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The Relationship between Antioxidants Consumption and Insulin Resistance/Insulin Sensitivity in Type 2 Diabetes without and with Coronary Stenosis: A Case-Control Study

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ABSTRACT

Background: Type 2 diabetes (T2D) is known as a common chronic metabolic disease worldwide. Coronary artery diseases are one of the hazardous disorders in diabetic patients. The current study aimed to investigate the relationship between dietary antioxidants intake with insulin resistance and insulin sensitivity among T2D without and with coronary stenosis (CS). **Methods:** This case-control study was conducted on 247 participants (65 diabetic patients suffered from CS and 172 diabetic patients without CS). Dietary antioxidants intake (vitamin E, Vitamin C, selenium, beta-carotene, and zinc) were assessed with a valid and reliable 168-item semi-quantitative food frequency questionnaire (FFQ). Blood pressure, weight, and height were measured. Blood sample was collected for glycaemic control assessment. **Results:** Diabetic patients with CS had significantly higher HbA1c levels (P = 0.004). There was a negative significant association between vitamin E (r = -0.91; P < 0.001) and Beta-carotene (r =-0.88; P < 0.001) with HbA1c among all participants. There was also a positive significant association between vitamin E, vitamin C, and selenium with insulin sensitivity among all the participants; (r = 0.59; P = 0.004) for vitamin E, (r = 0.91; P < 0.001) for vitamin C, and (r = 0.27; P = 0.04) for Beta-carotene. **Conclusion:** Antioxidants intake especially vitamin C and beta-carotene may have an anti-insulin resistance effect in metabolic disorders.

Keywords: *Diabetes mellitus; Coronary stenosis; Dietary intake; Antioxidants; Insulin resistanc.e*

Introduction

Type 2 diabetes (T2D) is known as a serious metabolic disorder characterized by chronic hyperglycemia, which continues to disrupt the metabolism of carbohydrates, fats, and proteins

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(Tripathi and Srivastava, 2006). In a diabetic patient, the tissue's response to insulin or its production is impaired. As time progresses and the disorder becomes chronic, short-term and long-term complications occur in diabetes (Kaul K. *et al.*, 2013). Studies have shown increased prevalence of diabetes in the world. It is estimated that more than 5-8% of adults have T2D. In addition, the International Diabetes Federation reported that the number of people suffer from diabetes in 2010 was 285 million and is expected to reach more than 438 million in 2030. In addition, indirect and direct costs of diabetes in the United States (US) have been reported to be more than 174 billion dollars per year (Lau, 2009, Whiting *et al.*, 2011). Several studies have shown that the risk of premature death, cardiovascular disease (CVD), retinopathy, neuropathy, blindness in diabetic patients is two time more than people without diabetes (Deshpande *et al.*, 2008). Oxidative stress plays an important role in the development of diabetes. overproduction of free radicals and defect of antioxidants protection worsen metabolic and vascular function (Wiernsperger, 2003). Hyperglycaemia could induce reactive oxygen species (ROS) production by the mitochondrial electron-transport system. Oxidative stress due to high blood levels of glucose and the overproduction of ROS can damage the islet cells and impair its function (Savu *et al.*, 2012).

CVD is known as a major cause of morbidity and mortality all over the world, so that it can be one of the causes of increase in sudden death. Also, these diseases could cost a lot for the patients. The most common cause of heart disease vascular was recognized atherosclerosis. In spite of designing methods as well as new therapy for the prevention and treatment of heart disease, the number of deaths associated with CVD in most countries remains stagnant (Roth *et al.*, 2017). One of the most important causes of mortality among American men and women was known coronary artery disease (Khawaja *et al.*, 2009). The American Heart Association has reported that 20% of men and women suffer from coronary artery disease and its cost was about 368 billion dollars in the USA in 2004 (Berra, 2011). Increased incidence of coronary artery disease in last decades has been due to improving the economy, well-being, and comfort. Nutritional factor is a key factor in epidemiologic research and previous study demonstrated positive correlation between well-being and comfort among atherosclerosis (Barquera *et al.*, 2015).

