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Does Increased Fructose Consumption Increase Atherosclerosis Burden in Patients with NSTEMI?

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Abstract

Background and Aim: The pathophysiological process of coronary artery disease is not completely understood. According to some studies, fructose consumption is associated with coronary artery diameter change and blood flow; however, the relationship between fructose consumption and coronary atherosclerotic burden has not been adequately studied, and the purpose of our study was to investigate this relationship.

Materials and Methods: One hundred and fifty patients with non-ST-elevation myocardial infarction (NSTEMI) who underwent coronary angiography were divided into two groups: low (<23) and high (≥23) synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) scores. Fructose consumption was calculated for both groups, and the calculated fructose consumption was compared between the groups.

Results: Fructose consumption was higher in patients with a high SYNTAX score than in those with a low SYNTAX score (10.75 ± 2.04 and 6.86 ± 1.54 , $P < 0.001$). Receiver operating characteristic curve analysis showed that the cut-off value of fructose consumption was 41.50 (g) for the prediction of high SYNTAX score (area under the curve: 0.891, sensitivity: 94%, specificity: 73%, $P < 0.001$). Fructose consumption was determined to be a predictor of high SYNTAX score in patients with NSTEMI (odds ratio: 1,239; 95% confidence interval: 1,146-1,339; $P < 0.001$).

Conclusion: Patients with high SYNTAX scores consumed a higher amount of fructose than those with low SYNTAX scores. High intake of fructose may play a role in coronary atherosclerotic burden score in patients with NSTEMI.

Keywords: NSTEMI, fructose, coronary atherosclerotic burden, SYNTAX score

INTRODUCTION

Globally, acute coronary syndromes (ACS) are the leading cause of death.^[1,2] A sedentary lifestyle may increase risk factors for heart diseases in industrialized and developing countries because their calorie consumption is imbalanced with their needs.^[3] Furthermore, industrially produced foods are also important risk factors for heart disease.^[4] Several studies have demonstrated that consuming fructose, a natural sugar found in

fruits, which is widely used in foods as a sweetener, is associated with cardiometabolic diseases such as difficulty regulating insulin, type 2 diabetes, hyperlipidemia, hyperuricaemia, gout, and metabolic syndrome.^[5-7]

Excessive fructose consumption may lead to vascular deterioration due to endothelial dysfunction and atherosclerosis.^[8] This can cause cardiac dysfunction and damage to important systems such as the kidneys and brain.^[9]

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The synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score is derived from answering consecutive questions on a computer program. It provides important information, such as angiographic lesion number determination, functional significance, and lesion location, about coronary artery disease (CAD).^[10] In addition, with the use of the SYNTAX score, coronary atherosclerosis burden can be evaluated.^[11]

There is no evidence regarding fructose consumption and CAD. We aimed to investigate the role of fructose consumption in the pathophysiology of coronary atherosclerotic burden in patients with non-ST-elevation myocardial infarction (NSTEMI).

MATERIALS AND METHODS

Target population

We screened all consecutive patients who underwent coronary angiography with a diagnosis of NSTEMI at a tertiary health center. The Çanakkale Onsekiz Mart University Clinical Research Ethics Committee approved the study (decision no: 2022-09, date: 18.05.2022). The Declaration of Helsinki guided all study procedures. We obtained informed consent from the participants.

A total of 381 patients were screened. A total of 150 patients were included because of the presence of the exclusion criteria. We categorized the patients into two groups based on their SYNTAX scores: low SYNTAX score (group 1; $n = 40$) and high SYNTAX score (group 2; $n = 110$). A computer program calculates the SYNTAX score based on a series of sequential, interactive questions (www.syntaxscore.com). To determine the severity of CAD, the SYNTAX scoring system, which uses features such as the number of lesions, functional importance, and location of the lesions, provides important information. As part of the scoring process, vessels with a diameter of at least 1.5 mm and lesions with at least 50% stenosis were enrolled. SYNTAX score <23 was evaluated as a low SYNTAX score, while SYNTAX score ≥ 23 was assessed as a high SYNTAX score.

