Vitamin A Intake Is Inversely Related with Adiposity in Healthy Young Adults

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Summary Dietary intake, either through specific nutrients or representative food groups, can influence obesity-related oxidative stress markers. This study evaluated the potential associations between vitamin A intake and several anthropometrical, biochemical and dietary features in healthy young adults, emphasizing the putative relationships between total antioxidant consumption and vitamin A intake. This translational research enrolled 61 healthy young adults aged 18–22 y. Anthropometrical and blood pressure measurements, blood samples and nutritional intake data were collected. After adjusting for total energy intake, vitamin A intake showed a negative correlation with several adiposity measurements. Furthermore, vitamin A consumption was positively associated with serum total cholesterol as well as with the intake of antioxidant foodstuffs. So, vitamin A intake seems to be related, not only with the total antioxidant intake, but also with several anthropometrical and biochemical measurements linked to metabolic syndrome manifestations and other features related to oxidative stress in healthy young adults.

Key Words diet, vitamin A, antioxidant, adiposity, human

Vitamin A is a fat-soluble vitamin essential for a myriad of nutritional functions including growth and immune functions (1). In the habitual diet, there are a number of sources of dietary vitamin A as pro-vitamin A (from animal-derived foods) and as vitamin A carotenoids from darkly colored fruits and vegetables, oily fruits and red palm oil (2).

On the other hand, obesity has been defined as an excessive storage of body fat and has been associated with an increase of risk to develop type 2 diabetes and metabolic syndrome features, including hypertension, insulin resistance, dyslipaemia and atherosclerosis (3, 4). The role of oxidative stress on several chronic diseases is receiving increasing attention due to their link with these chronic diseases (5, 6). Thereby, systemic inflammation has been linked with oxidative stress (7–9) and has been also associated with reduced serum concentrations of vitamins A (10), B6 (11), and C (12), owing to a reduced liver production of transport proteins (such as albumin), increased turnover of antioxidant vitamins, or a shift in tissue distribution. Thus, an increase in body mass index (BMI) has been associated with lower concentrations of vitamins A, C, and E in the United States (13), and Western Europe (14, 15). Moreover, in obese patients with a low intake of fruit and vegetables, lower plasma concentrations of vitamins have been observed (16). In this context, a cross-sectional study found that vitamin A intake was significantly lower in subjects with morbid obesity and with higher CRP concentrations (17), suggesting the association between dietary vitamin A intake and obesity-related inflammatory processes.

This study, following a translational approach with well categorized subjects, evaluated the potential associations between dietary vitamin A intake and several anthropometrical, biochemical and dietary features in healthy young adults, emphasizing the putative relationship between total antioxidant consumption and vitamin A intake.

SUBJECTS AND METHODS

1. Subjects. Sixty-one healthy Caucasian subjects were recruited for this translational research to participate in the study (31 women and 30 men, aged 18.9 ± 1.1 y old). The initial enrolment screening evaluations included a medical history, physical examination and fasting blood profile, to exclude subjects with evidence of any disease related to chronic inflammation, oxidative stress, hydric imbalance, and nutrient absorption or nutrient metabolism. Other exclusion criteria were drug or dietetic treatment up to 6 mo before the participation in this study. In accordance with the Declaration of Helsinki, after a clear explanation of the study protocol, all subjects gave written informed consent to participate, which was previously approved by the Ethics Committee at the University of Navarra (ref:79/2005).

2. Anthropometry and body composition. All anthropometric measurements were carried out with the subjects barefoot, wearing only their underwear and after an overnight fast following standardized protocols (18).
All these measurements were done three times, but not consecutively. Body weight was measured to the nearest 0.1 kg by using a Tanita TBF 300 (New York, USA). BMI was calculated as the body weight divided by the squared height (kg/m²). Waist and hip circumferences were measured with an inelastic tape to the nearest 1 mm. Blood pressure was measured by a mercury sphygmomanometer Minimus II (Riester, Germany) to the nearest 5 mmHg.

