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Fructose Consumption is Associated with Non-Alcoholic Fatty Liver Disease Risk: A Case-Control Study from Iran

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Abstract

Objectives: This study aimed is to evaluate the association between dietary fructose intake and risk of nonalcoholic fatty liver disease (NAFLD).

Methods: Newly diagnosed patients with NAFLD and age matched controls were asked about their dietary intakes. Fructose consumption was assessed using a reliable and valid food frequency questionnaire and fructose intake was calculated using food composition table.

Results: In the crude model, subjects in the highest quartile had more than 3.08 times higher risk of NAFLD in comparison to those in the lowest quartile of the fructose intake (OR: 3.08; 95 percent CI: 1.87 - 5.06), ($P < 0.001$). Also, adjustment for age, sex, physical activity (MET-h/wk), body mass index (kg/m^2), energy intake (kcal/d) and simple sugar strengthened this association (OR: 3.54; 95 percent CI: 1.81 - 6.93) ($P = 0.003$).

Conclusions: Our results indicate that higher intake of fructose is significantly associated with the higher risk of NAFLD; this association remained significant after adjustment for known confounding factors. Further studies are required to find the cut point for safe daily fructose consumption alone or in combination with dietary fiber sources.

Keywords: Carbohydrate, Fatty liver, Fructose, Sucrose, Non-alcoholic Fatty Liver Disease

1. Background

Non-alcoholic fatty liver disease (NAFLD) is characterized by an accumulation of excess fat in the hepatocytes (1). The prevalence of disease is rapidly increasing in the world in association with growing prevalence of obesity (2-4).

Although no specific pharmacological treatment currently exists for NAFLD, the beneficial effects of lifestyle interventions such as weight loss and physical activity have been reported (5). Limited studies have shown that specific dietary factors are related to NAFLD management (6-9); however, studies are limited for the role of dietary components on prevention of the disease.

It has been shown that high fructose diet can induce NAFLD in experimental models of the disease (10, 11) through elevation of de novo lipogenesis, triglyceride formation and hepatic and skeletal muscle insulin resistance, postprandial hypertriglyceridemia, inflammation, obesity and suppression of β-oxidation of long-chain fatty acids (12-15).

2. Objectives

However, the studies in human subjects are scarce. Due to ethical issues, it is almost impossible to conduct clinical trials to evaluate the effects of high fructose diet in human subjects. Thus, we designed this case-control study to assess the association between fructose consumption and risk of NAFLD.

3. Methods

Study protocol details were reported previously (16, 17). Briefly, 169 patients with NAFLD and 782 controls were recruited from a tertiary hepatology clinic. The participants' enrollment flow chart is shown in Figure 1. Candidates had to be aged between 20 and 75 years to be included in the study. They were selected using convenience-sampling method based on inclusion criteria. Case participants were patients with NAFLD diagnosed by a gastroenterologist within previous month, and the diagnosis was confirmed by fibroscan results of controlled attenuation parameter (CAP) score of more than 263, and fibrosis score > 7. Control participants were individuals aged between

20 and 75 years who were recruited from the same clinic among subjects who had an ultrasound (US) exam with no evidence of hepatic steatosis. Cases and controls were matched in terms of age (± 5). All participants provided their written informed consent.

3.1. Dietary Assessment

Usual dietary intakes of the study participants during the preceding year (during the year before the diagnosis of NAFLD in the case group and during the year before the US exam in the control group) were examined using a valid and reliable semi-quantitative food frequency questionnaire (FFQ) (18-20). The FFQ consisted of 148 food items with standard portion sizes commonly consumed by this population. Trained interviewers, who were experienced in completing such questionnaires, administered the FFQ through face-to-face interviews. Interviews with all participants were conducted in the presence of individuals who were involved in the preparation and cooking of foods. Participants were asked to indicate their usual consumption frequency of foods containing fructose in the preceding year on a daily, weekly or monthly basis. All reported consumption frequencies were converted into grams per day using household measures. Then, mean daily intakes of energy, fructose and other nutrients for each individual were assessed using the United States Department of Agriculture (USDA) food composition table (21).

An expert dietician measured anthropometric indices. The interviewer was totally unaware of the research hypotheses; however, he was aware of the participants' condition. Participants' demographic information were collected through interview using the required questionnaires.

3.2. Statistical Analysis

Sample size was calculated with 80% power, type I error of 0.05 and desired CI of 95%, and the minimum required sample size was calculated to be 120 cases and 720 control subjects. All analyses were conducted using SPSS version 20 (SPSS Inc., Chicago, IL, USA). For assessment of differences in the of categorical and continuous variables, we used chi-square and independent *t* test respectively. Fructose intakes were categorized into tertiles. The first tertile provided the reference category for all regression analyses. Odds ratios (ORs) and the corresponding 95 percent confidence intervals (CIs) for tertile categories of dietary fructose intakes were derived from the multiple logistic regression. For comparison purposes, a base regression model and a fully adjusted model for each analysis was calculated. Estimates were presented in three models; the first model was crude. In the second model, we controlled analysis for age and sex, and in the third model, further adjustments were done for age, sex, physical activity (MET-h/wk), body mass index (kg/m^2), alcohol, energy intake (kcal/d), and simple sugar. All P values were based on two-sided tests and were considered statistically significant if $P < 0.05$.