NSTEMI was diagnosed according to the following criteria:^[12]

1. Symptoms of angina or angina equivalents (such as dyspnea) that persist for more than 30 min.
2. When cardiac troponin (cTn) levels are above the 99th percentile of the cut-off value for each assay, they typically increase rapidly and decrease slowly, which is typical for high-sensitivity (hs) cTn levels.
3. Absence of STEMI criteria as defined in the fourth universal definition of myocardial infarction.

Exclusion criteria included history of ACS, chronic renal disease (estimated glomerular filtration rate <30 mL/min/1.73 m²), peripheral vascular disease, stroke, coronary artery bypass graft, active infection, chronic inflammatory disease, malignant disease, thyroid dysfunction, reduced left ventricular dysfunction [left ventricular ejection fraction (LVEF) $\leq 40\%$], regular alcohol consumption (>20 g/day), or if they were aged <18 years.

Calculation of fructose consumption and blood samples

Blood drawn from the antecubital vein was used for simultaneous blood test measurements. Blood samples for the above-mentioned tests were collected within 6 h of admission. The literature commonly uses three-day (3 weekdays and 1 weekend) and seven-day diet records.^[13,14] According to our study, fructose consumption was calculated based on food records for three days (2 weekdays, 1 weekend). In this study, fructose and other nutrient consumption were calculated by an expert dietician using the Nutrition Information System (BeBiS) 9 program (BeBiS, İstanbul, Turkey). An important advantage of the program is that it is a scientific and professional computer program that calculates the nutritional value of more than 20,000 foods, 130 nutrients including fructose, and the Turkish diet.

Angiographic assessment

Coronary imaging was performed by an omniscient cardiologist. Two experienced cardiologists reviewed the angiographic images. Two interventional cardiologists who were unaware of the study evaluated the angiographic images. Automated systems (GE Medical Systems) were used to analyze the angiographic images. Significant stenosis is defined as at least 50% of the coronary artery lumen in vessels at or above 1.5 mm.

Statistical analysis

G-Power 3.1.9.7 was used for power analysis. According to the researchers, a sample size of 134 subjects would be required, with an effect size of 0.50, a margin of error of 0.05, and a power of 0.80 (80%). The study data were statistically analyzed using SPSS 19.0 software (SPSS Inc. in Chicago, IL, USA). Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Depending on the sampling distribution, data are expressed as mean (standard deviation) or median (interquartile range). Numbers (n) and percentages (%) were used to express categorical variables. In the case of normal distributions, Student's t-tests were used, and in the case of non-normal distributions, Mann-Whitney U tests were used. Fisher's exact test or chi-squared test were used to compare categorical variables. To estimate the high SYNTAX score, possible confounding independent variables were

included in the univariate analysis. Data with a non-adjusted *P*-value of less than 0.1 were deemed possible risk factors in univariate analysis and were incorporated into the multivariate analysis based on them. The independent predictors of high SYNTAX scores in patients with NSTEMI were investigated using multivariate analysis. The Hosmer-Lemeshow test was used to interpret model sufficiency. *P* < 0.05 was considered statistically significant.

RESULTS

Our study evaluated the data of 150 patients. The baseline clinical, laboratory, and angiographic data of the patients are summarized in Table 1. Groups 1 and 2 differed significantly in terms of some of the laboratory parameters, namely, Hs C-reactive protein (CRP) [1.77 (1.00-2.20) and 2.14 (1.07-1-0.60), *P* = 0.019], and LVEF (49.75 ± 6.15 and 47.24 ± 5.91, *P* = 0.029) (Table 1). Multivessel disease was more prevalent in the high SYNTAX group (Table 1).

