ORIGINAL ARTICLE

High fructose consumption may be associated with slow coronary flow

Artmış fruktoz tüketimi koroner yavaş akımla ilişkili olabilir

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ABSTRACT

Objective: The precise pathophysiology of slow coronary flow (SCF) has not yet been clarified; however, many studies have shown that significant fructose consumption is associated with oxidative stress and inflammation, which may play a role in the pathophysiology of SCF. The aim of this study was to investigate the association between fructose consumption and isolated SCF.

Methods: Patients with stable angina pectoris who underwent coronary angiography between December 2018 and April 2019 were evaluated for this study. In all, 45 patients with isolated SCF were selected as the patient group (SCF group) and 50 patients with a normal coronary flow pattern were enrolled as a control group. Participants used a dietary record to provide details of nutrient consumption and all of the data from the 2 groups were compared.

Results: The high-sensitivity C-reactive protein (Hs-CRP) level (p=0.024), white blood cell count (p=0.038), and smoking rate (p=0.012) were higher in the SCF group. Total energy (p=0.029), carbohydrate (p=0.047), and fructose consumption (p<0.001) were also higher in the SCF group. Multivariable logistic regression analysis demonstrated that a higher level of Hs-CRP, fructose consumption, and smoking were independently associated with SCF.

Conclusion: The SCF group demonstrated a higher level of fructose consumption. Excessive fructose consumption may play a role in SCF pathophysiology.

ÖZET

Amaç: Koroner yavaş akım (KYA) patofizyolojisi tam manasıyla açıklığa kavuşturulamamıştır, dahası artmış fruktoz tüketiminin, KYA patofizyolojisinde rol oynayabilecek oksidatif stres ve inflamasyon ile ilişkili olduğunu gösteren birçok çalışma vardır. Bu çalışmanın amacı, fruktoz tüketimi ile izole KYA arasındaki ilişkiyi araştırmaktır.

Yöntemler: Aralık 2018-Nisan 2019 tarihleri arasında koroner anjiyografi uygulanan kararlı anjina pektorisli hastalar değerlendirildi. İzole KYA'lı 45 hasta, hasta grubu (KYA grubu) ve 50 normal koroner akım paterni (NKAP) olan birey kontrol grubu olarak kabul edildi. Besin tüketiminin ayrıntılarını sağlamak için katılımcılar diyet kaydı kullandı, iki gruptan gelen tüm veriler karşılaştırıldı.

Bulgular: KYA grubunda yüksek-hassasiyetli CRP (Hs-CRP) düzeyleri (p=0.024), beyaz kan hücresi sayısı (p=0.038) ve sigara içme oranı (p=0.012) daha yüksekti. Toplam enerji (p=0.029), karbonhidrat (p=0.047) ve fruktoz tüketimi (p<0.001) KYA grubunda daha yüksekti. Çok değişkenli lojistik regresyon analizleri, daha yüksek Hs-CRP seviyeleri, fruktoz tüketimi ve sigara içmenin KYA ile bağımsız olarak ilişkili olduğunu gösterdi.

Sonuç: Çalışmamızda KYA grubunda fruktoz tüketimi daha yüksektir. Yüksek fruktoz tüketimi, KYA patofizyolojisinde rol oynama potansiyeline sahiptir.

Slow coronary flow (SCF) is an important coronary angiographic phenomenon characterized by delayed progression of angiographic contrast medium in the coronary arteries in the absence of obstructive coronary artery disease.[1] The incidence of SCF in patients undergoing coronary angiography varies between 1% and 7%.[2] SCF is known to be associated with angina pectoris, myocardial infarction, sud-

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den cardiac death, and fatal rhythm disorders.[3] The pathophysiological mechanisms underlying primary SCF are not yet clearly understood. Potential underlying mechanisms, such as microvascular dysfunction, endothelial dysfunction, vasomotor dysfunction, small vessel disease, atherosclerosis, inflammation, oxidative stress, and increased platelet aggregation have been evaluated.[4–6]

