

■ Original Article

High fructose intake may be related to carotid artery stenosis

Fruktoz tüketimi karotis arter hastalığı ile ilişkili olabilir

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Abstract

Aim: It is known that high fructose intake is related to cardiovascular diseases but there is a limited number of researches in this era. The objective of this research is to evaluate the relation between Carotid Artery Stenosis (CAS) and high fructose intake.

Material And Methods: The patients are categorized into three groups: Patients with CAS \geq 60% (60 patients), patients with CAS<60% (60 patients) and patients with no carotid atherosclerosis (60 patients). Nutrient intake level of patients is observed and recorded by 24-Hour Dietary Recall Forms and the intake frequency of high-fructose dietary is enquired. Physical activity levels are also evaluated. All the collected data is compared among the groups.

Results: Fructose intake among ordinary people is found to be lower than the patients with CAS<60% (p<0.001). Besides, fructose intake of patients with CAS<60% is lower than fructose intake of patients with CAS \geq 60%. Multivariate regression analysis showed that high fructose intake is an independent risk factor for carotid stenosis over 60% (p<0.001). Fructose intake levels were higher in the calcific plaque group than in the non-calcific plaque group (p<0.001).

Conclusions: We determined a high fructose intake in patients with CAS. In light of our research data, we consider high fructose intake to have a potential role in the pathophysiology of CAS.

Keywords: Carotid artery stenosis; fructose; atherosclerosis

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Received: 18/01/2021 accepted: 03/03/2021

Doi: 10.18663/tjcl.864019

Öz

Amaç: Yüksek fruktoz tüketiminin kardiyovasküler hastalıklar ile ilişkili olduğu bilinmektedir, fakat çalışmalar sınırlıdır. Bu çalışmanın amacı, karotis arter darlığı (KAD) ile yüksek fruktoz tüketimi arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntemler: Hastalar, KAD>60% olan (60 hasta), KAD <60% olan (60 hasta) ve karotis aterosklerotik hastalığı bulunmayan (60 hasta) olarak üç gruba ayrılmıştır. Hastaların geriye dönük 3 günlük besin tüketim kayıtları alınmıştır. Veriler gruplar arasında karşılaştırılmıştır.

Bulgular: Fruktoz tüketimi, KAD<60% olan hastalara göre normal bireylerde daha düşük bulunmuştur ($p<0.001$). Ayrıca, KAD>60% olanlara göre KAD<60% olanlarda fruktoz tüketimi daha düşüktür. Çok değişkenli regresyon analizinde yüksek fruktoz tüketimi 60% üzeri karotis stenozu için bağımsız risk faktörü olarak saptanmıştır ($p<0.001$).

Sonuç: Çalışmamızda KAD olan bireylerde fruktoz tüketimi yüksek saptanmıştır. Çalışmamız artmış fruktoz tüketiminin KAD'a etkisi olabileceğini gösteren literatürde ki ilk çalışmadır.

Anahtar kelimeler: Karotis arter hastalığı; fruktoz; ateroskleroz.

Introduction

Atherosclerosis is a rapidly progressive disease characterized by the hardening and narrowing of the arteries due to the buildup of plaques inside the arteries [1]. The progress of atherosclerosis often causes adverse impacts such as apparent luminal stenosis due to the thickening of arteries and occasional occlusion of peripheral, coronary and carotid arteries [2, 3]. Most of the epidemiologic studies indicate that carotid artery stenosis may be related to ischemic stroke risk [4, 5]. Besides, plaque morphology and the state of the carotid artery lesions have also a significant role in stroke risk [4].

Fructose naturally occurs as a component of the whole fruit. The accompanying fiber which is metabolized as a part of a complete food naturally decelerates and modulates fructose release [6]. The overconsumption of either natural or refined fructose increases in recent years and this increase is believed to have a relation with some diseases such as insulin resistance, type-2 diabetes, hyperglycemia, cardiovascular diseases and especially obesity [7-9].

High fructose intake increases the number of low-density lipoprotein, decreases particle sizes with atherogenic effect, increases the expression of adhesion molecules in endothelial cells and triggers coronary pathophysiology and thus may cause atherosclerosis [10]. Some researches also show the relation between increased fructose intake and oxidative stress and inflammation which have a role in the pathophysiology of carotid artery atherosclerosis [11-14].

In light of these findings, this study aims to evaluate the relationship between fructose intake and CAS.

