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The Relationship between Daily Fructose Consumption and Oxidized Low-Density Lipoprotein and Low-Density Lipoprotein Particle Size in Children with Obesity

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ABSTRACT

Purpose: Obesity has become a very significant health problem in childhood. Fructose taken in an uncontrolled manner and consumed in excessive amounts is rapidly metabolized in the body and gets converted into fatty acids. This single center prospective case-control study aims to investigate the relationship between fructose consumption and obesity and the role of fructose consumption in development of atherosclerotic diseases.
Methods: A total of 40 obese and 40 healthy children who were of similar ages (between 8 and 18 years) and sexes were included in the study. In the patient and control groups, the urine fructose levels, as well as the levels of oxidized low-density lipoprotein (LDL), small dense LDL, Apolipoprotein A and Apolipoprotein B values, which have been shown to play a role in development of atherosclerotic diseases, were measured.
Results: The levels of oxidized LDL and small dense LDL and the ratio of Apolipoprotein A/Apolipoprotein B were found to be significantly higher in the patient group.
Conclusion: We found that urinary fructose levels were higher in the obese children than the healthy children. Our results suggest that overconsumption of fructose in children triggers atherogenic diseases by increasing the levels of small dense LDL and oxidized LDL and the ratio of Apolipoprotein B/Apolipoprotein A.

Keywords: Eating; Dyslipidemias; Fructose; Child; Obesity

INTRODUCTION

The problem of our age, obesity, is an energy metabolism disorder in which excess body fat accumulates in the body. The prevalence of the disease has increased also in children like in adults, whereas the prevalence of complications of diseases such as cardiovascular disease, psychological disease and hypertension in childhood has increased, too [1,2].

Genetic and environmental factors (such as sedentary lifestyle, malnutrition habits) play a role in the epidemiology of obesity, which is a multifactorial disease [3]. One of the most important environmental factors in the epidemiology of obesity is overconsumption of high-calorie beverages in which fructose is used as a sweetener in recent years. It has been revealed that overconsumption of fructose causes obesity regardless of other nutrients taken [4]. It is believed that overconsumption of fructose contributes to the epidemiology of atherosclerotic disease, one of the most important complications of obesity, not only by causing obesity, but also by leading to formation of dyslipidemia [4,5].

Although the exact cause of atherosclerosis is not known, the "response-to-injury hypothesis" is accepted in general. Smoking, high low-density lipoprotein (LDL)-cholesterol, oxidized LDL (ox-LDL), hypertension, small dense LDL (sd-LDL) and degenerative changes are factors leading to the epidemiology of atherosclerotic diseases [6,7]. sd-LDL particles have a high susceptibility to oxidation and a low affinity for LDL receptors. As their half-life is longer, it is difficult to remove them from circulation. The fact that they stay longer in the serum increases their possibility of being oxidized and the risk of developing atherosclerosis. ox-LDL and sd-LDL levels, therefore, are used as markers to evaluate the risk of developing atherosclerosis [8-11].

This study aims to examine the relationship between overconsumption of fructose in children and ox-LDL and sd-LDL levels used to predict development of atherosclerotic diseases.

MATERIALS AND METHODS

Determination of groups

This study was carried out between June 2012 and January 2014 at the Pediatrics Clinic of GATA (Gülhane Military Medical Academy, [Gülhane Training and Research Hospital since 2016]). A total of 40 children with obesity (20 male and 20 female children) aged between 8 and 18 who were diagnosed with obesity formed the patient group. Those who were previously diagnosed with obesity, who were using any medicines or herbal products, who had a syndromic, endocrinologic or chronic disease, or who had a family history of dyslipidemia were excluded from the study. Moreover, a total of 40 healthy children who were of similar ages and sexes with to the patient group, who did not take any medication and diet therapy, had a body mass index (BMI) below the 85th percentile, and who had no family history of dyslipidemia were assigned as the control group.

