFO

Article history:
Received 20 July 2010
Accepted 9 December 2010

Keywords:
Metabolic syndrome
Carotenoids
Obesity
Antioxidant
Cross-sectional studies

SUMMARY

Background & aims: Several epidemiological studies have shown that circulating antioxidant levels are inversely associated with metabolic syndrome status. The purpose of this study was to examine the association of serum carotenoid levels, which have potent antioxidant effects, with metabolic syndrome and metabolic syndrome components in Japanese subjects.
Methods: We conducted a cross-sectional study of 931 subjects (318 men and 613 women), aged 39–70 years, who attended a health examination. Metabolic syndrome was defined according to the diagnostic definition from the Japanese Examination Committee of Criteria for Metabolic Syndrome, which was released in 2005. Serum carotenoids were measured by high-performance liquid chromatography.
Results: A significantly lower odds ratio (OR) for metabolic syndrome was observed in the highest tertile of serum β-cryptoxanthin (OR:0.45; 95% CI:0.22–0.93 in men and 0.41; 0.17–0.93 in women) and β-carotene (OR:0.45; 95% CI:0.21–0.95 in men and 0.37; 0.15–0.83 in women) compared to the lowest tertiles, in both sexes, but no significant association was found in male smokers. In women, moreover, OR for metabolic syndrome in the highest tertile of serum zeaxanthin/lutein (OR:0.37; 95% CI:0.16–0.84) was significantly lower than in the lowest tertile. Serum levels of β-cryptoxanthin, α-carotene, and β-carotene were significantly decreased with an increasing number of metabolic syndrome components in both sexes.
Conclusions: These findings indicate that carotenoids may be important factors in the prevention of metabolic syndrome in nonsmokers, but further studies are required in smokers.

1. Introduction

Metabolic syndrome is a combination of disorders that increase the risk of developing cardiovascular disease (CVD) and diabetes.[1–3] In Japan, the original diagnostic definition of metabolic syndrome was presented by the Examination Committee of Criteria for Metabolic Syndrome in 2005.[4] According to these diagnostic criteria, metabolic syndrome is defined as evidence of visceral fat accumulation (measured by waist circumference) and 2 or more of the following risk factors: elevated blood pressure, hyperglycemia, and dyslipidemia.

Serum carotenoids levels are strongly associated with diets, smoking and drinking status. Carotenoid intake comes mostly from fruits and vegetables consumption. In human beings, carotenoids are absorbed in the intestinal mucosa and then transported in the blood in association with plasma lipoproteins.[5] It is known that compared to nonsmokers, individuals who smoke have reduced concentrations of certain serum carotenoids, although the intake of green yellow vegetables, fruits, and seaweeds which contain large amounts of carotenoids showed no significant difference between Japanese smokers and nonsmokers.[6] Widome R et al.[7] reported that passive smoke exposure was also associated with lower serum β-carotene and other provitamin A, after adjustment for dietary factors. Cigarette smoke contains reactive free radicals and other pro-oxidants that are known to cause oxidative damage.[8] Alcohol consumption is inversely associated with serum carotenoid levels.[6] Alcohol drinking also induces reactive oxygen species during its metabolism in the liver.[9]Circulating antioxidant nutrients, such as carotenoids, may play important roles in defending against oxidative stress by quenching the production of singlet oxygen and free radicals.

Obesity is a principal causative factor in the development of metabolic syndrome. Despite obese individuals consume adequate

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; CVD, Cardiovascular disease; DBP, diastolic blood pressure; HDL, high density lipoprotein; OR, odds ratio; SBP, systolic blood pressure.

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0261-5614/$ – see front matter
doi:10.1016/j.clnu.2010.12.006

total energy, low micronutrients levels observed with increasing adiposity.[10] Low serum levels of carotenoids have associated with increases in oxidative stress, diabetes, hypertension, and CVD.[11–16] Low carotenoid levels among obese individuals may result from the increased systemic and adipose tissue-specific oxidative stress found in obese persons. Fat accumulation closely correlated with the markers of systemic oxidative stress. Increased oxidative stress in accumulated fat may be an important pathogenic mechanism of obesity-associated metabolic syndrome. Oxidative stress impairs glucose uptake in muscle and fat[17,18] and decreases insulin secretion from pancreatic β cells.[19] Increased oxidative stress also underlies the pathophysiology of hypertension[20] and atherosclerosis[21] by directly affecting vascular wall cells.

Three cross-sectional studies[22–24] have reported an inverse association between serum carotenoids and metabolic syndrome. In the Third National Health and Nutrition Examination Survey (NHANES III), Ford et al.[22] reported that adults with metabolic syndrome had low serum levels of several carotenoids and vitamins C and E. Sugiura et al.[23] showed that metabolic syndrome is inversely associated with serum β-carotene in nonsmokers and with serum α-carotene, β-carotene, and β-cryptoxanthin in current smokers. However, their Japanese population-based study was conducted using body mass index (BMI) as a measurement of obesity instead of waist circumference.

In the present study, to confirm this association using the original Japanese definition of metabolic syndrome, we investigated the association of serum carotenoids with metabolic syndrome and its components in a Japanese sample. This association was analyzed by sex in this study, because there are sex differences in the definition of metabolic syndrome and serum carotenoids.

