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Original Article

High fructose consumption may have part in the pathophysiology of coronary artery ectasia

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Abstract

Aim: A coronary artery may partly become a half or one diameter larger than an adjoining normal one as observed on angiograms, which is called coronary artery ectasia (CAE). There is strong evidence that oxidative stress and inflammation may contribute to the CAE pathophysiology, potentially due to higher fructose intake. Our study aims to determine the effects of the amount of fructose consumed on isolated CAE.

Material and Methods: The study group consists of the patients with stable angina pectoris who had coronary angiography (CAG) reports dated from December 2018 to April 2019. Based on these reports, sampling was made as follow: the patient or CAE group of 50 patients also with isolated CAE and the control group of 50 patients with normal coronary flow pattern (NCF). A comparative analysis was performed using the exact data of both groups including nutrient consumption.

Results: The patient group with higher high-sensitivity C-reactive protein levels (p = 0.029), greater platelet count (p = 0.015), and increased hypertension rate (p = 0.012) were observed to have higher energy in total (p = 0.008), carbohydrate (p = 0.003), and fructose intake (p<0.001). Multivariable logistic regression analyses demonstrated that rising Hs-CRP levels (p = 0.031), greater platelet count (p = 0.017), higher fructose intake (p = 0.029), and increased hypertension (p = 0.032) were individually associated with CAE.

Conclusion: In the CAE group higher fructose consumption was observed and thus determined to potentially contribute to the CAE pathophysiology.

Keywords: Atherosclerosis; Coronary artery ectasia; fructose consumption

INTRODUCTION

Coronary angiography provides good evidence on the diagnosis of coronary artery ectasia (CAE) compared to other measurements (1). It can be typically identified as the local or wider expansion of a coronary artery by a half diameter larger than an adjoining normal artery (1). CAE is considered a variant of coronary atherosclerosis. In a study of Markis et al. an anatomical classification of CAE determined a two-year mortality rate of 15% as similar to 3-vessel coronary artery stenosis (2). Pathophysiology and clinical importance of CAE are not totally understood. CAE is a disease of coronary atherosclerosis variant (3). The pathophysiological underlying mechanisms of CAE have been already studied and however not so far understood well, including diffuse atherosclerosis, endothelial insufficiency, microvascular dysfunction, vasomotor dysfunction, increased platelet aggregation, connective tissue diseases, inflammation, and oxidative stress (4-8).

Many epidemiological, clinical, and experimental studies have shown that fructose naturally found in fruit and known as fruit sugar has become the most popular sweetener in food industry and that increased fructose intake is associated with diseases such as obesity, type 2 diabetes, insulin resistance, poor glucose tolerance, hyperlipidemia, metabolic syndrome, gout, hyperuricemia, and cardiovascular diseases (9).

The atherosclerotic process may start with high fructose consumption which increases the number of low-density lipoprotein (LDL) particles, reduces the amount of particles with atherogenic effects, and also it increases adhesion molecules in endothelial cells and triggers thrombosis pathophysiology (10). Also, there is strong evidence in literature that increased fructose intake has association with inflammation as well as oxidative stress that both have part in the pathophysiology of CAE (11,12).

In light of these findings, this study aims to determine the effects of the amount of fructose intake on isolated CAE.

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MATERIAL and METHODS

Between December 2018 and April 2019, 944 patients who underwent coronary angiography due to clinical suspicion or myocardial ischemia demonstrated by exercise stress testing or myocardial perfusion scintigraphy were evaluated at Suleyman Demirel University Faculty of Medicine Training and Research Hospital. The study group constituted two groups: the patient or CAE group of 50 patients with isolated CAE and the control group of 50 patients with normal coronary artery anatomy (NCA).

A complete physical examination was performed in addition to a detailed medical history for all the subjects. A 12-lead electrocardiogram was used to assess their conditions. A cardiologist conducted transthoracic echocardiography. Diagnosis with hypertension was made based on at least three different measurements of a diastolic blood pressure (not less than 90 mm Hg) or a systolic blood pressure (not less than 140 mmHg), or antihypertensive medication history. Fasting blood glucose (not less than 126 mg/dl) determined diabetes mellitus for the patients other than the anti-diabetic medicine users. The cases with total cholesterol level (not less than 200 mg/dl) or those using statin except for the last three months were considered as hyperlipidemia. The patients who have smoked before were accepted as smokers in hospitalization.