Clinical evaluation

The medical history of all participants included in the study was taken, and physical examinations were performed. Anthropometric measurements including body weight, height, waist and hip circumference measurements were made. Arterial blood pressure measurements of all children were performed.

Anthropometric measurements were made with an empty bladder and on an empty stomach in the morning, without shoes. Height was measured with a wall-mounted and fixed stadiometer, measuring to the nearest 0.1 cm, and weight was measured with a digital scale, measuring to the nearest 0.1 kg (Seca®, Hamburg, Germany). All anthropometric measurements were made according to The International Society for the Advancement of Kinanthropometry (ISAK)-standards with the same method and by the same professional. BMI percentiles and standard deviation values were obtained by using percentile curves

prepared by the Centers for Disease Control and Prevention according to sex and age. Values of 95th percentile and above were accepted as obesity.

Determination of food and nutrient consumption status

The nutrition and food consumption statuses of all individuals in the study were determined by a dietician using the Nutritional Information System (BEBİS) [12] software with the 3-day food consumption record method.

A standard food consumption registration form was used to determine the 3-day food consumption status of the children included in the study. The food consumption registration form was filled on the days of Sunday, Monday, Tuesday or Thursday, Friday and Saturday (one day on the weekend, two days on weekdays). Explanations and controls were provided by the same dietician.

The 3-Day Food Consumption Form data were entered into the BEBİS program. Thanks to the evaluation and conversion with the program, the daily average of 3-day food consumption and the following food items was recorded. The recorded daily average parameters were determined as follows: energy intake (kcal/day), protein intake percentage (%), fat intake percentage (%), fat intake amount (g), carbohydrate intake percentage (g), carbohydrate intake amount (g), fructose intake percentage (%), fructose intake amount (g), and cholesterol intake amount (g).

Biochemical measurements

To determine the levels of fasting plasma glucose (FPG), total cholesterol (Tchol), triglyceride (TG), high-density lipoprotein (HDL), LDL, Apolipoprotein A (apoA), Apolipoprotein B (apoB), ox-LDL and sd-LDL, 8 mL venous blood samples obtained after 12 hours of fasting were taken into routine biochemistry tubes (Vacuette®; Greiner Bio-One, Kremsmünster, Austria) without any additives.

To determine fructose consumption, following the disposal of the first urine in the morning, 24-hour urine was collected by the participants into a container without any additives.

Collection, preparation and storage of samples

Blood samples obtained after 8–12-hour fasting were quickly separated from plasma/serum by centrifugation at 4,000 rpm for 15 minutes. The plasma layer was quickly placed into a cryotube and kept in a refrigerator at −80°C. To determine fructose consumption, 24-hour urine samples collected and were rapidly centrifuged at 4,000 rpm for 15 minutes, and the supernatant layer was quickly placed into a cryotube and kept in a refrigerator at −80°C.

The levels of FPG, alanine aminotransferase (ALT), Tchol, TG, and HDL were measured using Olympus original kits in an Olympus AU2700 auto analyzer (Beckman-Coulter, Inc., Fullerton, CA, USA). apoA and apoB immunoturbidimetric, LDL and sd-LDL enzymatic, urine creatinine measurement was performed with the Jaffe methods using an Olympus AU2700 device (Beckman-Coulter, Inc.). LDL particle size measurement was made by the defecation method using a 'small dense LDL cholesterol kit' (Cat no: CSB-E13350h, Cusabio Technology LLC, Houston, TX, USA). Serum ox-LDL levels were measured using an Ox-LDL ELISA Kit (Cat No: E0527h, USCN Life Science Inc., Wuhan, China) as specified in the manufacturer's test guide. Fructose measurement was made using a Fructose Assay kit (ab83380 Fructose Assay Kit; Abcam, Cambridge, UK).