Many epidemiological, clinical, and experimental studies have shown that fructose, which is naturally found in fruit and known as fruit sugar, has become the most widely used sweetener in the food industry, and that high intake has been shown to be associated with diseases such as obesity, insulin resistance, impaired glucose tolerance, type 2 diabetes, hyperlipidemia, cardiovascular disease, hyperuricemia, gout, and metabolic syndrome.[7]

A high intake of fructose can advance the atherosclerotic process by increasing the number of low-density lipoprotein (LDL) particles, reducing the quantity of particles with atherogenic effects, increasing the expression of adhesion molecules in endothelial cells, and triggering thrombosis pathophysiology.[8] There are also many studies demonstrating that substantial fructose consumption was associated with oxidative stress and inflammation, which appear to have a role in the pathophysiology of SCF.[9,10]

In light of these findings, the objective of this study was to examine the relationship between fructose consumption and SCF.

METHODS

In all, 496 patients who underwent coronary angiography between December 2018 and April 2019 at a single hospital due to a clinical suspicion based on an exercise stress test, myocardial perfusion scintigraphy, or myocardial ischemia were evaluated. Two groups were formed. Forty-five patients with normal coronary artery anatomy and SCF were selected as the patient group (SCF group), and 50 patients with a normal coronary flow (NCF) pattern were included as the control group.

A detailed medical history was obtained from all of the patients and a complete physical examination was performed. A 12-lead electrocardiogram examination was administered, and transthoracic echocardiography was performed by a cardiologist. Hypertension was identified with at least 3 measurements of systolic blood pressure of 140 mmHg or higher, a diastolic blood pressure of 90 mmHg or higher, or the use of antihypertensive drugs. Diabetes mellitus was diagnosed with a fasting blood glucose of 126 mg/dL or higher or the use of anti-diabetic medication. Hyperlipidemia was defined as a total cholesterol level of 200 mg/dL or higher or a history of statin use prior to the previous 3 months. Patients who had used tobacco products before hospitalization were accepted as smokers. A family history of heart disease was defined as a first-degree male relative (i.e., father or brother) who had a heart attack by age 55 or a first-degree female relative (i.e., mother or sister) by age 65.

Abbreviations:

Cx	*Circumflex*
Hs-CRP	*High-sensitivity C-reactive protein*
LAD	*Left anterior descending*
LDL	*Low-density lipoprotein*
NCF	*Normal coronary flow*
RCA	*Right coronary artery*
SCF	*Slow coronary flow*
TFC	*Thrombolysis in Myocardial Infarction frame count*
TNF-α	*Tumor necrosis factor alpha*

Patients with known coronary artery disease, or a history of acute coronary syndrome, peripheral arterial disease, congestive heart failure with an ejection fraction of <55%, surgical or interventional cardiovascular procedure, stroke, pulmonary hypertension, valvular heart disease, cardiomyopathy, myocardial history, myocardia disease history or renal dysfunction, chronic inflammatory disease, malignancy, active infection, or an endocrine or metabolic disorder other than diabetes mellitus were excluded from the study. Patients who had used an antiaggregant, anticoagulant, corticosteroid, statin, antioxidant vitamins, and/or alcohol in the previous 3 months were also excluded.

In order to measure the fructose consumption and nutritional status of the patients, a trained dietician interviewed participants about food consumption records kept for 3 days (2 weekdays and 1 weekend day).[11,12] Daily food and energy consumption can also be determined with direct measurement methods, such as the doubly labeled water technique.[13] However, these are invasive techniques and more expensive to implement. Currently, 3- and 7-day dietary records are commonly used as a preferred method of assessment.[14,15] However, consumption records may underestimate the true intake of macronutrients and fructose; underestimates range widely from 4% to

