

ORIGINAL ARTICLE

The Correlation between Intake of Vitamin C and β -Carotene and Fasting Blood Sugar: A Cross-Sectional Analysis in Diabetic Patients of Fasa Cohort Study

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ARTICLE INFO

Keywords:

Vitamin C
 β -carotene
Fasting blood glucose
Type 2 diabetes mellitus
Fasa Cohort Study

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Received: August 2, 2023
Revised: November 3, 2023
Accepted: November 13, 2023

ABSTRACT

Background: Diet and nutrition are strongly implicated in the etiology of type 2 diabetes. This study has investigated whether low vitamin C and β -carotene intakes were associated with glycemic control in diabetic patients.

Methods: In a cross-sectional analysis of diabetic adult patients participating in Fasa Cohort Study, a 24-h dietary recall was used to assess intake of fruits, vegetables, vitamin C and β -carotene. The associations between vitamin C and β -carotene intakes and glycemic control were determined in 3 groups of normal glucose tolerance, pre-diabetes mellitus, and type 2 diabetes mellitus (T2DM) and the relationship between fasting blood glucose (FBS) and vitamin C and β -carotene intakes was investigated.

Results: There were no differences between groups for intake of total vitamin C and β -carotene ($p>0.05$). An inverse relation was recognized between intake of total vitamin C and β -carotene and FBS ($p<0.05$).

Conclusion: A negative association was observed between FBS and intake of vitamin C and β -carotene; however more experimental studies are needed to establish whether increase in intake of vitamin C and β -carotene can improve FBS level and prevent T2DM.

Please cite this article as: Rajabi S, Rajabi F, Farhangdoost S, Haghighat N, Banihashemi SH. The Correlation between Intake of Vitamin C and β -Carotene and Fasting Blood Sugar: A Cross-Sectional Analysis in Diabetic Patients of Fasa Cohort Study. Int J Nutr Sci. 2023;8(4):216-222. doi: 10.30476/IJNS.2023.99515.1247.

Introduction

Type 2 diabetes mellitus (T2DM) is considered to be a global major public health issue. It was estimated that 415 million people suffered from T2DM in 2015, while it can be increased to 642 million by 2040. According to the World Health Organization (WHO) report, diabetes is the leading cause of death for people aged 20-79 years in the

Middle East and North Africa (MENA) region with the prevalence of 10.9% (1). Diet and nutrition were shown to be strongly implicated in the etiology of T2DM, while multiple factors have been reported in T2DM to be associated with an elevated oxidative stress. These factors can incorporate glucose oxidation and result in free radical production, an increment in protein glycation (glucooxidation)

and a decrease in antioxidant defense mechanisms. Enhanced oxidative stress is considered an underlying condition that is responsible for some of the complications of diabetes (2).

Carotenoids and vitamins C and E (tocopherols) are critical components of the body's defense system against oxidative stress. Insulin action may be impaired by oxidative stress altering the physical state of the plasma membranes of target cells for insulin action (3, 4). According to earlier studies in adults, low intakes of fruits, vegetables and vitamin C were demonstrated to contribute in the risk for T2DM (5). A recent meta-analysis has indicated a weak association between intakes of fruits and vegetables and the risk of T2DM (6). Carotenoids are a wide range of compounds derived exclusively from plants; and the most abundant of which can be found in serum as α -carotene, β -carotene, β -cryptoxanthin, lutein/zeaxanthin, and lycopene. Several epidemiologic evidences have illustrated that some carotenoids can function as antioxidants and may be involved in the prevention or treatment of chronic diseases (2).

In a cross-sectional study, it was shown that serum carotenoid level was conversely correlated with insulin resistance and blood glucose concentrations (2). Additionally, an inverse relationship between inverse glycated hemoglobin level and with vitamin C intake (7), plasma vitamin C level (8), and vitamin E intake (9) has been reported among non-diabetic subjects, whereas no association was seen with β -carotene (3). In this study, the performance of antioxidants in a population at high risk of T2DM has been investigated by examining cross-sectional correlations between vitamin C and β -carotene intakes and fasting blood sugar (FBS) and the non-diabetic relatives of subjects were compared with pre-diabetic and diabetic ones.

Materials and Methods

Due to the unavailability of follow-up data, in this cross-sectional study, the basic data of Fasa Cohort Study was used (9). This study was a population-based study in which all rural residents of Fasa aged 35-70 who were consent to participate in the study were enrolled, that was equivalent to 10138 participants. The Shiraz University of Medical Sciences Ethics Committee approved this study protocol based on the code of IR.SUMS.REC.1400.314.