Some of the most important risk factors affecting coronary artery disease and T2D are lifestyle, diet, and physical activity. Similarly, proper diet consumption can prevent coronary artery disease in patients with diabetes, and one of causes of coronary artery disease are excessive intakes of energy and fat in the diet (de Souza *et al.*, 2015, Maki, 2004). Several studies have indicated that increasing intakes of fresh vegetables, fruits, and grains can prevent coronary artery disease and diabetes (Alissa and Ferns, 2017, Di Angelantonio *et al.*, 2016). Also, high dietary intakes of fruits and vegetables can improve insulin levels and insulin sensitivity (Mathews *et al.*, 2017, Wang *et al.*, 2016). High antioxidants diet could inhibit oxidant formation and intercepting oxidants which have been formed, and repair oxidant-induced injury (Diaz *et al.*, 1997). Vitamin E and C can reduce the damaging effects of free radicals on the structure and function of cells and vessel walls (Ashor *et al.*, 2015). Some of trace elements (selenium, copper, zinc, and manganese) act as cofactors for enzymes with antioxidant activity like superoxide dismutase and glutathione peroxidase (Diplock, 1991). Previous studies have indicated the association between some vitamins and hemoglobin A1c (HbA1c) levels; for example high intakes of carotenoids are associated with low levels of HbA1c and vitamin D deficiency can be along with high levels of HbA1c (Abd Elgadir *et al.*, 2018, Randhawa *et al.*, 2017). However, a study showed that supplementation of vitamins E and C in pharmacological does have no impact on HbA1c levels (Regensteiner *et al.*, 2003).

Antioxidants in dietary intake, such as vitamin C, vitamin E, selenium, beta-carotene, and zinc

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associated to HbA1c level in T2D patients with and without coronary stenosis (CS) have not been examined. Therefore, the present study aimed to compare dietary intakes of antioxidants and insulin resistance levels in T2D patients with CS and T2D patients without CS. This study also examined the association between antioxidant components of dietary intakes with HbA1c and QUICKI index in T2D patients with and without CS.

Materials and Methods

Study design and participants: This case-control prospective study was conducted on T2D patients referred to the hospital. The study was carried out on 283 adult patients with newly diagnosed T2D without CS that were diagnosed with glucose tolerance test (GTT) and fasting blood glucose of 65 adult diabetic patients with CS that were diagnosed with angiography, GTT and fasting blood glucose that diagnosed by cardiologist. Subjects included if they diagnosed as having T2D and CS without any medical comorbidities or any other major chronic diseases. The subjects were excluded if they followed any especial diet, consumed any dietary supplements, multi-vitamin or mineral supplementation and fortified foods during the last four months. Finally, 111 T2D were excluded from the study, since they were on a diet or consumed dietary supplements.

Measurements: A valid and reliable 168- item semi-quantitative food frequency questionnaire (FFQ) modified for Iranian foods was completed in the present study (Esfahani *et al.*, 2010). Frequencies of food intakes during the last four months were reported in day, week, or month. Vitamin C, vitamin E, selenium, beta-carotene, and zinc of foods were derived from Nutritionist 4 software. Written informed consent was signed by all the participants. This study was ethically approved by the university.

The demographic and clinical characteristics, including gender, age, body mass index (BMI), weight, systolic and diastolic blood pressure, and history of other disease were completed by using a structured questionnaire. All the patients had been taking 1500 mg/day oral doses of metformin. They had not taken any insulin therapy. HbA1c levels were measured by Diazyme direct enzymatic assay of HbA1c using auto-analyzer and whole blood samples (Penttilä *et al.*, 2011).

Ethical considerations: Written informed consent was obtained from all the participants. This study was approved by the School of Nutrition and Food Sciences, Isfahan University of Medical Sciences (project code: 293113) and Qazvin University of Medical Sciences (project code: IR.QUMS.REC.2015).

Data analysis: Normal distribution of variables among the two groups of participants was determined by Shapiro-Wilk test. All variables, including vitamin C, vitamin E, selenium, beta-carotene, zinc, HbA1c, and QUICKI index (Quantitative insulin sensitivity check index) were normally distributed. Independent samples t-test was applied to compare the mean score of variables among T2D patients with and without CS. Gender and age was considered in Chi-square test and one-way ANOVA and independent samples t-test were used for quantitative variables. However, they did not change the results and therefore excluded from analysis. Pearson correlation test was used to assess the Chi-square test and one-way ANOVA and independent samples t-test were used for quantitative variables. However, they did not change the results and therefore excluded from analysis. Pearson correlation test was used to assess the relationship between vitamin C, vitamin E, selenium, beta-carotene, and zinc with HbA1c and QUICKI index among all the participants and in sub groups of T2D patients with CS and patients with T2D. All statistical analyses were performed by using SPSS version 20.0. P-values less than 0.05 were considered significant.

Results

Participants' general characteristics are demonstrated in **Table 1**. There were no significant differences regarding age, gender, BMI, weight, systolic and diastolic blood pressure, and energy intake between the two groups.