In this study, the exclusion criteria were defined and applied including known coronary artery disease, history of acute coronary syndrome, peripheral arterial disease, congestive heart failure with ejection fraction <55%, history of surgical or interventional cardiovascular procedures, history of stroke, pulmonary hypertension, valvular heart

Table 1. Baseline characteristics and laboratory parameters of the study groups (n=100)

Parameters	Normal Coronary Artery (n=50)	Coronary Artery Ectasia (n=50)	p value
Age, years	57.0 ± 10.6	59.3 ± 11.2	0.308
BMI, kg/m^2	27.0 ± 4.3	27.9 ± 4.3	0.205
Female, n (%)	21 (42.0)	16 (32.0)	0.300
Diabetes Mellitus, n (%)	9 (18.0)	15 (30.0)	0.160
Hypertension, n (%)	18 (36.0)	29 (58.0)	**0.028**
Dyslipidemia, n (%)	13 (26.0)	15 (30.0)	0.656
Family history, n (%)	4 (8.0)	8 (16.0)	0.218
Smoking, n (%)	16 (32.0)	22 (44.0)	0.216
Glucose, mg/dl	116.4 ± 47.6	123.5 ± 54.9	0.505
Creatinine, mg/dl	0.97 ± 0.20	1.07 ± 0.39	0.208
Uric Acid, mg/dl	5.5 ± 2.1	5.9 ± 2.2	0.825
WBC count, 10^3/mm^3	9.6 ± 2.3	10.2 ± 2.3	0.338
Hemoglobin, g/dL	13.2 ± 1.7	13.2 ± 1.7	0.113
Platelet count, 10^3/mm^3	221.0 ± 57.4	262.4 ± 60.9	**0.015**
Total cholesterol, mg/dL	193.0 ± 86.6	187.5 ± 83.1	0.848
Triglyceride, mg/dL	160.1 ± 78.9	176.48 ± 80.7	0.456
LDL-cholesterol, mg/dL	116.6 ± 64.7	112.7 ± 59.9	0.786
HDL-cholesterol, mg/dL	45.5 ± 28.0	45.7 ± 24.3	0.931
Hs-CRP, mg/L	3.6 ± 2.3	5.1 ± 2.3	**0.029**
LVEF, %	58.7 ± 5.2	56.0 ± 4.0	0.307
Diameter of ectasia (mm)	-	4.23 (3.70-5.21)	-
Ectasia type			
Type I		9	
Type II		7	
Type III		5	
Type IV		29	

Data are given as mean ± SD, n or median (interquartile range). BMI: Body Mass Index; HDL: High Density Lipoprotein; Hs-CRP: High-Sensitivity C-Reactive Protein; LDL: Low-Density Lipoprotein; LVEF: Left Ventricle Ejection Fraction; WBC: White Blood Cells

disease, cardiomyopathy, myocarditis, pericarditis, renal dysfunction, chronic inflammatory disease, malignancy, active infection, and endocrine or metabolic disorder rather than diabetes mellitus. Patients who received antiaggregant, anticoagulant, corticosteroid, statin, antioxidant vitamins, and/or alcohol in the last 3 months were also excluded.

In order to determine the fructose consumption and nutritional status of the patients, the dietician questioned the food consumption records of the patients for three days (two weekdays and one weekend). Regarding the patients' nutrient consumption status, their daily intake of energy, macronutrients, and fructose was calculated in BEBIS (*Nutrition Information Systems*) program and the results were evaluated.