Table 1: Baseline clinical, laboratory, and angiographic data of the study patients

	Low SYNTAX score (n=40)	High SYNTAX score (n=110)	<i>P</i> -value
Age (years)	60.73±12.57	61.53±13.08	0.734
Gender (M/F)	30/10	87/23	0.755
Body mass index (kg/m ²)	25.77±2.13	26.49±2.82	0.147
Smoking, n (%)	13 (32.5)	24 (21.8)	0.202
Diabetes mellitus, n (%)	9 (22.5)	20 (18.2)	0.641
Hypertension, n (%)	12 (30)	22 (20)	0.269
Hypercholesterolemia, n (%)	8 (20)	14 (12.7)	0.299
SBP (mmHg)	130.70±22.95	129.93±21.68	0.854
DBP (mmHg)	82.20±17.21	80.67±16.27	0.628
Laboratory data			
Glucose, mg/dL	106.70±27.28	109.45±26.29	0.584
Creatinine, mg/dL	0.89±0.18	0.92±0.19	0.325
Uric acid, mg/dL	5.00±1.18	5.00±1.15	0.991
Hemoglobin (g/dL)	12.89±1.95	12.99±1.94	0.774
WBC count 10 ⁹ /L	8.52±3.02	8.47±2.92	0.931
Platelet count, 10 ⁹ /L	228.90±55.4	224.65±53.74	0.677
LDL-cholesterol, mg/dL	110.07±40.60	119.52±40.55	0.212
HDL-cholesterol, mg/dL	40.48±8.75	40.13±8.31	0.824
Triglyceride, mg/dL	174.72 (132.0-214.25)	162.00 (128.0-215.0)	0.978
Cardiac Tn, ng/L	172.85 (46.55-497.15)	334.0 (71.77-740.05)	0.108
TSH (uIU/mL)	2.12 (1.55-3.14)	2.27 (1.56-3.19)	0.688
HbA1C (%)	7.07±0.95	7.12±0.97	0.790
Hs-CRP, mg/L	1.77 (1.00-2.20)	2.14 (1.07-10.60)	0.019
LVEF, %	49.75±6.15	47.24±5.91	0.029
Angiographic data			
Number of vessels diseased			<0.001
1	23 (57.5)	17 (15.5)	
2	14 (35.0)	48 (43.6)	
3	3 (7.5)	45 (40.9)	
Chronic occlusion	3 (7.5)	27 (24.5)	0.021
Multi-vessel disease	18 (45)	77 (70)	0.009
SYNTAX score	12.75±4.55	26.09±1.48	<0.001
Decision, n (%)			<0.001
Stent implantation	31 (93.9)	40 (36.4)	
CABG	2 (6.1)	70 (63.6)	
CABG: Coronary artery bypass graft, DBP: Diastolic blood pressure, HbA1C: Glycated hemoglobin, Hs-CRP: High-sensitivity C-reactive protein, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, LVEF: Left ventricle ejection fraction, SBP: Systolic blood pressure, Tn: Troponin, WBC: White blood cell count, M/F: Male/female, TSH: Thyroid stimulating hormone, SYNTAX: Synergy between percutaneous coronary intervention with taxus and cardiac surgery			

When the daily dietary energy and fructose consumption of the patients were compared, total energy (2646.68 ± 333.83 and 2813.90 ± 393.27, *P* = 0.018), carbohydrate (255.35 ± 47.36 and 283.38 ± 74.48, *P* = 0.008), and fructose consumption (10.75 ± 2.04 and 6.86 ± 1.54) were higher in the high SYNTAX score group (Table 2).

Univariate analysis identified LVEF, Hs-CRP, total carbohydrate consumption, total energy consumption, and fructose consumption as significant predictors of high SYNTAX score in patients with NSTEMI. Multivariate analysis identified LVEF [odds ratio (OR): 0.912, 95% confidence interval (CI): 0.831-1.000, *P* = 0.049] and fructose consumption (OR: 1.239, 95% CI: 1.146-1.339, *P* < 0.001) as significant predictors of high SYNTAX score in patients with NSTEMI (Table 3). The Hosmer-Lemeshow test results show that the model was well fitted, as indicated by the positive results of the test ($\chi^2=6.12$; *P* = 0.380).

The predictive value of fructose consumption for predicting high SYNTAX score was confirmed using receiver operating characteristic curve analysis. The cut-off value of fructose consumption was 41.50 (g) (area under the curve: 0.891; 95% CI: 0.830-0.951; *P* < 0.001; sensitivity, 94%, specificity, 73%; positive predictive value, 94.55% and negative predictive value, 72.50%) (Figure 1).