Mean ± SD values of HbA1c, QUICKI index,

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vitamin E, vitamin C, selenium, beta-carotene, and zinc are shown in **Table 2**. Diabetic patients with CS had significantly higher HbA1c levels compared to the other group (*P* = 0.004). In addition, the index of insulin sensitivity in diabetic patients without CS higher than diabetic patients with CS (*P* = 0.03). The diabetic patients without CS consumed higher doses of dietary antioxidant components compared to diabetic patients with CS group. However, diabetic patients with CS had higher intakes of vitamin C and zinc compared to the other group.

Table 3 reveals the results of Pearson correlation test between variables and HbA1c levels in the two groups. There was negative correlation between all antioxidant components and HbA1c. In addition, there was a negative significant association between vitamin E and Beta-carotene with HbA1c among all the participants; (r = -0.88; *P* < 0.001) for vitamin E and (r = -0.80; *P* < 0.001) for Beta-carotene as well as T2D patients with CS, (r = -0.92; *P* < 0.001) for vitamin E, and (r = -0.92; *P* < 0.001) for Beta-carotene in T2D patients without CS. In addition, there was a marginally negative association between selenium with HbA1c in T2D group with CS (r =-0.20; *P* = 0.05), although this negative correlation in T2D group without CS was significant (r = -0.49; *P* < 0.001).

The results of Pearson correlation between antioxidants intake and QUICKI index in the two groups are presented in **Table 4**. There was a positive association between dietary intake of antioxidants and insulin sensitivity in QUICKI index. In addition, there was a positive significant association between vitamin C, vitamin E and selenium with insulin sensitivity among all the participants; (r = 0.59; *P* = 0.004) for vitamin E, (r = 0.91; *P* < 0.001) for vitamin C, and (r = 0.27; *P* = 0.04) for Beta-carotene.

Table 1. General characteristics of the study population.

Variables	T2D patients with CS (N= 65)	T2D patients without CS (N=172)	P-value[a]
Gender			
Male	26 (40.0)[b]	70 (37.2)	0.75
Female	39 (60.0)	102 (62.8)	
Age (year)	50.14 ± 9.57[c]	48.44 ± 9.21	0.12
Body mass index (kg/m^2)	29.14 ± 3.26	27.58 ± 3.02	0.11
Weight (kg)	77.57 ± 7.82	74.88 ± 7.79	0.11
SBP (mm Hg)	13.98 ± 0.87	12.13 ± 0.65	0.07
DBP (mm Hg)	9.41 ± 0.54	8.13 ± 0.46	0.28
Energy intake (kcal/day)	2587.28 ± 248.12	2386.25 ± 233.50	0.06

[a]: P-values are obtained from independent samples t-test and Chi-square test; [b]: N (%); [c]: Mean ± SD; T2D: Type 2 diabetes; CS: coronary stenosis; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Table 2. Mean (±SD) values of variables between T2D patients with and without CS.

Variables	T2D patients with CS (N = 65)	T2D patients without CS (N = 172)	P-value[a]
Vitamin E (IU/day)	29.19 ± 5.12	33.24 ± 7.33	0.01
Vitamin C (mg/day)	298.32 ± 81.15	300.30 ± 85.77	0.17
Selenium (mg/day)	0.09 ± 0.04	0.10 ± 0.05	0.04
Beta-carotene (mg/day)	1081.74 ± 413.24	1393.49 ± 509.96	<0.001
Zinc (mg/day)	8.98 ± 1.49	9.67 ± 1.59	0.19
HbA1c (%)	7.62 ± 0.97	7.11 ± 0.63	0.004
QUICKI index (%)	0.28 ± 0.02	0.30 ± 0.03	0.03

[a]: P-values are obtained from independent samples t-test; T2D: Type 2 diabetes; CS: coronary stenosis; HbA1c: Hemoglobin A1c; QUICKI: Quantitative insulin sensitivity check index.

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Table 3: Pearson correlation of HbA1c in the groups with antioxidant components.

Variables	T2D patients with CS (N = 65)		T2D patients without CS (N = 172)	
	R	P-value[a]	R	P-value
Vitamin E	-0.88	<0.001	-0.92	<0.001
Vitamin C	-0.19	0.06	-0.20	0.05
Selenium	-0.20	0.05	-0.49	<0.001
Beta-carotene	-0.80	<0.001	-0.92	<0.001
Zinc	-0.05	0.60	-0.02	0.34

[a:] P-values are obtained from Pearson correlation.; T2D: Type 2 diabetes; CS: coronary stenosis; HbA1c: Hemoglobin A1c.

Table 4: Pearson correlation of QUICKI index in the groups with the study components.