Statistical analysis

The data were processed and analyzed by using the SPSS for Windows 15.0 package program (SPSS Inc., Chicago, IL, USA). In descriptive statistics, frequencies and percentages were used for the discrete variables, and mean ± standard deviation (SD) values were used for the continuous variables. Chi-squared (χ^2) test was used to compare the discrete variables in the patient and control groups, while Student's *t*-test and Mann–Whitney U-test were used to compare the continuous variables. The relationship between variables was evaluated with the Spearman's correlation coefficient. $p<0.05$ was accepted as statistically significant.

Ethics approval

Ethics committee approval (dated 30.05.2012 and numbered 2012-026) was obtained from the Non-Pharmaceutical Clinical Research Ethics Committee of Ankara Pediatrics Hematology Oncology Training and Research Hospital, Ministry of Health, Turkey. The manuscript does not contain clinical studies.

RESULTS

Table 1 shows the demographic characteristics of the patient and control groups. There were 40 participants (20 males, 50%; 20 females, 50%) in the patient group. There were also 40 participants (20 males, 50%; 20 females, 50%) in the control group. There was no difference between the patient group and the control group in terms of age and sex.

The BMI, standardized BMI, waist circumference, hip circumference, waist-to-hip ratio, body fat percentage and systolic and diastolic blood pressure values of the patient group were significantly higher than those of the control group ($p<0.001$).

The 3-Day Food Consumption Record parameters of the patient and control groups were evaluated. There was no statistically significant difference between the patient group and the control group in terms of daily energy intake, protein intake percentage and amount, fat intake amount and fructose intake amount.

We compared biochemical parameters of the patient group and the control group, there was no statistically significant difference in the FPG and Tchol values between the patient group and the control group. The levels of ALT and LDL and the values of TG of the patient

Table 1. Demographic characteristics of the patient group and the control group

Variable	Patient group (n=40)	Control group (n=40)	*p*-value
Sex			>0.999
Male	20 (50.0)	20 (50.0)	
Female	20 (50.0)	20 (50.0)	
Age (y)	12.62±2.25	12.67±1.93	0.881
BMI (kg/m²)	28.79±3.90	18.70±2.47	<0.001
BMI-SDS	2.03±0.29	0.00±0.68	<0.001
Waist circumference (cm)	87.80±10.16	62.18±6.65	<0.001
Hip circumference (cm)	99.20±10.77	76.86±8.39	<0.001
Waist to hip ratio	0.88±0.08	0.81±0.04	<0.001
Body fat percentage (%)	40.32±7.39	17.58±6.60	<0.001
Systolic blood pressure (mmHg)	116.37±12.54	105.62±11.78	<0.001
Diastolic blood pressure (mmHg)	74.98±8.96	67.00±9.18	<0.001

Values are presented as number (%) or mean±standard deviation.
BMI: body mass index, BMI-SDS: standardized BMI.

Table 2. Urinary fructose, apoA, apoB, apoA/apoB, oxidized LDL, sd-LDL values of the patient group and the control group

Variable	Patient group (n=40)	Control group (n=40)	p-value
Urinary fructose (mg/dL)	16.87±12.82	10.50±13.47	0.000
ApoA (mg/dL)	73.86±36.14	135.36±35.04	0.000
ApoB (mg/dL)	111.58±42.57	73.65±24.46	0.000
ApoA/ApoB	0.75±0.45	2.24±1.84	0.000
Oxidized LDL (ng/mL)	3.12±0.82	2.28±1.47	0.023
sd-LDL (mg/dL)	25.60±16.48	11.19±7.94	0.000

Values are presented as mean±standard deviation.
ApoA: Apolipoprotein A, ApoB: Apolipoprotein B, LDL: low-density lipoprotein, sd-LDL: small dense LDL.

group were significantly higher than those of the control group ($p=0.000$, $p<0.001$, $p<0.001$, respectively). The HDL levels of the patient group were significantly lower than those of the control group ($p=0.000$).