Coronary angiography

The Judkins technique was radially or femorally applied for selective coronary angiography. An experienced interventional cardiologist examined all the angiograms. Angiograms without atherosclerotic plaque or constrictive lesions in any major epicardial artery and its branches were considered normal angiograms. CAE was defined as an increase in vascular lumen by more than 1.5-fold compared to an adjoining normal coronary artery or its own normal portions. Quantitative methods were used to estimate the diameter of ectasia on digital angiograms. Types of ectasia were categorized by Markis classification (2). Markis classification was typically described as: (type I) includes diffuse ectasia involving two or three vessels, (type II) includes diffuse ectasia in one vessel and discrete ectasia in another vessel, (type III) includes diffuse ectasia in only one vessel and (type IV) includes localized or segmental ectasia in only one vessel.

The necessary approval process was completed for the study protocol endorsed by the local ethics committee and the written informed consent forms signed by all patients. The Declaration of Helsinki, Good Clinical Practice, and International Conference on Harmonization guidelines were fully complied with in our study.

Statistical analysis

SPSS for Windows version 19.0 (SPSS, Chicago, IL, USA) was used for the statistical analyses. The descriptive statistics (i.e. mean, standard deviation, rate, and frequency) were used. The Kolmogorov-Smirnov test determined if the continuous variables were normally distributed. Student's t-test was used for our parametrical analysis, and Mann-Whitney U test for the non-parametric data. The inter-group comparative analysis for the categorical variables was made using $\chi 2$ test. Logistic regression analysis explained the association of the dependent and independent parameters. Standardized β coefficients and 95% confidence intervals (CI) were determined. Significance level was defined as $p < 0.05$.

RESULTS

The CAE group had higher levels of serum CRP ($p = 0.029$), platelet count ($p = 0.015$) and Hypertension rate ($p = 0.012$) (Table 1). Similarly, total energy ($p = 0.008$), carbohydrate ($p = 0.003$) and fructose consumption ($p<0.001$) were found higher in the CAE group (Table 2).

Univariate and multiple linear regression models were established for major clinical factors and predictors of CAE (Table 1 and 2). Multivariable logistic regression analyses demonstrated that the CAE was associated with higher Hs-CRP levels ($p = 0.031$), greater platelet count ($p = 0.017$) and increased fructose intake ($p = 0.029$), and hypertension ($p = 0.032$) on an individual basis (Table 3).

Table 2. Comparisons daily diet energy, macro nutrients and fructose consumption

Parameters	Normal Coronary Artery (n=50)	Coronary Artery Ectasia (n=50)	p value
Energy (kcal)	2472.9 ± 571.9	2807.2 ± 659.6	**0.008**
CHO (g)	245.5 ± 90.1	298.1 ± 106.9	**0.003**
CHO (TE%)	41.4 ± 8.4	42.0 ± 9.6	0.764
Protein (g)	84.4 ± 23.4	92.0 ± 28.3	0.147
Protein (TE%)	14.1 ± 3.0	13.5 ± 2.9	0.269
Lipid (g)	122.6 ± 35.7	137.7 ± 38.9	0.046
Lipid (TE%)	44.5 ± 7.7	44.3 ± 8.9	0.943
Fiber (g)	26.5 ± 8.1	27.5 ± 8.8	0.566
Fructose (g)	34.2 ± 14.8	46.4 ± 16.5	**<0.001**
Fructose (TE%)	5.5 ± 2.0	6.6 ± 1.7	**0.005**

Data are given as mean ± SD, n or median (interquartile range). CHO: Carbohydrate; TE: Total Energy

Table 3. Multivariate logistic regression analysis to predictig the slow coronary flow

	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Hypertension	2.455 (1.097- 5.494)	**0.029**	2.960 (1.100 -7.964)	**0.032**
Platelet count	1.011 (1.002-1.021)	**0.020**	1.014 (1.002-1.025)	**0.017**
Hs-CRP	1.136 (1.006-1.283)	**0.040**	1.169 (1.015-1.347)	**0.031**
Fructose consumption	1.051 (1.022-1.081)	**<0.001**	1.048 (1.005-1.092)	**0.029**
Total energy consumption	1.001 (1.000-1.002)	**0.011**	1.000 (0.999-1.002)	0.143
Total carbohydrate consumption	1.005 (1.000-1.009)	**0.036**	1.000 (0.993-1.007)	0.198

CI: Confidence Interval; Hs-CRP: High-Sensitivity C-Reactive Protein; OR: Odds Ratio

DISCUSSION

Our study was the first to examine the relationship of fructose consumption and CAE. In the study, fructose consumption of individuals with CAE was found to be high. Furthermore, the study showed that excessive fructose consumption is an independent risk indicator for CAE.