3. Analysis of biological samples. All serum blood samples were drawn after an overnight (12-h) fast, centrifuged immediately for 15 min at 3,500 rpm and 4°C, and stored at –80°C. Serum glucose, triglycerides, total cholesterol and high-density lipoprotein cholesterol (HDL-c), were assessed by an automatized colorimetric assay (COBAS MIRA, Roche, Switzerland) with specific commercial kits (ABX Pentra, Roche, Switzerland). The reported plasma low-density lipoprotein cholesterol (LDL-c) data were calculated by the Friedewald equation as described elsewhere (19). Serum insulin concentrations were measured by using an enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden). For estimating insulin sensitivity, the homeostasis model assessment of insulin resistance (HOMA-IR) (glucose concentration/insulin concentration/22.5) was calculated (20).

4. Dietary intake assessment. Dietary intake was assessed by the questionnaire of Seguimiento Universidad de Navarra (SUN) Study (21). This semi-quantitative food frequency questionnaire, which is validated for Spanish people (22), includes 136 items and open-labeled questions for information about the use of dietary supplements and other foods not specified. Nutrient and food intake was computed using an ad hoc computer program specifically developed for this aim (23). A dietician updated the nutrient data bank using the latest available information included in the food composition tables for Spain (24, 25).

5. Statistical analysis. The Shapiro-Wilks test was used to determine variable distribution. Accordingly, to detect significant differences between subjects with vitamin A intake higher and lower than the median (1,238.2 μg/d), a parametric Student’s t test or non-parametric Mann-Whitney U test for continuous variables, or chi-square test for dichotomous variables was performed. Partial correlations after adjusting for total energy intake were used to evaluate potential associations between variables. Results are presented as mean±SD, and a p<0.05 was considered statistically significant, while values of p<0.10 were considered as marginally significant. Statistical analysis were performed by using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) for Windows XP (Microsoft, Redmond, WA, USA).

RESULTS

Anthropometrical measurements and biochemical determinations from subjects categorized according to gender and vitamin A intake classification are described in Table 1. Age distribution was similar in the two categorized groups, while women showed a higher frequency in the group with higher intake of vitamin A (64.5% vs. 36.7%). Statistically significant differences between subjects with higher and lower vitamin A consumption were found for body weight, BMI, waist circumference and waist-to-hip ratio (WHR), while systolic blood pressure, HOMA-IR and HDL-cholesterol showed only a statistical trend when split by vitamin A intake. No relevant changes were found for diastolic blood pressure or circulating concentrations of glucose, insulin, total cholesterol, LDL-c or triglycerides when these criteria were applied (Table 1). Regarding the ana-