Participants were divided into three groups. FBS cut-off values for normal glucose tolerance (NGT), prediabetes, and T2DM were based on the American Diabetes Association (ADA) criteria (10). Those taking metformin were also included in the

group with T2DM and the required information was provided. The anthropometric data including weight, height, body mass index (BMI) and waist circumference (WC) and demographic data including gender and age were collected based on the existing patient's medical history. In order to measure the dietary parameters of the participants, the 125-part semi-quantitative food frequency questionnaire (FFQ) was completed for them at the beginning of the study; which indicated the food intake of the participants in the previous year.

These variables were (i) intake of food groups including bread and cereals, fruits, vegetables, dairy products, meats and their substitutes, oils and sweets. In order to obtain these data, the received answers of the FFQ were divided into the desired groups; (ii) intake of energy, micronutrients and macronutrients; while Nutritionist 4 software was used to obtain these data. All nutrients were energy-adjusted and finally, the relationship between FBS and the amount of vitamin C and β -carotene intakes was measured in the 3 groups. Participants taking supplements containing β -carotene or vitamin C were excluded from the study.

Statistical analysis was done utilizing the SPSS software (Version 20, Chicago, IL, USA). ANOVA test was used to compare intakes between groups and Pearson's correlation coefficient and linear regression tests were employed to investigate the relationship between FBS and vitamin C and β -carotene intakes in T2DM patients. The Kolmogorov-Smirnov test was applied to check the normality of data. All findings were adjusted by sex, age and BMI.

Results

The NGT group was slightly younger than the prediabetes and T2DM groups and there were more females in the T2DM and prediabetes groups and less in the NGT group. General characteristics of participants were shown in Table 1. The mean BMI for the 3 groups reflects the international BMI cut-off points for overweight (25.00-29.99 kg/m²), which is slightly higher in prediabetes and T2DM groups. The WC increased across the groups from NGT to T2DM groups along with the BMI, showing that a higher weight could be a risk factor for T2DM. FBS was used as a basis for defining prediabetes and T2DM, that increased from NGT to T2DM groups, while differed significantly between the study groups ($p=0.029$).

There were no significant differences in macronutrient intake and dietary vitamin C and β -carotene intakes across the groups (Table 2). The acceptable macronutrient distribution range (AMDR) range for protein was 15-25% of the total

Table 1: General characteristics of participants classified as having NGT (n=8225), prediabetes (n=659) and T2DM (n=1249).

Characteristics		NGT	T2DM	Prediabetes	Total	P value
Sex	Male N (%)	3958 (48.1)	355 (28.4)	262 (39.8)	4575 (45.1)	0.725
	Female N (%)	4267 (51.9)	894 (71.6)	397 (60.2)	5558 (54.9)	0.166
Age (y)		47.57 (9.38)	53.61 (8.82)	52.53 (9.33)	48.63 (9.57)	0.379
Height (cm)		162.21 (9.00)	159.17 (8.07)	160.86 (9.09)	161.75 (8.95)	0.545
Weight (kg)		66.55 (13.17)	69.02 (13.15)	69.48 (13.83)	67.05 (13.25)	0.841
Waist circumference (cm)		92.11(11.59)	98.15 (11.20)	96.59 (12.28)	93.14 (11.79)	0.962
BMI (kg/m ²)		25.3 (4.80)	27.19 (4.68)	26.87 (5.01)	25.6 (4.85)	0.734
FBS (mg/dl)		85.44 (13.1)	131.83 (62.4)	107.53 (6.33)	92.59 (29.44)	0.23

BMI: Body mass index, FBS: Fasting blood sugar, T2DM: Type 2 diabetes mellitus, NGT: Normal glucose tolerance. Values represented as mean±SD unless stated otherwise. *All *p* values from ANOVA tests denotes the study groups that do not differ significantly from each other at the 0.05 level based on characteristics from Post Hoc analysis.

Table 2: Dietary intake of participants classified as having NGT (n=8225), prediabetes (n=659), and T2DM (n=1249).

Total daily dietary intake	NGT	Prediabetes	T2DM	Total	P value
Protein (g)	90.85±37.00	85.19±39.43	83.16±33.34	89.15±37.41	0.494
Total lipid, fat (g)	68.33±28.35	60.24±26.61	62.49±27.42	66.22±28.13	0.436
Carbohydrate (g)	480.33±193.43	428.25±194.57	439.45±164.59	466.56±193.22	0.143
Energy (Kcal)	2920.98±1150.07	2829.90±1167.37	2900.85±1093.52	2900.19±1150.60	0.280
β-Carotene (μg/d)	5123.30±3848.41	5219.67±3770.41	5080.02±3260.04	5141.17±3796.21	0.651
Vitamin C, total ascorbic acid (mg)	147.07±97.64	150.67±98.06	155.30±105.17	148.37±98.23	0.714

T2DM: Type 2 diabetes mellitus, NGT: Normal glucose tolerance. *All *p* values from ANOVA tests denotes the study groups that did not differ significantly from each other at the 0.05 level based on characteristics from post hoc analysis.