4. Results

Table 1 demonstrates the baseline characteristics of study participants in two groups. Patients with NAFLD had significantly higher body mass index (BMI), serum level of fasting blood sugar (FBS), triglyceride (TG), LDL-cholesterol, lower physically activity and lower level of HDL-cholesterol compared with control group ($P < 0.01$). Furthermore, patients had significantly higher intakes of protein (percent of energy), total fat, poly unsaturated fatty acids (PUFAs), simple sugar, dietary fiber, fruits, vegetables, fructose, sucrose and lower intake of total energy (kcal), saturated fatty acids (SFAs) and mono unsaturated fatty acids (MUFAs) in comparison to controls ($P < 0.01$) (Table 1).

Basic characteristics and dietary intakes of study participants by quartiles of total dietary fructose intake are demonstrated in Table 2. Higher fructose intake was associated with older age, male sex and higher total energy intake (kcal). Moreover, the cases with higher fructose consumption tended to consume more energy, carbohydrate (% of energy), SFA, PUFA, simple sugar, sucrose, fruits and vegetables (g/1,000 kcal) but less consumption of MUFA and total fat in comparison to the lower quartiles (Table 2).

Multivariate adjusted odds ratios for occurrence of the NAFLD in each quartile categories of fructose consumption are shown in Table 3. In the unadjusted model, subjects in the highest quartile had more than 3.08 times higher risk of NAFLD in comparison to those in the lowest quartile of the fructose intake (OR: 3.08; 95 percent CI: 1.87 - 5.06), ($P < 0.001$). Also, adjustment for age, sex, body mass index (kg/m^2), physical activity (MET-h/wk), alcohol, energy intake (kcal/d) and simple sugar strengthened significantly this association (OR: 3.54; 95 percent CI: 1.81 - 6.93), ($P = 0.003$). So that higher intake of fructose was significantly associated with the higher risk of NAFLD.

5. Discussion

Our results have shown a significant linear association between dietary fructose intake and NAFLD risk, which remained significant after adjustment for known confounding variables. These results are in accordance with previous experimental studies, which have shown that high fructose intake induced NAFLD through increased lipogenesis and TG accumulation in hepatic tissue (10). It is suggested that the susceptibility to fatty liver is linked to the metabolism of fructose by fructokinase C, which results in ATP consumption, nucleotide turnover and uric acid generation that induce accumulation of TG in hepatocytes

