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Vitamin A nutritional status in patients with coronary artery disease and its correlation with the severity of the disease

Andrea Mato[1], Vanessa Moreira da Silveira Gonçalves[1], Gisele Souza[1], Suelem Pereira da Cruz[2], Sabrina Cruz[1] and Andréa Ramalho[3]

[1]School of Medicine. Federal University of Rio de Janeiro. Center for Research on Micronutrients (NPqM). Institute of Nutrition Josué de Castro - Federal University of Rio de Janeiro. [2]School of Medicine. Universidade Estácio de Sá (UNESA). [3]ENSP/FIOCRUZ. Department of Social and Applied Nutrition. Institute of Nutrition at UFRJ. Brazil

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Correspondence: Suelem Cruz. Universidade Estácio de Sá (UNESA). Rio de Janeiro, Brazil

e-mail: suelemcruz.med@gmail.com

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ABSTRACT

Indroduction: the purpose of this study was to assess the vitamin A (VA) nutritional status of patients with coronary artery disease (CAD) and its correlation with the severity of the disease, taking into consideration zinc concentration and oxidative stress.

Methods: the patients were preoperative inpatients awaiting myocardial revascularization surgery. The serum concentrations of retinol, β-carotene, zinc, malondialdehyde (MDA) and C-reactive protein (CRP) were quantified. CAD severity was assessed by cineangiography, observing the parameters of severity, extent and occlusion. An echocardiogram was performed to assess the ejection fraction.

Results: ninety individuals were studied (64.5 ± 9.6 years). Zinc did not correlate with retinol ($r = -0.009/p = 0.40$), β-carotene ($r = -0.06/p = 0.73$) or MDA ($r = 0.03/p = 0.70$), but zinc deficiency was more frequent amongst the patients with high MDA (quartiles 50 and 75). CRP was found to be associated with retinol ($x^2 = 3.95/p = 0.04$). The individuals with retinol deficiency had more severe CAD, and β-carotene diminished as the extent score rose, although this was not statistically significant ($p = 0.12$). The degree of severity was associated to extent ($x^2 = 67.9$)/($p < 0.001$), occlusion ($x^2 = 34.5/p < 0.001$) and CRP ($x^2 = 5.9/p = 0.05$), while extent was associated with MDA ($x^2 = 42.1$)/($p < 0.001$). There was a positive correlation between the ejection fraction and β-carotene ($r = 0.42/p = 0.02$).

Conclusion: findings from this study indicate that chronic inflammation resulting from atherosclerosis is related to disease severity and consequent influence on nutritional status of VA.

Key words: Vitamin A. Nutrition status. Severity coronary artery disease.

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INTRODUCTION

Epidemiological studies indicate that the main leading causes of death in the population, especially in the young elderly (60-69 years), result from cardiovascular diseases (CVDs), mainly those of ischemic origin (1-3).

Ischemic heart diseases are associated with damage to the blood supply of coronary arteries caused by blockage of these vessels by atherosclerotic plaques that stimulate the circulation and aggregation of pro-inflammatory molecules, favoring increased local oxidative stress and organic antioxidant activity (4). Thus, it is suggested that ischemic diseases demand large amounts of antioxidants for their prevention and treatment when compared to other non-ischemic CVDs.

The increased demand of antioxidants by ischemic CVDs creates a greater dependency level of exogenous antioxidants in the control of oxidative stress. It has been suggested that retinol plays an important role in this context (5), which consists in delaying or preventing the initiation of atherosclerotic processes in the cellular lipid component, such as peroxidation, and the generation of hydroperoxides (6).

Among the micronutrients that participate synergistically in the metabolism of vitamin A we can find zinc, a micronutrient that has an antioxidant function and is required for hepatic synthesis and secretion of the retinol transport protein, retinol binding-protein (RBP). On the other hand, β-carotene has an antioxidant function and is considered as the main precursor of retinol. In addition, the conversion of β-carotene into retinol is mediated by the enzyme retinal reductase, zinc-dependent (7-9).

An inverse association between antioxidant intake and cardiovascular events has been found in the literature. This is corroborated by Zhanget et al. in a study that has shown that adequate supplementation of vitamin A significantly decreases lipid peroxide levels in plasma (10).

It has been reported that vitamin A supplementation has a beneficial effect on the antioxidant system (11,12). On the other hand, randomized clinical trials have not demonstrated any benefit of antioxidants in the prevention of cardiovascular events (13). However, these studies have not assessed vitamin A nutritional status, the synergistic action of zinc on the metabolism of this vitamin in patients with coronary artery disease (CAD) and its correlation with the severity of the disease.