Table 2 shows the urine fructose values, apoA values, apoB values, apoA/apoB ratio, ox-LDL values and sd-LDL values of the patient and control groups. The urine fructose values, apoB values, ox-LDL values and sd-LDL values were found to be significantly higher in the patient group ($p=0.000$, $p=0.000$, $p=0.023$, $p=0.000$, respectively).

The apoA and apo A/apo B ratio values were significantly lower in the patient group ($p=0.000$, $p=0.000$, respectively).

Table 3 shows the results of the correlation analysis of the biochemical parameters in the patient group. There was a significant and moderate negative correlation between the urine fructose levels and apoA/apoB and a moderate positive correlation between the urine fructose levels and apoB values.

DISCUSSION

Obesity occurs when the body's energy balance is positive, and it is directly related to consuming excessive carbohydrates and fats with nutrients [13,14]. How much of the energy that is taken is derived from fats, proteins and carbohydrates and the types and rates of carbohydrates consumed play an important role in development of obesity. The most commonly used method for determining food consumption in children today is the method where 3–7-day food consumption records are kept, and the amount of food consumption is

Table 3. The correlation analysis of biochemical parameters in the patient group

Correlation analysis		Urinary fructose	ApoA	ApoB	Oxidized LDL	sd-LDL
ApoA	r	−0.239				
	p	0.033				
ApoB	r	0.342	−0.350			
	p	0.002	0.001			
Oxidized LDL	r	0.115	−0.088	0.115		
	p	0.311	0.439	0.311		
sd-LDL	r	0.248	−0.424	0.405	0.273	
	p	0.027	0.000	0.000	0.14	
ApoA/ApoB	r	−0.354	−0.839	−0.743	−0.163	−0.551
	p	0.010	0.000	0.000	0.149	0.000

If p-value <0.05 and r<0.2 there is very poor correlation or no correlation, If p-value <0.05 and 0.2≤r<0.4, there is poor correlation, If p-value <0.05 and 0.4≤r<0.6, there is moderate correlation, If p-value <0.05 and 0.6≤r<0.8, there is high correlation, If p-value <0.05 and r≥0.8, there is strong correlation.
ApoA: Apolipoprotein A, ApoB: Apolipoprotein B, LDL: low-density lipoprotein, sd-LDL: small dense LDL, r: correlation coefficient, p: significance value.

measured. When the 3-day food consumption records were examined in this study, there was no statistically significant difference between the patient group and the control group in terms of daily energy, protein, fat, carbohydrate and fructose amounts. The result of this study showed that 3-day food consumption records were insufficient in determining the average amount of food consumption in children and supported justification of the aforementioned reasons.

Vigorous efforts proceed to find methods and markers that can accurately measure food consumption amounts and contents, rather than keeping food records in pediatric patients. Accordingly, studies to measure daily fructose consumption show that urine fructose amount measurement provides much more accurate and reliable results than measurements made by keeping food consumption records. Studies show that non-absorbable fructose from ultrafiltration is reliable in determining the amount of daily consumed fructose in both people with obesity and normally weighted individuals, urine fructose content measurement accurately reflects fructose consumption, and this may be used as a biomarker to determine daily fructose consumption [15]. In our study, no significant difference was found in fructose consumption between the patient and control groups by the food consumption records, while the urine fructose levels in the patient group were significantly higher than the control group by the results of the 24-hour urinary fructose levels measurement. This result showed that it is not a reliable method to detect daily fructose intake through food consumption records in children, instead, 24-hour urinary fructose amount measurement would be a more reliable method.

It was reported that today, overconsumption of fructose causes fat storage especially in the abdominal region, while it also increases the risk of developing obesity-related complications such as atherosclerotic diseases [16]. Moreover, recent studies have reported that fructose consumption is directly related to blood lipid levels [17,18]. In our study, the TG and LDL levels in the children with obesity were found to be significantly higher than those in the control group, while the HDL levels were found to be significantly lower. Our results strongly supported studies which argued that overconsumption of fructose is associated with development of dyslipidemia in children.