37%, depending on the particular study sample.[16] To assess the patients' nutrient consumption status in this study, the daily intake of energy, macronutrients, and fructose was calculated using the Beslenme Bilgi Sistemleri (BeBiS, Nutrition Information System) 7.1 program (BeBiS, Istanbul, Turkey) and the results were analyzed. This nutrient analysis program was designed to include features of the Turkish diet. More than 20,000 foods and more than 130 nutrients can be calculated, including fructose.[17] One experienced interventional cardiologist performed the coronary angiography for all of the study patients and control subjects using the standard Judkins technique. Iohexol was used as a nonionic contrast agent and 6–10 mL was manually injected at the catheter position. Visualization of the coronary arteries was obtained in the standard planes. The coronary flow rate of all of the study participants was documented using the Thrombolysis in Myocardial Infarction frame count (TFC) method described by Gibson et al.[18] The TFC of the left anterior descending (LAD) and the circumflex (Cx) arteries was assessed in either the right anterior oblique projection with caudal angulations or the left anterior oblique projection with cranial angulations, and that of the right coronary artery (RCA) was usually evaluated in the straight left anterior oblique projection.[19] The initial frame was defined as the frame in which concentrated dye occupied the full width of the proximal coronary artery lumen, touching both borders of the lumen, and exhibited forward motion down the artery. The final frame was defined as the frame in which the leading edge of the contrast column initially arrived at the distal end. The last frames used for the LAD, Cx, and RCA were those in which the dye first entered the distal bifurcation segment, also known as the moustache segment, and the first branch of the posterolateral artery. The final count was then subtracted from the initial count and the exact TFC was calculated for the artery. The TFC of the LAD artery was corrected by dividing the final count by 1.7. Due to different durations required for normal visualization of coronary arteries, the corrected cut-off value was 36.2±2.6 frames for the LAD, 22.2±4.1 frames for the Cx, and 20.4±3.0 frames for the RCA, as has been reported previously in the literature.[18] Patients with a TFC >2 SD from the published normal range for any 1 of the 3 vessels were assigned to the SCF group. The mean TFC for each member of the study was calculated by adding the TFC for the LAD, Cx, and RCA and then dividing the obtained value by 3.

The protocol for this study was approved by the local ethics committee and written, informed consent was obtained from all of the participants. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guideline.

Statistical analysis

All of the statistical analyses were performed using IBM SPSS Statistics for Windows, Version 19.0 software (IBM Corp., Armonk, NY, USA). The mean, SD, rate, and frequency values were used as descriptive statistics of the data. The Kolmogorov-Smirnov test was used to evaluate the normality of the distribution of continuous variables. For the analysis of parametric data, Student's t-test was used, and the Mann-Whitney U test was used for the analysis of non-parametric data. A chi-squared test was used to compare categorical variables between groups. Logistic regression analysis was used to determine the impact of variables. Standardized beta coefficients and 95% confidence intervals were calculated. Statistical significance was defined as $p<0.05$.

RESULTS

Baseline clinical and demographic characteristics of the study population are shown in Table 1. There was no statistically significant difference between the groups in terms of age, body mass index, gender, diabetes mellitus, hypertension, dyslipidemia, or family history status. The number of smokers was significantly higher ($p=0.012$) in the SCF group compared with the NCF group. The laboratory findings of the patients and controls are shown in Table 2. There were no statistically significant differences between the groups with the exception of the serum CRP level ($p=0.024$) and white blood cell count ($p=0.038$). A comparison of the daily diet energy, macronutrients, and fructose consumption is provided in Table 3. The total energy ($p=0.029$), carbohydrate ($p=0.047$), and fructose intake ($p<0.001$) values were higher in the SCF group. No significant difference was found when comparing other macronutrients.