This study therefore aims to assess vitamin A nutritional status of patients with CAD and its correlation with the severity of the disease, considering zinc nutritional status and oxidative stress.

METHODS

This cross-sectional observational study was conducted in a cohort of pre-operative inpatients with CAD awaiting myocardial revascularization surgery at the National Institute of Cardiology (Instituto Nacional de Cardiologia, INC) from July 2008 to December 2009, in Rio de Janeiro, Brazil. The project was approved by the INC Research Ethics Committee and all the participants signed an informed consent form.

Population

The study investigated 90 individuals of both sexes attended in the outpatient department, where they had clinical, biochemical and imaging assessments. A 5% significance level was adopted and 80% power was set to calculate the sample size (14).

Inclusion criteria were as follows: individuals with CAD aged 20 or over (15) who had been indicated for revascularization surgery according to the TIMI Risk Score, that is, patients who had medium or high risk classification according to the TIMI Risk Score (16).

Exclusion criteria were as follows: patients who had malabsorption syndrome, acute or chronic infections, liver disease, kidney disease, alcoholism or acquired immune deficiency syndrome, or patients who were pregnant, breast-feeding or who used or had used medications or supplements containing vitamin A or zinc in the last six months. Patients who had low risk classification by the TIMI Score were also excluded, since these patients are discharged after 12-24 hours of clinical stabilization with a provocative test of negative ischemia (16).

Prognosis of acute coronary syndrome

The TIMI Risk Score determines the prognosis and management of patients with acute coronary syndrome (ACS). It consists of seven dichotomous variables: age ≥ 65 years, use of aspirin in the previous seven days, coronary stenosis ≥ 50%, ≥ 3 risk factors for atherosclerotic disease, > 1 episode of angina in 24 hours, ST segment depression, and elevation of myocardial necrosis marker. Each variable mentioned above equals one point, so the score of this score ranges from zero to seven. These points are classified as low risk when it reaches the score of 0-2, medium risk with 3-4 points and high risk with 5-7 (16).

Clinical and laboratorial evaluation

For biochemical assessments, a sample of approximately 20 ml of blood was collected in a specific tube for each test after eight hours of fasting. The samples were immediately sent to the laboratory of the INC and were duly protected from oxidation and ultraviolet radiation for further analysis. This collection was performed on the day of the myocardial revascularization surgery in the morning period.

The method used to quantify serum retinol and β-carotene was high performance liquid chromatography with ultra-violet detector (HPLC-UV). In the current study, cut-offs were < 30 μg/dl and ≤ 40 μg/dl, respectively (17).

Zinc was assessed through atomic absorption spectrometry, and values less than 0.7 mg/l were considered as deficient (18). Malonaldehyde (MDA) was assessed using spectrophotometry (19).

C-reactive protein (CRP) was measured by a nephelometry method and values over 3.0 mg/l were used as the reference value for CRP (20).

CAD severity was determined by coronary cineangiography using a classification criteria adapted from the method proposed by Bogaty et al. (21). An echocardiogram was performed (22) and systolic dysfunction was considered to occur when the ejection fraction < 50% (23).

Data collection instruments consisted of a form filled out by only one interviewer with information gathered from a structured questionnaire and medical records. The diagnosis of hypertension, dyslipidemia and/or diabetes mellitus was obtained from the patient's medical records.

The general characteristics of the sample related to smoking were defined according to the World Health Organization (WHO, 1998) as follows: regular smoker, a consumer of at least 1 cigarette/day that consumed at least 100 cigarettes in his/her lifetime; ex-smoker, a smoker who consumed at least 100 cigarettes in his/her lifetime and stopped smoking; occasional smoker, a consumer of less than one cigarette/day or who consumes sporadically; and non-smokers, individuals who do not fit into any of these categories (24). Recent studies have suggested that a 30-minute exposure to environmental tobacco smoke is sufficient to affect the endothelial cells of the coronary arteries of non-smokers. Therefore, passive smoking is defined as smoking exposure by non-smokers, at home, at work or in other enclosed places, excluding outdoor occupations (25).

Statistical evaluation

In data assessment, central tendency and dispersion were calculated using the Chi-square test to assess the association between categorical variables, while the Student's t-test and the ANOVA test (normal distributions), Mann-Whitney and Kruskal-Wallis tests (non-normal distributions) and Spearman's correlation coefficient were used to compare continuous variations. A 5% significance level was set ($p \leq 0.05$). Statistical analysis was undertaken using the Statistical Package for the Social Sciences (SPSS) for Windows, version 17.