Table 1. Clinical and anthropometrical characteristics of the subjects, categorized according to the median (1,238.2 μg/d) of vitamin A intake.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men (n=30)</th>
<th>Women (n=31)</th>
<th>p value</th>
<th>Lower vitamin A intake (n=30)</th>
<th>Higher vitamin A intake (n=31)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>19.4±1.2</td>
<td>18.5±0.8</td>
<td>0.002</td>
<td>18.9±1.0</td>
<td>19.0±1.2</td>
<td>0.840</td>
</tr>
<tr>
<td>Sex (% of men)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.9±8.8</td>
<td>55.8±8.6</td>
<td>&lt;0.001</td>
<td>69.2±12.4</td>
<td>62.3±13.4</td>
<td>0.042</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.0±2.2</td>
<td>21.1±2.5</td>
<td>&lt;0.001</td>
<td>23.5±2.9</td>
<td>21.6±2.2</td>
<td>0.006</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>83.2±6.4</td>
<td>75.2±9.0</td>
<td>&lt;0.001</td>
<td>81.5±3.5</td>
<td>76.9±8.6</td>
<td>0.036</td>
</tr>
<tr>
<td>Waist-to-hip ratio (cm/cm)</td>
<td>0.8±0.0</td>
<td>0.8±0.0</td>
<td>0.005</td>
<td>0.8±0.0</td>
<td>0.8±0.0</td>
<td>0.042</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>115.0±10.6</td>
<td>98.4±9.3</td>
<td>&lt;0.001</td>
<td>109.8±13.8</td>
<td>103.4±11.4</td>
<td>0.063</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>69.7±8.3</td>
<td>63.5±7.5</td>
<td>0.005</td>
<td>67.3±9.2</td>
<td>65.8±7.8</td>
<td>0.425</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.0±0.4</td>
<td>4.9±0.3</td>
<td>0.064</td>
<td>5.0±0.4</td>
<td>4.9±0.3</td>
<td>0.178</td>
</tr>
<tr>
<td>Insulin (μU/mL)</td>
<td>7.7±4.2</td>
<td>8.4±4.7</td>
<td>0.428</td>
<td>8.9±5.1</td>
<td>7.2±3.7</td>
<td>0.403</td>
</tr>
<tr>
<td>HOMA-IR index</td>
<td>1.7±1.0</td>
<td>1.8±1.1</td>
<td>0.669</td>
<td>2.0±1.2</td>
<td>1.6±0.8</td>
<td>0.109</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.8±0.3</td>
<td>0.8±0.3</td>
<td>0.996</td>
<td>0.8±0.3</td>
<td>0.8±0.3</td>
<td>0.966</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.2±0.7</td>
<td>4.5±0.7</td>
<td>0.076</td>
<td>4.2±0.7</td>
<td>4.4±0.7</td>
<td>0.267</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.3±0.2</td>
<td>1.7±0.4</td>
<td>&lt;0.001</td>
<td>1.4±0.4</td>
<td>1.6±0.4</td>
<td>0.106</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/L)</td>
<td>2.5±0.7</td>
<td>2.4±0.5</td>
<td>0.522</td>
<td>2.4±0.6</td>
<td>2.5±0.6</td>
<td>0.696</td>
</tr>
</tbody>
</table>

BP, blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Because of the differences found in total caloric intake and antioxidant intake considering the dietary content of vitamins A, C and E, folic acid, selenium, zinc, and magnesium, total fiber, vegetables, fruits and nuts (Table 2). Because of the differences found in total caloric consumption between groups, partially adjusted energy intake correlations were performed to further investigate the relationships of anthropometrical and biochemical features with vitamin A intake as continuous variables. Thus, statistically significant negative correlations were found for body weight, BMI, waist circumference and WHR (Table 3) once adjusted by energy intake, which is of interest given the small sample size of this translational study. Furthermore, total cholesterol values showed a positive and significant association with vitamin A consumption (Table 3). Regarding antioxidant dietary intake, positive and statistically significant partial correlations were found between vitamin A consumption and vitamin C, folic acid, magnesium, total fiber, vegetables, fruits and nuts, while a negative correlation was found with vitamin E consumption. The lack of significant correlation with vitamin E consumption may be attributed to the low intake of vitamin E (Table 3). Nonetheless, these results highlight the importance of vitamin A intake in relation to body composition and health outcomes in young adults.
DISCUSSION