2. Subjects and methods

Health examinations of inhabitants aged 39 years and older have been performed in Yakumo-Town, Hokkaido Prefecture, Japan, since 1982. We have conducted cross-sectional and longitudinal studies of lifestyle-related diseases using subjects who participated in this health examination (Yakumo Study). In this study there were 973 subjects (330 men and 639 women), aged 39–70 years, who attended a health examination held in August between the years 2005 and 2008. We excluded 38 subjects who did not provide informed consent for the present study. The remaining 931 subjects (318 men and 613 women) were eligible for the analysis. We obtained informed consent with the participants' signatures for providing information and serum to our epidemiologic study.

Trained nurses administered a questionnaire regarding health and daily lifestyle habits, including information about medication for hypertension, diabetes mellitus, and hyperlipidemia; smoking habits (current smoker, ex-smoker, or never-smoker); and alcohol consumption (regular drinker, ex-drinker, or never-drinker). Waist circumference and blood pressure were measured during the health examination.

Fasting serum samples were taken during the health examination and sera were separated from blood cells within 1 h by centrifugation. Serum levels of 5 carotenoids (β-carotene, α-carotene, β-cryptoxanthin, lycopene, and zeaxanthin/lutein) were measured separately by high-performance liquid chromatography[25] at the Department of Public Health, Fujita Health University School of Health Sciences. The range of repeatability and day-to-day variation (coefficients of variation) were 4.6%–6.9% and 9.2%–15.6%, respectively, for the assays of carotenoid.[25] The sampled sera were stored in a deep freezer at −80 °C until the carotenoids were analyzed. Other biochemical analyses of sera were performed using an auto-analyzer (JCS-BM1650, Nihon Denshi Co., Ltd., Tokyo, Japan) at the laboratory of Yakumo General Hospital on the day of the health examination.

We defined metabolic syndrome according to the definition released in 2005 by the Examination Committee of Criteria for Metabolic Syndrome of Japan.[4] These criteria are: visceral fat accumulation (waist circumference ≥85 cm for men, ≥90 cm for women) and 2 or more of the following risk factors: (1) elevated blood pressure (systolic blood pressure [SBP] ≥130 mmHg, diastolic blood pressure [DBP] ≥85 mmHg, or treatment for previously diagnosed hypertension), (2) hyperglycemia (fasting glucose ≥110 mg/dl or treatment for previously diagnosed diabetes mellitus), and (3) dyslipidemia (triglyceride ≥150 mg/dl, high density lipoprotein [HDL]-cholesterol < 40 mg/dl, or treatment for previously diagnosed dyslipidemia).

All statistical analyses were conducted using the statistical software JMP ver. 8.0 (SAS Institute). Since serum levels of carotenoids and triglycerides are distributed logarithmically, we used logarithms of these data for the analyses. The *t* and chi-squared tests were used to compare various continuous and categorical variables of participants with and without metabolic syndrome, respectively. Serum levels of carotenoids and triglycerides are represented as geometric means and 25th–75th percentile ranges. Other variables are represented as mean ± standard deviation. Relations between serum carotenoid levels and metabolic syndrome components were evaluated by partial correlation analysis. We used age, smoking habit, alcohol use, and serum total cholesterol levels as potential confounders. Serum total cholesterol levels were included in models because serum carotenoids are transported in the blood via lipoprotein carriers. After the subjects were divided into 5 groups (0, 1, 2, 3, 4) according to the number of metabolic syndrome components, the geometric mean for each serum carotenoid level adjusted for confounding factors was also calculated. Odds ratios (OR) with 95% confidence intervals (CI), adjusted for potential confounders, were estimated by logistic regression analysis. When the association of serum carotenoids and metabolic syndrome by smoking habit were analyzed in men, they were separated into nonsmoking subjects (never-smoker and ex-smoker) and current smokers. A probability value <0.05 was considered statistically significant.

3. Results

Table 1 shows the characteristics of the study subjects by metabolic syndrome status. The prevalence of metabolic syndrome was significantly higher in men than in women (22.3% vs. 7.5%, $p < 0.001$). Waist circumference, BMI, SBP, DBP, and serum levels of glucose and triglycerides were significantly higher in men and women with metabolic syndrome than in those without metabolic syndrome (*p* ranged from <0.001 to 0.034). Serum HDL-cholesterol levels were significantly lower in men and women with metabolic syndrome than in those without metabolic syndrome ($p < 0.001$). Women with metabolic syndrome were older than those without metabolic syndrome. There was no significant difference in the percentages of smokers and drinkers between those with and without metabolic syndrome in both sexes. Serum levels of β-carotene were significantly lower in the metabolic syndrome group than in the non-metabolic syndrome group in both sexes. In women, serum levels of β-cryptoxanthin were significantly higher in the metabolic syndrome group than in the non-metabolic syndrome group. These levels tended to be higher in men with metabolic syndrome compared to those without metabolic syndrome, but the difference was not significant.

Table 2 shows the partial correlation coefficients between serum carotenoids and metabolic syndrome factors by sex. In men, waist circumference, SBP, and triglycerides were significantly and negatively associated with serum levels of β-cryptoxanthin, α-carotene, and β-carotene. DBP was negatively associated with serum β-carotene levels. HDL-cholesterol was positively associated with serum zeaxanthin/lutein levels. In women, waist circumference was