Material and Methods

We created three groups with the patients applying to our cardiology outpatient clinic between October 2016 and

October 2017. Patients to whom were performed carotid ultrasonography for carotid artery stenosis or to assess cardiovascular risk were included in the study [15]. The patients having carotid ultrasound are categorized into three groups according to the level of stenosis: patients with C less than 60% (CAS<60), patients with carotid artery stenosis more than or equal to 60% (CAS≥60) and the patients without stenosis. The total number of evaluated patients was 543. The evaluation was completed after the number of each group reached 60. During the research, a dietitian surveyed the patients for 70 different types of fructose-rich nutrients (beverages and foods) to determine the intake frequency. The dietitian also recorded the nutrient intake of the patients with 24-hour Dietary Recall Forms. The records of dietary intake data were evaluated with Nutrient Information Systems (BeBIS 7.1) software.

The patients with symptomatic CAS, having cerebrovascular accident 6 months were excluded from this research. The patients with systemic inflammatory disease, acute coronary syndrome, cancer, previous myocardial infarction, congestive heart failure, serious valvular heart disease, chronic obstructive pulmonary disease, respiratory or kidney failure, hematologic disease and active infection were refused from this research. Local Ethical Committee reviewed and approved the research protocol of our study.

Definitions

Hypertension patients: patients with arterial blood pressure ≥140/90 mmHg or using antihypertensive drugs regularly. Diabetes mellitus patients: patients with fasting plasma glucose ≥126mg/dL and/or patients using anti-diabetics or insulin. Hyperglycemia is defined as total cholesterol level ≥200 mg/dL. Body Mass Index (BMI) is a person's weight in kilograms divided by the square of height in meters.



Doppler Ultrasonography Assessment

Esaote s.p.a MyLabClass C (Florence-Italy) and a linear 3-11MHz probe is used for Carotid artery examination. The stenosis classification is based on NASCET (The North American Symptomatic Carotid Endarterectomy Trial) [16].

Computed Tomography Angiography Assessment

Carotid Artery Stenosis was first examined with carotid artery Doppler ultrasound and then the computed tomography (CT). We CT scanned the patients with a CT device and a Philips Brilliance 64 detector.

Statistical Analysis

The collected data were analyzed using SPSS 18.0 statistics software (SPSS Inc., Chicago, IL, USA). Number of each group was adjusted as 60 patients. Because we calculated the minimum number of individuals that should be sampled with 90% power and 0.05 Type I error as at least 46 (R 3.0.1. open source program). The primary effect variable was determined as the QRS angle. 1% change in CAS rate was accepted as clinically relevant. Standard deviation of the primary effect

variable was calculated as ± 0.15 . The student's t-test was used to compare the normally distributed parameters. If there were two groups and the parameters were not normally distributed, we used the Mann-Whitney U test. One-way analysis of variance test was used to compare normally distributed variables between 3 groups. Tukey test was used for post-hoc analysis. Categorical variables were compared by the Chi-Squared test or Fischer's exact test. Major clinical factors and predictors of $CAS \geq 60$ as depicted in Table 1 and 2 were used in univariate and multivariate linear regression analysis. In all statistics $p < 0.05$ was considered statistically significant.

Results

Baseline clinical characteristics and laboratory parameters of the study population are shown in Table 1. Smoking rates were found to be higher in the group of patients with CAS of 60% or more compared to other two groups ($p=0.017$). There was also no difference in terms of biochemical and hematological parameters between the 3 groups except white blood cell (WBC) ($p=0.004$) and platelet count ($p=0.012$).

Table 1. Baseline characteristics and laboratory parameters of groups.