Table 3: Linear regression analysis: T2DM as dependent variable, and anthropometry indices and dietary intake as independent variables.

Variable	B	SE	Sig	Exp (B)	95% CI for Exp (B)	
					Lower	Upper
Age (y)	0.056	0.003	0.000	1.057	1.051	1.064
Weight (Kg)	-0.015	0.004	0.000	0.986	0.978	0.993
Waist Circumference (cm)	0.036	0.005	0.000	1.037	1.026	1.047
BMI (kg/m ²)	0.036	0.014	0.009	1.037	1.009	1.066
Protein (g)	0.007	0.002	0.000	1.007	1.004	1.011
Total lipid fat (g)	-0.007	0.002	0.000	0.993	0.990	0.996
Carbohydrate (g)	-0.002	0.000	0.000	0.998	0.998	0.999
Vitamin A (IU)	0.000	0.000	0.065	1.000	1.000	1.000
Energy (Kcal)	0.000	0.000	0.842	1.000	1.000	1.000
β-Carotene (mg)	0.000	0.000	0.471	1.000	1.000	1.000
Total ascorbic acid (mg)	0.000	0.000	0.735	1.000	1.000	1.001

T2DM: Type 2 diabetes mellitus, SE: Standard error, Sig: Significant, Exp:exponential value

energy, for total fat was 20-35% of total energy, and for carbohydrates was 45-65% of the total energy (11). All study groups had a slightly higher total fat intake and a slightly lower CHO intake than recommended normal range, but the average protein intake for all groups fell within the recommended normal range. A negative association was observed between vitamin C ($p=0.003$) and β-carotene intakes ($p=0.037$) and FBS, while the findings did not change after adjustment for age and sex. The results of linear regression was significant for age, weight, WC, BMI,

protein, total lipid fat and carbohydrate intakes, but it was not significant for intakes of vitamin A, energy, β-carotene, and total ascorbic acid (Table 3).

Discussion

In the present study, a negative relationship was recognized between total vitamin C and β-carotene intakes and FBS concentrations in normal, prediabetic and diabetic patients. It was suggested that chronic low grade inflammation and oxidative stress play a pivotal role in insulin resistance

and the development of T2DM and its associated complications (12). Vitamin C and carotenoids are essential micronutrients with potent antioxidant properties. Vitamin C can protect important biomolecules from oxidation through participating in oxidation reduction reactions; whereby it is easily oxidized to dehydroascorbic acid, which is then rapidly reduced back to ascorbic acid (13). Earlier reports revealed that people with newly diagnosed T2DM had low circulating vitamin C concentrations (14, 15).

There are several proposed mechanisms for that, including (i) increased ascorbate excretion among those with microalbuminuria, (ii) blood glucose may compete with vitamin C for uptake into cells due to its structural similarity to the oxidized form (dehydroascorbic acid), and (iii) increased oxidative stress may deplete antioxidant stores (15). Subsequent investigations reflected lower intakes of dietary vitamin C (16, 17). These findings are consistent with earlier reports in adults, describing that vitamin C supplementation is associated with reduced risk for T2DM (18). Since dietary vitamin C contributes to plasma vitamin C levels, potential differences in the intake between individuals with normal glucose control and T2DM should also be considered. The results of a prospective study revealed that while the baseline consumption of fruits and vegetables was similar, men who developed T2DM increased their consumption of fruits and vegetables by 1.6 serves/week compared to an increase of 0.7 serves/week in men who remained diabetes free (19).

Therefore, people with T2DM appear to change their diet to control their blood sugar levels. Indeed, counseling for newly diagnosed T2DM focuses on improving their diet. However, dietary changes appear to be small, and moreover, people with T2DM appear to have an identical intake of fruits and vegetables to those without T2DM (19), which is in line with the results of the present study that no difference was noticed in vitamin C intake between the 3 groups. The findings of the systematic reviews of prospective studies in adults did not show any consistent evidences of an association between total fruit and vegetable intakes and risk of T2DM (20) or for association between vitamin C intake and risk of T2DM (16). In a study by Wilson *et al.*, plasma vitamin C level had an inverse association with insulin resistance, while intakes of fruits, vegetables and vitamin C did not display any association (7).