DISCUSSION

To date, no research has been conducted on fructose consumption and coronary atherosclerotic burden in patients with NSTEMI. Our study showed an association between fructose consumption and coronary atherosclerotic burden.

Atherosclerosis is a chronic inflammatory disease of the vascular system that occurs when laminar flow is disrupted, leading to the accumulation of lipid particles and immune cells in the subendothelial space.^[15] When reactive oxygen species

Table 2: Comparison of fructose consumption with daily dietary energy

	Low SYNTAX score	High SYNTAX score	P-value
Energy (kcal)	2646.68±333.83	2813.90±393.27	0.018
Carbohydrate (g)	255.35±47.36	283.38±74.48	0.008
Carbohydrate (TE %)	51.74±15.47	60.37±25.95	0.015
Protein (g)	81.18±35.68	85.26±37.75	0.543
Protein (TE %)	16.44±8.25	17.80±8.55	0.381
Lipid (g)	153.63±13.66	157.17±16.48	0.188
Lipid (TE %)	30.84±5.56	32.93±7.73	0.072
Fructose (g)	34.25±6.56	51.82±6.36	<0.001
Fructose (TE %)	6.86±1.54	10.75±2.04	<0.001

TE: Total energy, SYNTAX: Synergy between percutaneous coronary intervention with taxus and cardiac surgery

Table 3: Predictors of high SYNTAX scores in patients with non-ST elevation myocardial infarction

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Current smoking	1.725	0.774-3.846	0.182			
Gender	1.261	0.539-2.951	0.593			
LVEF	0.898	0.844-0.956	0.001	0.912	0.831-1.000	0.049
Hypertension	1.714	0.754-3.900	0.199			
Diabetes mellitus	1.306	0.538-3.170	0.554			
Triglyceride	1.000	0.996-1.004	0.985			
Hs-CRP	1.193	1.052-1.351	0.006	1.087	0.918-1.288	0.332
Cardiac Tn	1.001	1.000-1.002	0.063			
Creatinine	2.698	0.369-19.721	0.328			
Uric acid	1.002	0.733-1.370	0.990			
Total carbohydrate consumption	1.009	0.982-1.017	0.031	1.004	0.994-1.015	0.401
Total energy consumption	1.001	0.967-1.002	0.020	0.998	0.994-1.001	0.757
Fructose consumption	1.250	1.165-1.341	<0.001	1.239	1.146-1.339	<0.001

LVEF: Left ventricular ejection fraction, Hs-CRP: High-sensitivity C-reactive protein, Tn: Troponin, CI: Confidence interval, OR: Odds ratio

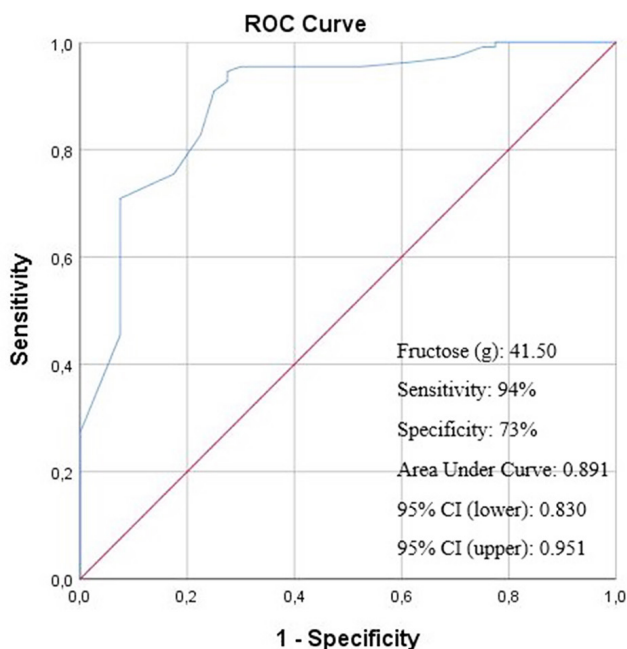


Figure 1: ROC curve analysis for fructose consumption in predicting high SYNTAX scores