| Variables | Control (n=60) | Carotid artery stenosis <60 % (n=60) | Carotid artery stenosis $\geq 60\%$ (n=60) | Difference between groups by ANOVA | P Value | | |
|---|-------------------|---|---|---|---------------------------------------|----------------------------------|---------------------------|
| | | | | | CAS; <60% vs $\geq 60\%$ CAS | Control vs $\geq 60\%$ CAS | Control vs <60% CAS |
| Age, years | 55,98 \pm 9,07 | 57,43 \pm 9,75 | 59,48 \pm 10,27 | 0,143 | - | - | - |
| Female, n(%) | 27 (45,0%) | 25 (41,7%) | 27 (45,0%) | 0,809 | - | - | - |
| BMI, kg/m ² | 28,14 \pm 2,80 | 28,26 \pm 2,43 | 28,98 \pm 3,00 | 0,200 | - | - | - |
| Diabetes mellitus, n(%) | 51 (34,2) | 47 (31,5) | 51 (34,2) | 0,536 | - | - | - |
| Hypertension, n(%) | 15 (25,0%) | 21 (35,0%) | 24 (40,0%) | 0,207 | - | - | - |
| Hyperlipidemia, n(%) | 19 (29,2%) | 24 (36,9%) | 22 (33,8%) | 0,633 | - | - | - |
| Smoking, n(%) | 15 (37,1%) | 14 (22,2%) | 27 (24,1%) | 0,017 | 0,010 | 0,022 | 0,831 |
| Coronary artery disease, n(%) | 6 (10,0%) | 6 (10,0%) | 8 (13,3%) | 0,799 | - | - | - |
| Peripheral vascular disease, n(%) | 3 (5,0%) | 4 (6,7%) | 8 (13,3%) | 0,217 | - | - | - |
| Grade of carotid artery stenosis, (%) | 0 \pm 0,00 | 30,17 \pm 12,73 | 69,33 \pm 10,53 | <0,001 | <0,001 | <0,001 | <0,001 |
| Calcified plaque, n(%) | 0 (0,0%) | 34 (57,6%) | 33 (55,0%) | <0,001 | 0,854 | <0,001 | <0,001 |
| LVEF, % | 58,0 \pm 4,9 | 57,7 \pm 5,9 | 58,4 \pm 5,0 | 0,769 | - | - | - |
| Glucose, mg/dL | 115,4 \pm 44,1 | 114,2 \pm 44,8 | 129,3 \pm 52,3 | 0,153 | - | - | - |
| Creatinine, mg/dL | 1,00 \pm 0,16 | 1,05 \pm 0,65 | 0,95 \pm 0,21 | 0,403 | - | - | - |
| Uric acid, mg/dL | 5,78 \pm 2,06 | 5,87 \pm 2,06 | 5,98 \pm 2,16 | 0,878 | - | - | - |
| WBC, 10 ³ /mm ³ | 8,4 \pm 2,1 | 9,0 \pm 2,2 | 9,8 \pm 2,4 | 0,004 | 0,068 | 0,001 | 0,120 |
| Hemoglobin, g/dL | 13,4 \pm 1,7 | 13,7 \pm 1,6 | 14,1 \pm 1,6 | 0,088 | - | - | - |
| Platelets, 10 ³ /mm ³ | 236,5 \pm 62,4 | 238,1 \pm 70,0 | 270,5 \pm 71,6 | 0,012 | 0,018 | 0,009 | 0,894 |
| CRP, mg/L | 3,7 \pm 3,7 | 4,0 \pm 3,6 | 4,9 \pm 4,6 | 0,207 | - | - | - |
| Total cholesterol, mg/dL | 184,1 \pm 79,6 | 190,4 \pm 50,2 | 189,8 \pm 46,7 | 0,812 | - | - | - |
| LDL cholesterol, mg/dL | 113,1 \pm 57,3 | 114,3 \pm 42,0 | 115,9 \pm 38,2 | 0,947 | - | - | - |
| HDL cholesterol, mg/dL | 44,0 \pm 24,2 | 45,3 \pm 9,5 | 49,2 \pm 13,1 | 0,206 | - | - | - |
| Triglyceride, mg/dL | 168,1 \pm 145,0 | 167,1 \pm 106,0 | 139,1 \pm 89,0 | 0,391 | - | - | - |

Data are given as mean \pm SD, n (%) or median (lower-upper limit). BMI body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; WBC, white blood cell. Carotid artery stenosis rate was calculated according to NASCET.

Macronutrient and fructose consumption is shown in table 2. Fructose consumption was lower in the control group than CAS<60 group and lower in CAS<60 group than CAS≥60 group (p<0.001). Total energy consumption also different between groups (p=0.011).

In order to determine the variables affecting CAS≥60, we applied multivariate and univariate regression analysis for the significant variables in Table 2 and major clinical factors (Table 3). In univariate regression analysis, CAS≥60% is associated with smoking (p=0.005), platelet (p=0.007) and

WBC (p=0.004) count and fructose intake (p<0.001). In the multivariate regression analysis, higher platelet (p=0.007) and WBC level (p=0.001) and higher fructose intake (p<0.001) are determined as independent risk factors.