Variables	T2D patients with CS (N = 65)		T2D patients without CS (N = 172)	
	R	P-value[1]	R	P-value
Vitamin E	0.568	<0.008	0.612	<0.003
Vitamin C	0.847	0.001	0.941	0.001
Selenium	0.812	<0.001	0.918	<0.001
Beta-carotene	0.218	<0.061	0.294	0.042
Zinc	0.053	0.612	0.058	0.608

[a:] P-values are obtained from Pearson correlation.; T2D: Type 2 diabetes; CS: coronary stenosis; QUICKI: Quantitative insulin sensitivity check index.

Discussion

The present study was conducted as the first attempt to investigate the association between dietary intake of antioxidants with insulin sensitivity and insulin resistance in T2D with and without CS. HbA1c levels among T2D with CS compared to the other group were significantly higher. In addition, the insulin sensitivity index compared to the two groups was significantly lower. There was a positive significant correlation between vitamin C, vitamin E, and selenium intake with insulin sensitivity among all the participants.

Cardiovascular risk factors and their pathologic factors begin predominantly from the childhood (Hong, 2010). Several studies have acknowledged that obesity with abnormal lipid profile among youth was strongly associated with insulin resistance (Polgreen *et al.*, 2012, Steinberger *et al.*, 2001). Studies have shown that lots of factors, such as overweight or obesity, abnormal lipid profiles, and insulin resistance play a significant role in the incidence of heart disease (DeBoer, 2013).

Under physiological conditions, insulin stimulates the utility of metabolic subclass in several tissues, such as heart, liver, skeletal muscle, and adipose tissue. In heart cells (cardiomyocytes), insulin increases glucose and fatty acid absorption, but inhibits the use of fatty acids as an energy source. As a result of this insulin resistance, the pancreas tries to compensate for insulin activity by secreting greater insulin (Abel *et al.*, 2012). During insulin resistance, the natural tolerance of sugar is maintained due to physiological changes activated by this phenomenon (Ferrannini *et al.*, 2003). It is very interesting to note that there is a direct and strong relationship between insulin resistance and the risk of heart disease (Nesto, 2003). Molecular and cellular mechanisms contribute to this direct relationship between insulin resistance and CVD (Saltiel, 2000, Wang *et al.*, 2004, Zeadin *et al.*, 2013). Insulin resistance helps increase oxidative stress, then results in mitochondrial function alteration which should aggravate insulin resistance. Atherosclerosis increased because of insulin resistance, vascular dysfunction, hypertension and accumulation of macrophages (Razani *et al.*, 2008). Also, according to recent

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studies smoking, high levels of low density lipoprotein (LDL), high blood pressure, and diabetes are known some risk factors for CVD. In addition, hyperglycemia, insulin resistance and inflammation can also lead to a prognosis of cardiovascular events. Also, insulin resistance is associated with disorders, such as hypertriglyceridemia and low high density lipoprotein (HDL) (Howard *et al.*, 2008).

In 1996, investigation of insulin resistant in atherosclerosis studies (Garcia-Bailo *et al.*, 2011) showed a direct and consistent relationship between insulin resistance and atherosclerosis. A prospective study in a group of 2,938 patients showed insulin resistance as an important risk factor for the disease Cardiopulmonary bypass (De Hert *et al.*, 2018, Wagenknecht *et al.*, 1995). A meta-analysis in 2012 from 65 studies indicated that insulin resistance and HOMA-IR index were good predictors for CVD (Gast *et al.*, 2012). Researchers also found that preventing insulin resistance could reduce about 42% of heart attacks in participants who had over 60-year follow-up period (Kozakova and Palombo, 2016, Laakso and Kuusisto, 2014). In addition to insulin resistance, compensatory hyperinsulinemia associated with insulin resistance which can play a key role in the formation of atherosclerotic plaques. It can be linked to a change in the gene expression pattern related to estrogen receptor (Min *et al.*, 2016). Moreover, hyperglycemia causes changes in various metabolic and cellular levels (Wang *et al.*, 2004), including schizophrenia, high blood pressure, oxidative stress, endothelial dysfunction, and changes in heart metabolism.

Studies have suggested that approximately 70-50% of the ATP needed as fuel for heart cells is produced by oxidation of long chain fatty acids. Glycolysis accounts for less than (10%) of total ATP production in the heart tissue. Although fatty acids are used for the production of preferential energy for the heart, the heart has the ability to alter the substrate to produce it for ATP. Substrate transducers, GLUT4 for glucose, and CD36 for fatty acids play a key role in this dynamic balance using substrate (Grynberg and Demaison, 1996).