The factor that initiates the formation of atherosclerosis, the most significant complication of obesity, is the oxidation of LDL in the endothelium. Endothelial cells and lipoxygenase enzyme produced in monocytes/macrophages may lead to conversion of unsaturated fatty acids to lipid hydroperoxides and subsequently to ox-LDL [19-21]. Factors affecting LDL oxidation may be listed as fatty acid composition, antioxidant content of LDL, phospholipase A2 activity, LDL particle size and density [22]. Obesity is accompanied by the presence of high TG concentration, low density of HDL and sd-LDL [16]. By accelerating uncontrolled lipid synthesis, overconsumption of fructose plays a role in increasing oxidation [17]. Ross et al. [18] revealed that a fructose-rich diet increases metabolic syndrome and oxidative stress. In accordance with the literature, we found in this study that the ox-LDL levels were significantly higher in the children with high fructose consumption. These results supported the results of studies showing that overconsumption of fructose increases the oxidation of LDL.

By increasing fatty acid synthesis, esterification of fatty acids and secretion of very-low-density lipoprotein, overconsumption of fructose induces cardiovascular diseases by increasing the amounts of serum triacylglycerol (TAG) and LDL cholesterol [22]. sd-LDL particles were found together with increased TG and decreased HDL-cholesterol levels. This is called 'atherogenic dyslipidemia' [23]. The relationship between sd-LDL cholesterol and the risk

of having coronary heart disease at an early age exists in studies showing that it is independent of lipid factors such as HDL cholesterol and TGs, non-lipid risk factors and apoB levels [8,24]. Aeberli et al. [25] reported that LDL particle size was smaller in children aged between 6 and 14 with high fructose consumption, while TAG levels were higher, and HDL concentrations lower. In our study, we found that the sd-LDL levels were significantly higher in the children with obesity with high urinary fructose levels in comparison to the control group.

Apolipoproteins are responsible for the further metabolism and catabolism of inactive lipid particles in the structure of lipoproteins. It was revealed that overconsumption of fructose increases hepatic *de novo* lipogenesis through various mechanisms and triggers dyslipidemia and development of atherogenicity [22]. In this study, we found that the level of apoA, which shows anti-atherogenic properties, in the patient group with high fructose consumption was significantly lower than that in the control group, whereas the apoB level, whose atherogenic effect was proven, was significantly higher in the patient group in comparison to the control group. The apoB/apoA ratio was found to be high in people with each component of metabolic syndrome, and this ratio was shown to increase as the number of these components increases [26]. Wallenfeldt et al. [27] confirmed the relationship between the apoA/apoB ratio and metabolic syndrome components and reported that the probability of progressive changes in carotid intima-media thickness is related to the apoA/apoB ratio. This result confirmed a previous report showing that a decreased apoA/apoB ratio in patients with metabolic syndrome increases the degree of angiographically shown coronary artery disease [27]. In our study, we found that the apoA/apoB ratio was significantly lower in the group with high fructose consumption. These results strongly supported the results of studies reporting that overconsumption of fructose increases the risk of atherogenic diseases.

Consequently,
1. The 24-hour urinary fructose levels were significantly higher in the children with obesity than the control group. Measurement of fructose content in 24-hour urine is more reliable than the food consumption records method in determining fructose consumption in children.
2. The children with obesity were found to has more urinary fructose excretion than the healthy children. This supported the thesis that excessive fructose consumption plays a role in development of obesity in children.
3. We found that the biological particles (ox-LDL, sd-LDL, and apoB) inducing atherogenic diseases were higher in the group that was overconsuming fructose. We found a moderate negative correlation between the urinary fructose levels and apoA/apo B and a moderate positive correlation between the urine fructose levels and apo B values. Overconsumption of fructose contributes to development of atherosclerotic diseases at an early age.

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