Patients with carotid artery stenosis were divided into 2 subgroups as patients with calcific (n=67) and non-calcific (n=53) carotid artery stenosis according to plaque morphological features (Table 4). No statistically significant difference was determined between these parameters except fructose intake (p<0.001).

Table 2. Evaluation of daily fructose and macronutrient consumption of groups.

| | | | | Difference between groups by ANOVA | CAS; <60% vs ≥60% CAS | Control vs ≥60% CAS | Control vs <60% CAS |
|------------------|----------------|---------------|----------------|------------------------------------|-----------------------|---------------------|---------------------|
| Energy (kcal) | 2522,2 ± 646,6 | 2673,7 ± 9,75 | 2877,0 ± 676,0 | 0,011 | 0.015 | 0.004 | 0.16 |
| Carbohydrate (g) | 266,2 ± 100,7 | 269,1 ± 89,6 | 300,0 ± 112,4 | 0,132 | - | - | - |
| Protein (g) | 85,2 ± 28,1 | 90,2 ± 24,4 | 93,2 ± 27,7 | 0,260 | - | - | - |
| Lipid (g) | 119,5 ± 37,5 | 132,2 ± 38,7 | 139,9 ± 39,9 | 0,058 | - | - | - |
| Fiber (g) | 27,1 ± 7,7 | 26,7 ± 7,9 | 27,7 ± 8,4 | 0,235 | - | - | - |
| Fructose (g) | 34,9 ± 12,7 | 37,9 ± 14,2 | 46,4 ± 16,4 | <0,001 | <0,001 | <0,001 | <0,001 |

Data are given as mean ± SD, n (%) or median (lower-upper limit). TE, total energy. Carotid artery stenosis rate was calculated according to NASCET.

Table 3. Multivariate logistic regression analysis showing the predictors for ≥60% carotid artery stenosis .

| Variables | Univariable | | Multivariable | |
|----------------------|---------------------|---------|----------------------|---------|
| | Beta (95% CI) | p value | Beta (95% CI) | p value |
| Diabetes mellitus | 0,786 (0,337-1,832) | 0,577 | - | - |
| Hypertension | 1,556 (0,814-2,972) | 0,181 | - | - |
| Hyperlipidemia | 1,037 (0,544-1,974) | 0,913 | - | - |
| Smoking | 2,567 (1,329-4,959) | 0,005 | 3,774 (1,740 -8,186) | 0,059 |
| Platelets | 1,007 (1,002-1,011) | 0,007 | 1,004 (1,002-1,012) | 0,007 |
| White blood cell | 0,814 (0,701-0,944) | 0,004 | 0,743 (0,623-0,887) | 0,001 |
| Energy consumption | 1,005 (0,995-1,015) | 0,069 | - | - |
| Fructose consumption | 1,045 (1,023-1,069) | <0,001 | 1,054 (1,027-1,082) | <0,001 |

CI, confidence interval

Discussion

This is one of the preliminary researches in the literature exploring the relationship between CAS and fructose intake. We determined in our research that patients with CAS have a high fructose intake. Also, this research shows that the overconsumption of fructose may be an independent risk factor for CAS.

While scientific researches in animals report that fructose affects the inflammatory processes and may be related to many diseases [17, 18], the researches in human bodies have not revealed the safe dose of fructose for human intake yet. The consumption of sugar and sweetened food increases every year and this increase is believed to be responsible for a series of emerging diseases. World Health Organization's

(WHO) current suggestion is to decrease the energy from the added sugar below 5% and WHO states that the a decrease in the consumption of added sugar from the manufactured beverages and packaged food will also decrease the intake of fructose [19]. The mild level of intake was considered to be helpful in glycemic control but high and very high fructose intake was stated to have the risk of dysglycemia and dyslipidemia [20]. In this classification, the patients with CAS≥60 determined to have a fructose intake close to the upper limit of mild consumption. Although there is no certain medical treatment procedure developed for CAS today, the use of some therapeutic drugs such as statins, antiplatelet drugs, antihypertensive in combination with a healthy lifestyle will lead to the positive progress of the disease [15].