It was shown that higher intakes of vitamin C were not associated with T2DM (21), which is in line with the previous studies (22, 23). Supplementation of vitamin C was demonstrated to be helpful to improve insulin action and help to control secondary

complications of T2DM (24). Additionally some studies found significant inverse association between FBS and plasma ascorbate levels (25, 26), which is in line with the result of the present study that negative association was found between vitamin C intake and FBS. In particular, the inverse association between plasma vitamin C concentration and insulin resistance was consistent with a former report which suggested that circulating vitamin C level was more positively and inversely associated with the risk of T2DM when compared to the intake of fruits and vegetables (14).

There could be some explanations for the lack of a clear association between intake of fruits and vegetables and total vitamin C and insulin resistance, despite the association between plasma vitamin C level and insulin resistance. This contrasting pattern could reflect a stronger role for circulating vitamin C as a marker of systemic vitamin C status, more likely to be related to emerging risk of T2DM when compared to intake of vitamin C; however, the absence of associations could also reflect the fact that dietary vitamin C intake was an important determinant of plasma concentration, which was difficult to assess precisely (27). These issues need to be considered in order to increase the circulating level of vitamin C. Based on the supplementary analytical report (7), vitamin C intake above 200 mg/L to maintain higher plasma vitamin C levels (approximately 30 μ mol/L, associated with significantly lower insulin resistance) needs a sustained increase in intake of vitamin C. Such an increase would require a large and perhaps infeasible increase in consumption of fruits and vegetables and would be easier to achieve with vitamin C supplementation. Confirmation of this conclusion requires experimental testing of various strategies to increase circulating vitamin C level, especially in relevant ethnic minorities (7).

Antioxidants and reactive oxygen species have been shown to affect cellular signaling and genes (28). The biological activity of carotenoids is the induction of cell-cell communication (29). Communication of B cell junctions has been shown to contribute to the regulation of insulin secretion and glucose tolerance (30). In some studies, serum carotenoid concentrations were inversely associated with insulin resistance (31, 32) and blood glucose concentration (33). In a study by Ylönen *et al.*, dietary intake of α - and β -carotene and of lycopene, as well as plasma β -carotene concentrations, showed positive associations with glucose metabolism in the male population with high risk of T2DM; while an inverse association with FBS concentration was observed for the former, and an inverse association with insulin resistance was noticed for the latter (3).

In a prospective cohort study, an inverse correlation was noted with risk of T2DM regarding dietary intake of β -carotene among men, but not women (27). Two cross-sectional studies failed to show a relationship between β -carotene intake and glycated hemoglobin (5, 34). Also in Lampousi *et al.*'s study, there was no indication to show a high intake of β -carotene would reduce the risk of T2DM (21), and this finding was supported by a previous observational study (35). Therefore, studies conducted so far do not consistently support the independent role of β -carotene in the development of diabetes. In our study, although there was no difference in β -carotene intake between 3 groups, it had an inverse association with FBS, which is in line with the result of another study reporting that higher cis- β -carotene level was associated with lower FBS level (36).

The combined relationship of vitamin C and β -carotene were not reported in previous studies and the main strength of this study was the large population. The cross-sectional design of our study limited the strength of evidences supporting a potentially causal association between plasma vitamin C and β -carotene and emerging risk of T2DM, and this design is nevertheless particularly appropriate for examining short term associations between nutritional status and markers of T2DM. There was also lack of data for plasma vitamin C level, which were more positively and inversely associated with risk of T2DM in comparison to the intake of fruits and vegetables according to findings of EPIC-Norfolk Study (14). Absence of data for HbA1c to detect its relationship with antioxidant intake, that was reported in previous study (37), can be another limitation of our study.

Conclusion

In conclusion, although there was no difference in β -carotene and vitamin C intakes between 3 groups, an inverse association was found between the intakes and FBS. Further researches, particularly by using randomized controlled trials, are essential to demonstrate whether the circulating vitamin C–insulin resistance association is causal and whether it reflects the influence of fruits and vegetables rich in carotenoid and vitamin C and their role in prevention of diabetes in a high-risk population.

Acknowledgment

We wish to thank Shiraz University of Medical Sciences to financially support this study (Approval code: 23369).

Authors' Contributions

Study concept and design: N.H. and Sh.R.;

acquisition of data: F.R., S.F. and S.H.B.; analysis and interpretation of data: N.H.; drafting of the manuscript: Sh.R.; critical revision of the manuscript: N.H.; statistical analysis: Sh.R.; obtained funding: N.H.; administrative, technical, or material support: Sh.R.; and study supervision: N.H.

Conflict of Interest

None declared.

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