RESULTS

A total of 90 individuals were studied, aged 39-88 (mean age: 64.5 ± 9.6 years), of whom 27.8% were female and 72.2% were male. Data were adjusted for gender and age. The general characteristics of the sample are shown in table I.

The percentage of patients with deficiency of serum concentrations of retinol, β-carotene and zinc was 7.8%, 86% and 17.8%, respectively (Table II).

No correlation was found between zinc concentrations and retinol ($r = -0.009/p = 0.40$), β-carotene ($r = -0.06/p = 0.73$) or MDA ($r = 0.03/p = 0.70$). However, it was found that zinc deficiency was more frequent in patients with higher serum MDA levels (quartiles 50 and 75), although this trend was not statistically significant ($p = 0.44$).

Mean CRP was 5.9 ± 14.6 mg/dl, with 36.7% of the individuals falling above the cut-off established, which showed that this was associated with deficiency of serum retinol concentrations ($x^2 = 3.95/p = 0.04$). Furthermore, a trend concerning β-carotene was noted: amongst the patients with deficient serum levels, 48% had high CRP ($p = 0.07$).

In the assessment of CAD severity, a correlation was found between severity and extent ($x^2 = 67.9/p < 0.001$), occlusion ($x^2 = 34.5/p < 0.001$) and CRP ($x^2 = 5.9/p = 0.05$) (Table III).

All the individuals with retinol deficiency had a higher degree of severity, i.e., over 90% arterial stenosis, although this was not statistically significant. β-carotene, zinc and MDA did not correlate with severity. It was found that serum β-carotene levels diminished as the extension score rose, but not significantly ($p = 0.12$). Extension was the only factor found to be associated with MDA ($x^2 = 42.1/p < 0.001$). Occlusion did not correlate with any variable.

When assessing the ejection faction, a positive correlation was found with serum β-carotene concentrations ($r = 0.42/p = 0.02$).

When investigating the relation between oxidative stress and vitamin A serum concentrations in the total sample, a negative and significant correlation was found between retinol, β-carotene and thiobarbituric acid reactive substances (TBARS) serum concentrations (Table IV). It is important to mention that the patients with zinc inadequacy (69%) concomitantly presented retinol and β-carotene deficiency, which was more frequent in patients with higher circulating concentrations of TBARS.

DISCUSSION

In this study, β-carotene and retinol deficiency was found in 86% and 7.8% of the patients, respectively. Such results could be related to the greater mobilization of β-carotene for conversion into retinol, since β-carotene is recognized as the most powerful retinol precursor (26,27). This finding deserves attention, since reduced serum β-carotene concentrations are associated with increased oxidative stress, showing that this antioxidant could be diverted to other important functions, such as combating oxidative stress, in order to maintain an adequate retinol nutritional status. As such, adequate retinol levels are important for preserving the antioxidant function of β-carotene.

There was no correlation between serum vitamin A and zinc concentrations. No studies have been found in the literature that concomitantly assessed these nutrients in the target public studied. This result could be masked because, due to strict homeostatic control, serum zinc levels could fluctuate to limits above the real values, even in individuals with low levels of this mineral.

A significant association was found between CRP and serum retinol levels. This finding is corroborated by Nogueira et al. (28), who have found that individuals with high CRP had lower retinol levels in their blood. This could be related to the fact that when the liver is inflamed, it prioritizes the production of acute-phase proteins needed for the defense of the host, resulting in reduced production of RBP, the carrier protein for retinol. This leads to a reduction in the nutrients involved in combating oxidative stress, possibly due to the increased demand for nutrients with antioxidant function in such individuals.

According to epidemiological research (29,30), a high consumption of carotenoid-rich fruits and vegetables is associated with reduced CRP. Although this study did not assess the individuals' diets, it was found that 48% of the patients with hypocarotenemia had high CRP. Suárez et al. (31) found that the lower β-carotene was associated with higher CRP, therefore, this micronutrient is involved in reducing lipid peroxidation inactivation of reactive oxygen species, as well as in the greater mobilization of β-carotene for conversion into retinol.

There was a significant association between CRP levels and the severity of stenosis. This shows that CRP concentrations are related to the severity of the disease, suggesting that inflammation is not just a mechanism related to plaque rupture, but is also is correlated with the participation of chronic atherosclerosis. Similar results have been found by Shen et al. (32) and Pan et al. (33), who have identified a positive correlation between CRP and the severity of CAD using angiography.