Univariate and multiple logistic regression analysis was performed for the major clinical factors and predictors of SCF shown in Tables 1–3. The logistic

Table 1. Baseline characteristics of the study groups (n=95)

Parameters	Patients with NCF (n=50)			Patients with SCF (n=45)			*p* value
	n	%	Mean±SD	n	%	Mean±SD	
Age, years			57.0±10.6			55.1±9.4	0.354
BMI, kg/m^2			27.0±4.3			28.2±5.0	0.218
Female	21	42.0		17	37.8		0.675
Diabetes mellitus	9	18.0		8	17.8		0.977
Hypertension	18	36.0		14	31.1		0.615
Dyslipidemia	13	26.0		17	37.8	0.218	
Family history	4	8.0		9	20.0	0.089	
Smoker	16	32.0		26	57.8	0.012	

Data are given as mean±SD, number, or median (interquartile range). Categorical variables were compared using Pearson's chi-squared test, continuity correction chi squared testing, or Fisher's exact test, as appropriate, and an independent samples t-test and the Mann-Whitney U test were used to compare continuous variables. BMI: Body mass index; NCF: Normal coronary flow; SCF: Slow coronary flow; SD: Standard deviation.

Table 2. Comparison of laboratory findings and TIMI frame counts

Parameters	Patients with NCF (n=50)	Patients with SCF (n=45)	*p* value
	Mean±SD	Mean±SD	
Glucose, mg/dL	116.4±47.6	124.0±59.1	0.509
Creatinine, mg/dL	0.97±0.2	1.01±0.3	0.487
Uric acid, mg/dL	5.5±2.1	5.8±1.4	0.413
WBC count, 10^3/mm^3	9.6±2.3	10.9±2.8	0.038
Hemoglobin, g/dL	13.2±1.7	13.8±1.7	0.175
Platelet count, 10^3/mm^3*	221.0±57.4	231.2 ±64.8	0.311
Total cholesterol, mg/dL*	193.0±86.6	187.2±84.4	0.740
Triglyceride, mg/dL*	160.1±78.9	176.5±88.9	0.679
LDL cholesterol, mg/dL*	116.6±64.7	112.7±59.9	0.790
HDL cholesterol, mg/dL*	45.5±28.0	45.7±26.1	0.967
Hs-CRP, mg/L	3.6±2.3	5.1±3.7	0.024
LVEF, %	58.7±5.2	57.1±4.5	0.100
TFC-LAD	35.9±10.1	15.8±4.9	<0.001
TFC-Cx	28.9±6.3	15.7±6.1	<0.001
TFC-RCA	29.6±4.5	14.8±5.1	<0.001
TFC-mean	31.5±7.0	15.4±5.4	<0.001

Data are given as mean±SD, number, or median (interquartile range). An independent samples t-test and the Mann-Whitney U test were used to compare continuous variables. *: Parameters with abnormal distribution.
HDL: High-density lipoprotein; Hs-CRP: High-sensitivity C-reactive protein; LDL: Low-density lipoprotein; LVEF: Left ventricle ejection fraction; NCF: Normal coronary flow; SCF: Slow coronary flow; TFC: TIMI frame count; TIMI: Thrombolysis in Myocardial Infarction; WBC: White blood cell; SD: Standard deviation.

regression analysis model was found to be significant: Multivariable logistic regression analysis demonstrated that high fructose consumption (p<0.001) and smoking (p=0.027) were independently associated with SCF (Table 4).

DISCUSSION

To the best of our knowledge, this is the first study in the literature to examine the relationship between SCF and fructose consumption. Our results demon-

Table 3. Comparison of daily diet energy, macronutrient, and fructose consumption

Parameters	Patients with NCF (n=50)	Patients with SCF (n=45)	*p* value
	Mean±SD	Mean±SD	
Energy (kcal)	2472.9±571.9	2780.5±678.2	0.029
Carbohydrate (g)	245.5±90.1	285.1±101.2	0.047
Carbohydrate (TE %)	41.4±8.4	41.7±8.9	0.839
Protein (g)	84.4±23.4	90.8±29.2	0.235
Protein (TE %)	14.1±3.0	13.4±2.9	0.251
Lipid (g)	122.6±35.7	137.3±38.8	0.060
Lipid (TE %)	44.5±7.7	44.5±8.4	0.973
Fiber (g)*	26.5±8.1	27.4±8.9	0.632
Fructose (g)	34.2±14.8	48.9±16.9	<0.001
Fructose (TE %)	5.5±2.0	6.9±1.5	<0.001