However, under the effect of insulin resistance, fatty acid is known the only source of fuel that entered. Alterations in substrate increase the absorption and accumulation of fat in the heart, then cause fatty toxicity (Goldberg et al., 2012). In this way, the balance between fat degradation and glucose oxidation can reduce the activity of cardiac cells in patients with insulin resistance (Nagoshi *et al.*, 2011).

Researchers have shown that oxidative stress is associated not only with diabetes complications, but also with insulin resistance (Asmat *et al.*, 2016, Chueakula *et al.*, 2018, Henriksen *et al.*, 2011, Tangvarasittichai, 2015). Insulin resistance and declined insulin secretion are the main characteristics of T2D (Asmat *et al.*, 2016, Tangvarasittichai, 2015). Insulin resistance often precedes the onset of T2D, in most cases, among lots of the general population, and several factorials (Rosenberg *et al.*, 2005). Insulin resistance can be caused by effective factors, such as overweight or obesity, lifestyle, pregnancy, and excess in hormone secretin (Czech, 2017, McIntyre *et al.*, 2010). Initially, insulin resistance is compensated by hyperinsulinemia, so blood glucose levels remain normal. Facchini reported that at least 25% of non-diabetic people with insulin resistance were found in a range of patients with T2D, and these people were exposed to age-related illnesses. Declined glucose tolerance occurs when insulin resistance increases, or insulin secretion declines, or both of them (Facchini *et al.*, 2001).

Studies in diabetic animal models have indicated that antioxidants improve insulin sensitivity (Styskal *et al.*, 2012). Several antioxidants have been promising as new approaches to treating insulin resistance, such as N-acetyl-cysteine, a-lipoic acid (LA), and flavonoids. Some studies have shown that antioxidants LA, glutathione, vitamin E, and vitamin C increase insulin resistance in patients with insulin resistance, T2D and/or CVD (Garcia-Bailo *et al.*, 2011, Khodaeian *et al.*, 2015). Antioxidant defence system includes endogenous and exogenous diet derived compounds. Dietary antioxidants, including

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vitamin C or ascorbic acid, vitamin E or α-tocopherol, and β-carotene or pro-vitamin A have attracted the most attention to prevent coronary heart disease (Diplock, 1991).

Additionally, the short-term oral administration (6-wk) of LA reduced fructosamine levels in patients with T2D (Evans and Goldfine, 2000). Vitamin C, in addition to the main role of endothelial dysfunction improvement, can reduce insulin resistance (Khodaeian *et al.*, 2015). Oxidation may indirectly affect insulin sensitivity, declined peripheral blood flow, increased nitric-oxide, and declined glucose transport of insulin mobility in skeletal muscle (Krebs and Roden, 2005). Early reports aimed at investigating the effects of vitamin E on insulin activity in T2D with have been published more than 10 years ago and have shown positive effects in these patients (D. Pavithra *et al.*, 2018, Wagenknecht *et al.*, 1995). Twenty-five patients with T2D were treated with Vitamin E (tocopherol 900 mg/day) versus placebo for three months in a randomised controlled trial (RCT), cross-linked. The process of declining plasma glucose was associated with a significant reduction in HbA1c (7.8 vs. 7.1), triglycerides, free fatty acids, total cholesterol, low lipoprotein cholesterol, and apoprotein B. Cellular response to glucose was not observed. These interesting results increased the evaluation of Paolisso by using a more sensitive technique for estimating the insulin sensitivity index (Paolisso *et al.*, 1991, Park *et al.*, 2015).

Conclusion

This study showed that diabetic patients with CS have higher levels of HbA1c. In addition, there was a significant correlation between vitamin C and beta-carotene with HbA1c in patients with coronary artery disease and in patients without coronary artery disease. In addition, there was a significant correlation between selenium and HbA1c in T2D mellitus without coronary artery disease. There was a positive correlation between the amount of antioxidants and insulin sensitivity in the QUICKI index. In addition, there was a positive and significant correlation between insulin sensitivity of vitamin E, C, and beta-carotene among all the participants. It seems that antioxidants, especially vitamin C and beta-carotene, may have insulin resistance effects on metabolic disturbances.

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Conflict of interest

The authors declare that there is no conflict of interest.

Authors' contributions

Idea of study: Gerami H; Study design: Gerami H, Hosseini SK; Data collection: Gerami H, Hosseini SK, Jamalzehi A; Data analysis: Javadi M, Jamalzehi A, Lesani A; Manuscript draft: Javadi M, Gerami H, Hosseini SK, Jamalzehi A, Lesani A; Manuscript final edition: Gerami H, Lesani A, Jamalzehi A.

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