ROC: Receiver operator characteristic, SYNTAX: Synergy between percutaneous coronary intervention with taxus and cardiac surgery, CI: Confidence interval

(ROS) oxidize lipid molecules and immune cells, inflammatory responses result and the atherosclerotic cycle begins.^[16] Adenine dinucleotide phosphate oxidase in endothelial cells and ROS originating from mitochondria are the most important free oxygen radicals in vascular beds^[17], and oxidative stress and lipid metabolism play an important role in atherosclerosis in vascular structures as well as in the onset and severity.^[16,18] Fructose transporter (GLUT)-5 facilitates the transport of fructose to the intestinal cell, which is then metabolized via the glycolytic pathway, unlike glucose.^[19] Fructose consumption increases lipid particles, such as fatty acids, and increases the risk of endothelial damage caused by ROS.^[20] According to these data, fructose consumption may promote endothelial damage and oxidative stress, which may lead to the initiation and progression of atherosclerosis. In our study, no difference was observed in lipid parameters or glucose levels between the groups. Perhaps an important reason for this is that our number of patients was small and we calculated fructose consumption differently methodologically.

Conventional risk factors, such as advanced age, gender, dyslipidemia, and smoking, have been associated with CAD severity.^[21] In addition, the relationship between coronary atherosclerotic burden and fructose consumption was investigated in our study. Fructose consumption has been previously classified as moderate (0-50 g/day), high (50-100

g/day), and very high (100-150 g/day).^[22] In our study, more fructose consumption was found in the group with a high SYNTAX score.

There is a strong relationship between inflammation and atherosclerosis.^[23] Hs-CRP is an important inflammatory marker.^[24] In our study, Hs-CRP and increased fructose consumption were found to be higher in the high SYNTAX score group.

Animal experiments have shown that fructose consumption causes inflammation and may contribute to various diseases.^[25,26] In humans, its clinical effects remain unclear. Studies have shown that excessive fructose consumption may cause coronary slow flow and coronary ectasia.^[27,28] CAD development is influenced by inflammation, oxidative stress, and endothelial injury. All these pathogenetic processes are closely related to high fructose consumption, as observed in our study, and increased fructose consumption was found to be associated with coronary atherosclerotic burden. Atherosclerosis is continuous, and one of the factors that can accelerate this process is fructose consumption. As a matter of fact, as seen in our study, fructose consumption may affect the spread of atherosclerosis.

Study limitations

Our study was conducted in only one center with some patients. There are limitations to the study due to food. Although consumption records are a practical method for detecting daily fructose, measuring the amount of fructose in 24 h urine is a more reliable method; however, there are no study examples comparing both methods. In our study, we used the most commonly used method to calculate fructose consumption, but it is less effective than direct measurement. Because of the lack of follow-up, we could not determine whether fructose consumption was associated with significant adverse cardiac events. To address these shortcomings, prospective multicenter studies are needed. Until then, these results should be interpreted cautiously due to the limitations of this study.

CONCLUSIONS

It is unclear how fructose consumption affects the cardiovascular system. Increasing fructose consumption may trigger atherosclerosis in the vascular structures. Finally, we demonstrated that increased fructose consumption can play a role in the mechanisms of coronary atherosclerotic burden in patients with NSTEMI.

Ethics

Ethics Committee Approval: The Çanakkale Onsekiz Mart University Clinical Research Ethics Committee approved the study (decision no: 2022-09, date: 18.05.2022).

Informed Consent: Informed consent was obtained from the participants.

Authorship Contributions

Surgical and Medical Practices: U.K., B.T., K.P., Concept: U.K., B.T., K.P., Design: U.K., B.T., K.P., Data Collection or Processing: U.K., B.T., K.P., Analysis or Interpretation: U.K., B.T., K.P., Literature Search: U.K., B.T., K.P., Writing: U.K., B.T., K.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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