Data are given as mean±SD, number, or median (interquartile range). An independent samples t-test and the Mann-Whitney U test were used to compare continuous variables. *: Parameters with abnormal distribution. NCF: Normal coronary flow; SCF: Slow coronary flow; TE: Total energy; SD: Standard deviation.

Table 4. Multivariate logistic regression analysis to predict slow coronary flow

	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	*p* value
Smoker	2.908 (1.257–6.725)	0.013	3.086 (1.140–8.353)	0.027
WBC count	1.190 (1.007–1.406)	0.041	1.189 (0.967–1.462)	0.101
Hs-CRP	1.140 (1.001–1.298)	0.048	1.180 (1.020–1.365)	0.069
Fructose consumption	1.058 (1.028–1.090)	<0.001	1.087 (1.037–1.140)	<0.001
Total energy consumption	1.003 (0.998–1.008)	0.023	0.999 (0.997–1.000)	0.188
Total carbohydrate consumption	1.004 (1.000–1.009)	0.059	1.004 (0.993–1.009)	0.129

CI: Confidence interval; Hs-CRP: High-sensitivity C-reactive protein; OR: Odds ratio; WBC: White blood cell.

strated that fructose consumption among individuals with SCF was high and that high fructose consumption was an independent risk indicator for SCF.

While many animal studies have reported that fructose affects inflammatory processes and may be associated with many diseases, human studies have not yet established a safe level of fructose.[20,21] Moreover, the available data clearly show that people are already consuming more sugar than ever before, and this excessive consumption can contribute to a number of health problems.[21] While there is currently no definitive recommendation for daily fructose intake, the World Health Organization stated in its latest proposal that the main objective should be to reduce the ingestion of additional sugar to <5% of total energy intake and that decreasing the quantity of additional sugar consumed in manufactured foods and drinks will also reduce fructose consumption.[21] In a meta-analysis study conducted by Livesey and Taylor[22] to examine individual levels of fructose consumption, 0–50 g/day fructose consumption was classified as moderate, 50–100 g/day was categorized as high, and 100–150 g/day was graded as very high intake. While moderate consumption has potential benefits in controlling glycemia, high and very high consumption create the risk of dysglycemia and dyslipidemia. In our study, the fructose consumption in the SCF group was found to be close to the upper limit of normal according to this classification.

The pathophysiological mechanisms that cause SCF have not yet been clearly demonstrated. Studies have described medial hypertrophy, vascular myointimal proliferation, endothelial degeneration with the change of myofibrillary degenerative foci, and lipo-

fuscin accumulations at electron microscopic level, which may cause endothelial dysfunction in patients with SCF.[23,24] Coronary adrenergic hyperactivity due to high sympathetic activation may cause angina due to slowing of the coronary blood flow. Higher levels of adrenaline and noradrenaline have been detected in SCF patients than in NCF subjects. Therefore, adrenergic hyperactivity has the potential to play a role in the pathophysiology of SCF.[19] In a study conducted by Kurtoglu et al.,[25] vasodilator treatment resulted in improvement in microvascular tone and flow dynamics in SCF patients. In addition, numerous studies have suggested that inflammation plays a part in the pathogenesis of SCF[26,27]

Oxidative stress plays an important role in the pathogenesis of endothelial dysfunction and thus, SCF. Research has demonstrated that high fructose consumption stimulates oxidative stress, leading to an imbalance between free radical production and reduction of endogenous antioxidant levels.[10] Fructose has also been reported to accelerate the production of cardiac and vascular superoxide anions.[28]