Some studies have demonstrated the participation of CRP in since it exerts a pro-inflammatory effect (34). In addition, increased levels of CRP are considered as an independent risk factor for CVD, even for borderline dyslipidemic individuals as they have great risk of suffering acute myocardial infarction (AMI) (35).

When it comes to the severity of CAD, the overall patients with retinol deficiency presented a higher degree of severity, i.e., over 90% stenosis, although this was not statistically significant. This can be explained since CRP has been recognized as a marker of inflammation related to CAD severity and deficiency of serum retinol levels. Recent studies have shown that vitamin A concentration is increased in the ischemic heart, as this micronutrient is related to proliferative processes of cardiac progenitor cells such as cicatrization and cellular repair. Therefore, depletion of hepatic vitamin A stores affects the molecular structure of the heart (36,37). Furthermore, the studies that have assessed the severity of CAD have not checked vitamin A nutritional status, which prevents making comparisons with the results obtained here.

Atherosclerosis risk factors induce endothelial dysfunction and thereby, oxidative stress (38). In the present study, an association was observed between MDA and CAD extent, determined by the number of diseased vessels. This finding has been corroborated by Basarici et al. (39), who have found a correlation between several risk factors, the extent and severity of CAD with high urinary concentrations of 8-isoprostane, considered as a marker of oxidative stress.

It was found that serum β-carotene concentrations diminished as the extent score rose, which suggests a possible increase in β-carotene demand to combat the oxidative stress implicated in CAD. However, Riccioni et al. (40) have noted that this antioxidant is directly associated with arterial intima-media thickness.

Ejection fraction is an indicator used to determine the volume of blood pumped by the heart and is important for quantifying systolic function, besides supplying information for determining the prognosis of CAD (41). In this study, ejection fraction was found to correlate positively with the serum concentration of β-carotene.

Singh et al. (42) and Bockeria et al. (43) have observed that decreased ejection fraction in individuals after a myocardial infarction significantly reduced their quality of life measured by their physical and social function and physiological wellbeing. An ejection fraction of < 50% was also considered as a risk factor for predicting mortality after myocardial revascularization surgery (44).

Literature is scarce on the relationship between ejection fraction and nutrients with antioxidant function since only three studies corroborate the result found, as follows. Polidori et al. (45) have observed a correlation between vitamin A, lutein, lycopene, vitamin E and ejection fraction in patients with congestive heart failure. Witte et al. (46) have reported that they supplemented men over 60 with a mix of micronutrients and vitamins, including vitamin A, which resulted in a significant increase in ejection fraction and quality of life when compared to the control group. Finally, Zhu et al. have found that all-trans retinoic acid (ATRA) has anti-apoptotic activity and protective role on myocardial *in vivo*, because this micronutrient reduced the size of the infarcted area and rescued cardiac function loss (47).

In the current study, 73.3% of the patients were ex-smokers according to the WHO criteria (1998). Therefore, individuals who have recently quit smoking and those who have not smoked for years were in the same group, since the time in which an individual stopped smoking could interfere in the results found in the literature (48,49). This fact can be considered as a limiting factor in the study.

CONCLUSION

In view of the results presented, it may be concluded that the chronic inflammation caused by atherosclerosis and its relationship with the severity of the disease influence vitamin A nutritional status due to the negative repercussions that deficiency of this nutrient can have on the disease in question.

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Table I. General characteristics of the patients studied

Characteristics	*Mean*
Age (years)	64.5 ± 9.6
Gender (%)	
Male	72.2
Female	27.8
BMI (kg/m²)	27.67 ± 3.2
SH (%)	100
DLP (%)	94.9
DM (%)	32.5
Smoking (%)	
Regular smoker	2.4
Prior smoker	73.3
Occasional smoker	0
Non-smoker	24.1
Passive smoker	8.3

SH: systemic hypertension; DLP: dyslipidemia; DM: diabetes mellitus.

Table II. Percentage of patients with deficiency of serum retinol, β-carotene and zinc levels

	Retinol	*β-carotene*	*Zinc*
Inadequate	7.8%	86%	17.8%
Adequate	92.2%	14%	82.2%

Table III. Association between severity of coronary arterial stenosis and extent, occlusion and C-reactive protein

	Severity		
	n	x^2	*p-value*
Extent	90	67.9	< 0.001*
Occlusion	90	34.5	< 0.001*
CRP (mg/l)	90	5.9	< 0.05*

Table IV. Correlation between serum retinol and β-carotene and thiobarbituric acid reactive substances

	TBARS	
	R	p-value
Serum retinol	-0.3	0.003
Serum β-carotene	-0.31	0.02