**Table 4.** Baseline characteristics and laboratory parameters of the patients according to plaque calcification.

| Variables | Calcified plaque group (n=67) | Non-calcified plaque group (n=53) | p value |
|---|-------------------------------|-----------------------------------|---------|
| Age, years | 59,62 ± 9,94 | 57,57 ± 10,06 | 0,259 |
| Female, n(%) | 29 (43,3%) | 23 (43,4%) | 0,990 |
| BMI, kg/m ² | 28,36 ± 2,85 | 28,97 ± 2,58 | 0,254 |
| Diabetes mellitus, n(%) | 16 (23,9%) | 6 (11,3%) | 0,077 |
| Hypertension, n(%) | 27 (40,3%) | 18 (34,0%) | 0,570 |
| Hyperlipidemia, n(%) | 24 (35,8%) | 22 (41,5%) | 0,524 |
| Smoking, n(%) | 20 (28,9%) | 21 (39,6%) | 0,262 |
| Coronary artery disease, n(%) | 9 (13,4%) | 5 (9,4%) | 0,498 |
| Peripheral vascular disease, n(%) | 6 (9,0%) | 6 (11,3%) | 0,668 |
| Grade of carotid artery stenosis, (%) | 47,42 ± 22,70 | 53,04 ± 23,16 | 0,185 |
| LVEF, % | 58,0 ± 5,2 | 58,1 ± 5,8 | 0,841 |
| Glucose, mg/dL | 123,5 ± 55,1 | 119,6 ± 40,7 | 0,664 |
| Creatinine, mg/dL | 1,01 ± 0,26 | 0,99 ± 0,68 | 0,872 |
| Uric acid, mg/dL | 5,91 ± 2,10 | 5,93 ± 2,13 | 0,955 |
| WBC, 10 ³ /mm ³ | 8,5 ± 2,1 | 8,9 ± 2,7 | 0,274 |
| Hemoglobin, g/dL | 13,7 ± 1,5 | 14,0 ± 1,7 | 0,290 |
| Platelets, 10 ³ /mm ³ | 255,1 ± 82,6 | 253,2 ± 65,6 | 0,890 |
| CRP, mg/L | 4,6 ± 3,5 | 4,3 ± 3,7 | 0,733 |
| Total cholesterol, mg/dL | 192,6 ± 43,5 | 187,0 ± 54,0 | 0,531 |
| LDL cholesterol, mg/dL | 114,8 ± 39,3 | 115,6 ± 41,2 | 0,913 |
| HDL cholesterol, mg/dL | 47,3 ± 10,7 | 47,3 ± 12,7 | 0,975 |
| Triglyceride, mg/dL | 147,2 ± 82,8 | 160,7 ± 117,0 | 0,464 |
| Fructose (g) | 36,56 ± 13,80 | 45,12 ± 16,24 | <0,001 |

Data are given as mean ± SD, n (%) or median (lower-upper limit). BMI body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; WBC, white blood cell. Carotid artery stenosis rate was calculated according to NASCET

Oxidative stress has a significant role in endothelial dysfunction so in CAS pathogenesis [21-25]. Many researches state that high fructose intake induces oxidative stress by causing a decrease in the level of endogenous antioxidants and free radical production [12]. It is also reported that fructose increases the production speed of cardiac and vascular superoxide anions [26].

We have findings showing that high fructose intake is closely related to the inflammation that has a role in the pathophysiology of CAS [27]. Cigliano et al. determined in their research that the high fructose feeding in rats caused an increase in TNF- α levels which is an indication of systemic inflammation [28]. Another research determined that the high fructose diet in rats caused adipose tissue to express more immunosuppressive corticosteroids due to an increase in pro-inflammatory cytokines and macrophages. Besides, the TNF- α and other inflammatory cytokines increased in the liver and liver destruction was observed [29]. Another research stated that high fructose intake had a relationship with hypothalamic astrogliosis, neuroinflammation and high oxidative stress [30].

Limitations of the Study

The present study is a cross-sectional study with relatively small sample size. We don't have follow up on major adverse cardiovascular events data. So, our results should be verified in the multi-center prospective longitudinal studies with larger sample size. In addition, there is no evaluation system, which determines the diffuseness and severity of carotid artery disease, like SYNTAX score. The limitations of this study should be considered while interpreting the results.

Conclusion

This is one of the preliminary researches in the literature showing the the relationship between increased dietary fructose intake and CAS progress. Consequently, we can deduct that decreasing the consumption of high-fructose nutrients will have a constructive effect on the progress of atherosclerotic cardiovascular diseases. Additionally, this research will contribute to understand the pathophysiology of atherosclerosis and have the potential to enlighten new researches.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest

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