Although the current CAE has gained more and more attention over the years in the literature, the pathophysiological mechanism of CAE is still being explained. The association of CAE with coronary artery disease is very common and has similar pathophysiological mechanisms (13). However, it has been reported that there are significant differences between CAE and CAD in terms of clinical course, pathophysiology, and their biomarkers (14,15). In a study of Boles et al., one of the most striking differences is found to be higher level of inflammation in the patients with CAE in comparison to normal coronary arteries and unlike another coronary artery disease. The activation markers of intercellular adhesion molecule, vascular cell adhesion molecule, E-selectin, C-reactive protein and macrophages increase as markers of inflammation in CAE unlike a coronary artery disease (16-19). A key factor appears to be oxidative stress in the CAE pathophysiology. The relationship of oxidative stress with CAE is present as reported by Sezen et al. (20). Damage in the tunica media and tunica intima layers of the coroner arteries due to oxidative stress has also part in its pathophysiology (21).

While a number of animal studies have reported that fructose affects inflammatory processes potentially in association with many diseases, human studies have remained limited to determine the safety dosage. Moreover, the current figures and facts are clear that higher populations consume much more sugar today, and this excessive consumption raises a number of health problems. While no strong recommendation is universally available on daily fructose intake, the World Health Organization has stated in the latest proposal that the main objective should be to reduce the energy rate of additional sugar to less than 5% and that reducing the incremental sugar intake with ready foods and drinks will also decline fructose consumption (22). As a result of a meta-analysis study Livesey and Taylor determined the level of fructose consumption among the individuals and that fructose consumption levels were divided into 3 groups; 0-50 g/day fructose consumption was classified as moderate, 50-100 g/day as high, and 100-150 g/day as very high intake. It has been stated that moderate consumption has potential benefits in controlling glycemia, but in high and very high consumption, risks of dysglycemia and dyslipidemia will appear (23). According to this classification, fructose consumption in the CAE group was found to be normal but closer to the upper limit.

Oxidative stress is contributive to the pathogenesis of endothelial dysfunction and thus CAE. There is fairly a consensus on the fact that higher fructose intake initiates oxidative stress, leading to a non-equilibrium between free radical generation and reduction of endogenous antioxidant levels (12). Furthermore, it is suggested that fructose can proliferate the cardiac and vascular superoxide anions (24).

There is a close relationship between inflammation and CAE (25). In a study Cigliano et al. concluded that high fructose consumption led to higher TNF-alpha levels and thus systemic inflammation in rats (26). In an animal study, a high fructose diet increased immunosuppressive corticosterone among the subject rats compared to adipose tissue due to increased proinflammatory cytokines and macrophages. In addition, TNF-alpha and other inflammatory cytokines in the liver were increased and liver damage was observed (27). In another study, high fructose intake was found to be associated with hypothalamic astrogliosis, neuroinflammation, and high oxidative stress (28).

LIMITATIONS

A cross-sectional study with relatively small sample size could be limited like our study. The context of this study includes no follow-up for major adverse cardiac events. Therefore, the multi-center prospective longitudinal studies with larger sample size are required to raise the quality of our results. Until then, these outcomes should be carefully interpreted considering the study limitations.

CONCLUSION

Our study was the first to determine the effects of higher fructose intake upon coronary flow dynamics and hence coronary artery disease. The study has potential to provide insight into the pathophysiology of CAE and to shed light on further studies. It can be inferred that use of fructose should be controlled in the food sector, excessive consumption of sugary drinks should be limited, and necessary actions should be taken to limit fructose intake in risk groups in order to avoid chronic diseases.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki.

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