The role of oxidative processes on several chronic diseases is receiving increasing attention due to their links with atherosclerosis, obesity or type 2 diabetes (5, 6), and to the association of metabolic syndrome features with oxidative and inflammatory biomarkers (7–9). Thus, oxidative stress accompanying obesity and its complications can be reduced by weight loss, caloric restriction or antioxidant-rich diets (26) that may modulate the synthesis of inflammatory markers and contribute to the total antioxidant capacity of a diet (27), highlighting the relationships between inflammation and circulating concentrations of antioxidants. In this context, as found in the current research for body weight, BMI, waist circumference and WHR, several studies suggest a decrease in adiposity measurements related to antioxidant intake such as vitamins (15, 28–30), and other foodstuff components such as fiber (31). In the case of vitamin A, this outcome could be due to the association between vitamin A intake and its concentrations in adipose tissue and plasma (32). In addition, both serum cholesterol and triglyceride concentrations have been found significantly higher in subjects receiving vitamin A and/or a combination of vitamin A and β-carotene as compared to a placebo group (33), supporting the reported relationship between vitamin A intake and serum concentrations of total cholesterol. In this sense, white and brown adipose tissues are major sites of storage of vitamin A derivatives (retinoids) and they play an active role in whole body metabolism of these vitamin A derivatives (34). Moreover, adipose tissues are targets for the action of retinoic acid (34). Brown adipose tissue (BAT) is a main site of adaptive thermogenesis and, as such, it is likely to be involved in the control of energy efficiency and body weight (35, 36). The regulated dissipation of BAT energy stores largely depends on the activity of the uncoupling protein 1 (UCP1), a brown adipocyte-specific inner mitochondrial membrane protein that is able to short-circuit the proton gradient generated by the respiratory chain during nutrient oxidation, thus favouring heat dissipation instead of ATP synthesis (37, 38). Retinoic acid stimulates the transcription of the gene encoding UCP1, which is critical to BAT thermogenesis (34, 39). Pro-vitamin A carotenoids have also been shown to stimulate UCP1 expression in primary brown adipocytes differentiated in culture (40). Moreover, a relationship between vitamin A status and BAT thermogenic capacity was demonstrated in rodents (41). Furthermore, retinoic acid, which has been related to certain antioxidant properties (42), stimulates the expression not only of UCP1, but also of related uncoupling proteins, such as UCP2 (41) and UCP3 (43), and affects other aspects of white and brown adipose tissue development and function (44). The relationship between vitamin A intake and serum total cholesterol can be explained by a substantial body of evidence that synthetic retinoids and high doses of vitamin A alter lipid metabolism by increasing cholesterol (45–47).

Dietary intake has proven its importance in the risk to develop obesity-related diseases. Thus, in women, the fruit, vegetables, and dairy dietary pattern was inversely associated with BMI, waist circumference, and blood pressure (48, 49). Moreover, a healthy dietary pattern has been positively associated with antioxidant intake markers, such as red cell folate in women (48). Furthermore, following dietary recommendations may improve antioxidant intake and total antioxidant capacity of plasma (50), as occurs in vegetarians, in which there is a higher prevalence of adequate fiber and magnesium intake as well as a higher consumption of vegetables and fruits than in non-vegetarians (51). Additionally, adolescents consuming nuts more than once per week, also showed lower scores for BMI and serum glucose irrespective of their vegetarian status (52). Both magnesium and fiber have an increased intake related to higher vitamin A consumption in the present study, as well as vitamin C and folic acid. Thus, regarding ascorbic acid intake, it has been published that, in women, serum α-tocopherol concentrations were positively associated with intakes of vitamin C (15). Moreover, folic acid as well as vitamin C consumption appear to decrease risk to develop oxidative-associated breast cancer in women (53). Thus, we reported here an association between vitamin A intake and fiber. Previously, some investigations have linked serum β-carotene concentrations with total fiber intake (15), suggesting fiber consumption as a positive predictor of serum β-carotene intake. On the other hand, the inverse partial correlation found between vitamin A intake and cereal consumption can be explained because of the dietary pattern of our sample, in which fruit and vegetable consumption, a rich source of vitamin A (2), was inversely correlated with cereal intake (data not shown). The role of a collaborative effect of several antioxidants can not be discarded.

In conclusion, vitamin A intake seems to be related with several anthropometrical and biochemical measurements linked to metabolic syndrome manifestations and other features related to oxidative stress in apparently healthy young adults. This translational research carried out with a reduced number of volunteers demonstrated that vitamin A intake is associated with the total antioxidant intake. These findings support a relevant role for antioxidant intake in the putative decrease of metabolic syndrome manifestations and other features related to oxidative stress.

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