There is evidence that high fructose intake is closely related to inflammation, which is thought to play a role in the pathophysiology of SCF.[29–31] In a study conducted by Cigliano et al.,[32] high fructose consumption in rats was found to cause an increase in the tumor necrosis factor alpha (TNF-α) level, indicating systemic inflammation. In another study, rats fed a high fructose diet expressed more immunosuppressive corticosterone than adipose tissue due to the increase in proinflammatory cytokines and macrophages. The levels of TNF-α and other inflammatory cytokines were also high in the liver and liver damage was observed.[33] High fructose intake was also found to be associated with hypothalamic astrogliosis, neuroinflammation, and high oxidative stress.[34]

The Nurses' Health Study and the Nurses' Health Study II found a relationship between high fructose intake and high C-peptide levels, and it has been reported that fructose intake may be a risk factor in the development of insulin resistance and type 2 diabetes.[35] Insulin resistance and diabetes are associated with inflammation.[36] Insulin resistance has the potential to cause SCF through direct effects and inflammation.[37] Hs-CRP is a marker of inflammation. In our study, the glucose level and the Hs-CRP level were high in the SCF group. However, the high blood glucose level may have been due to the level of fructose consumption and the reason for the high level of Hs-CRP. The small size of the study population may have affected the rate of detection.

The arterial endothelium provides a continuous barrier between the blood and the arterial wall, and is a critical component in vascular homeostasis, actively responding to biochemical and physical stimuli through the release of a diverse set of vasoactive substances.[38] In the last 2 decades, there has been evidence that endothelial dysfunction and microvascular dysfunction may play a role in SCF pathophysiology.[39] Excess fructose and fatty acid nutrient overflow into cells prompts the electron transport chain to oxygen to occur without ATP production, and favors a state of increased reactive oxygen species, which potentially leads to oxidative damage within mitochondria.[40] In circumstances of high fructose consumption, oxygen radicals resulting from fructose metabolism and increased LDL in blood plasma invade the endothelium and become oxidized, creating a risk for a subsequent inflammatory response.[41] Monocytes enter the artery wall from the bloodstream with platelets adhering to the area of insult, differentiate into macrophages, and eventually form foam cells. Foam cells die and further propagate the inflammatory process.[41] As a result of all of these pathophysiological changes, endothelial nitric oxide synthase activity and nitric oxide production decreases.[42] Endothelium-dependent vasodilation is disrupted and microvascular dysfunction may be triggered.

In closing, endothelial dysfunction, inflammation, and oxidative stress may play an important role in SCF pathophysiology. All of these pathophysiological processes are closely related to high fructose consumption.

Limitations

The present study is a cross-sectional study with a relatively small sample. In addition, we did not have follow-up data of major adverse cardiac events. Our study used the indirect method of a questionnaire to record fructose consumption. While this is the most commonly used technique, it relies on memory and is not as valuable as direct measurement since the sensitivity is low.[14] Dietary consumption records may underestimate the true intake. Another important limitation is that since all of the study subjects con-

sumed different types of fructose-containing foods, other nutrient factors in the diet that improve diabetes or insulin resistance (e.g., magnesium or chromium) were not considered and could be potential confounders of the findings. Furthermore, fructose consumption was measured by a single dietician. Therefore, our results should be verified with multi-center, prospective, longitudinal studies with a larger sample size. The limitations of this study should be considered when interpreting the results.

Conclusion

To our knowledge, this is the first study in the literature to show that increased fructose consumption may have an effect on coronary flow dynamics and therefore on coronary artery disease. The results of this study have the potential to provide new insight into the pathophysiology of SCF and contribute to new studies. It can be inferred, however, that to help prevent chronic diseases, the use of fructose in the food sector could be controlled, consumption of sugary drinks and other high-fructose products should be limited, and measures should be taken to limit fructose intake in risk groups.

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