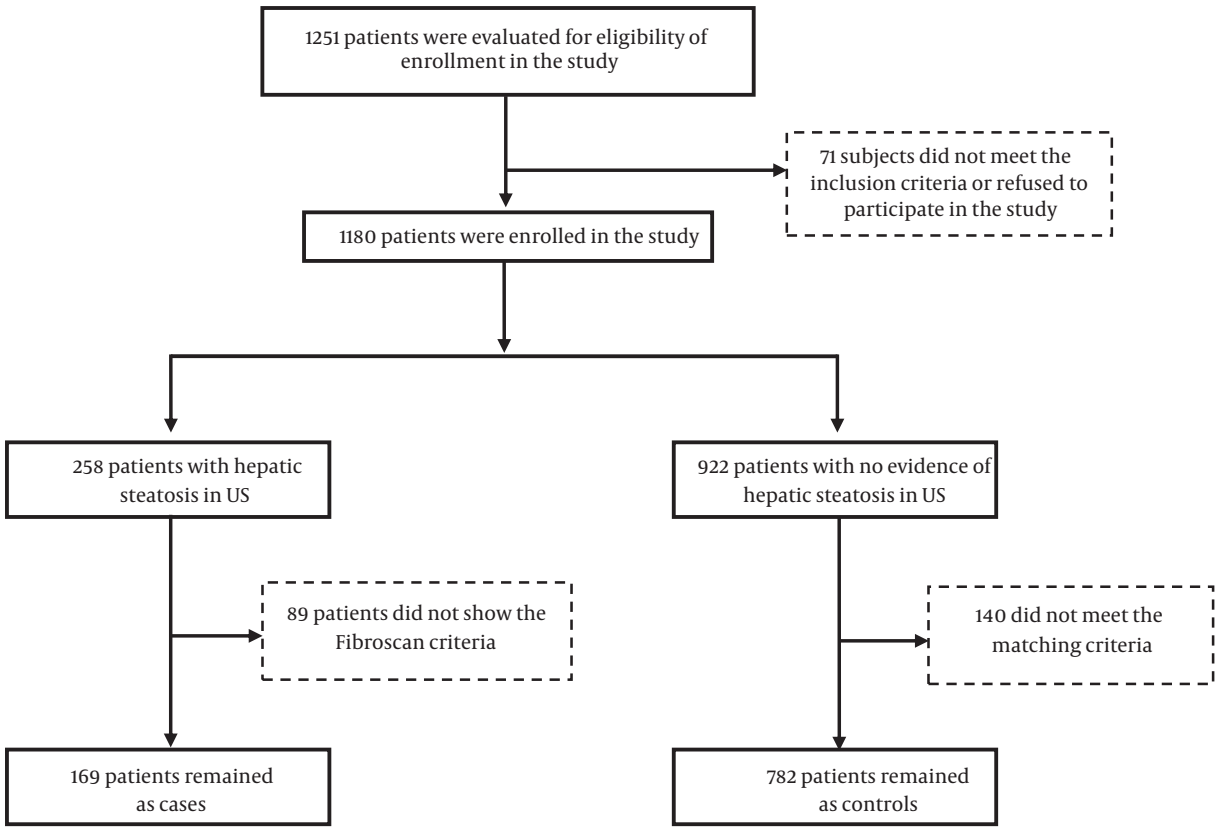

Figure 1. Patient recruitment flow chart

(22). Moreover, there are some other mechanisms explaining this relationship. It has been shown that the excessive consumption of high fructose corn syrup increased hepatic stress-related kinases, endoplasmic reticulum stress, mitochondrial dysfunction, and apoptosis. Furthermore, it has been reported that high dietary fructose intake increased hepatic glucose transporter type-5 (Glut5) (fructose transporter) gene expression and hepatic lipid peroxidation (23). In addition, there is an association between fructose intake and gut-derived endotoxemia leading to high expression of toll-like receptor-4 and production of inflammatory cytokines. Some of these effects of fructose are related to its transient ATP depletion by rapid phosphorylation within the cell (23).

Previous studies on human subjects have also showed that higher fructose intake is associated with higher disease progression (24, 25). Jin et al. reported that adipose insulin resistance, high sensitivity C-reactive protein (hs-CRP), and low-density lipoprotein (LDL) oxidation were significantly lower in glucose beverage consumers compared to fructose beverage consumers (26). Abdelmalek et al. (24) evaluated association of fructose intake with metabolic and histological features of NAFLD. They reported that excessive fructose consumption was associated with decreased hypertriglyceridemia, serum glucose, and hyperuricemia. In contrast, Kanerva et al. (27) reported an inverse association between fructose intake and NAFLD risk in a cross-sectional study. These controversies may be explained by different levels of exposures. Kanerva et al. reported the median intake of 20 gram/day in their population (27), while mean $\pm$ SD of fructose intakes were 28.07 $\pm$ 13.83, and 22.70 $\pm$ 10.15 in cases and controls respectively in our study. Thus, it seems that there might be a level for fructose intake that induces accumulation of fat in hepatocytes. Moreover, pattern of fructose consumption is important in pathogenesis of NAFLD because consumption of fructose accompanied with dietary fiber slows down fructose absorption, which reduces its conversion to fatty acids and TG in the liver. Moreover, methods of NAFLD assessment were different. We used fibroscan for confirmation of the disease diagnosis, which is a valid and reliable method for determination of hepatic steatosis and fibrosis (28), while Kanerva et al. used fatty liver index.

This study has several advantages. It has large sample

Table 1. Baseline General Characteristics, Biochemical Parameters and Dietary Intakes of Study Participants Based on the Patients with NAFLD and Control Group[a]

	Cases (N = 183)	Controls (N = 776)	P Value[b]
Age, y	38.8 ± 8.96	38.97 ± 9.96	0.114
Gender, %			0.024
Male	51	60	
Female	49	40	
BMI, kg/m^2	32.16 ± 8.54	27.80 ± 4.51	< 0.001
Physical activity, MET	32.21 ± 3.22	34.33 ± 2.85	< 0.001
Alcohol consumption, No. (%)	66 (8.5)	24 (13)	0.065
Biochemical parameters, mg/dL			
FBS	104.61 ± 38.23	90.27 ± 29.59	< 0.001
Triglyceride	161.21 ± 88.91	132.72 ± 82.11	0.002
Total cholesterol	184.79 ± 49.14	178.08 ± 39.14	0.168
LDL-C	118.70 ± 38.44	104.48 ± 31.99	< 0.001
HDL-C	43.11 ± 15.12	47.72 ± 10.58	< 0.001
Dietary factors			
Total energy intake, kcal	2696.39 ± 803.31	2719.16 ± 759.91	0.719
Carbohydrate, % of energy	57.99 ± 6.40	57.76 ± 8.19	0.7170
Protein, % of energy	15.67 ± 2.72	14.06 ± 2.32	< 0.001
Total fat, % of energy	30.18 ± 5.58	32.82 ± 5.77	< 0.001
SFA, % of energy	10.52 ± 4.21	12.96 ± 6.19	< 0.001
MUFA, % of energy	10.07 ± 2.11	10.68 ± 2.05	< 0.001
PUFA, % of energy	15.79 ± 4.47	12.14 ± 583	< 0.001
Simple sugar, g	142.97 ± 47.45	129.10 ± 47.75	< 0.001
Dietary fiber, g/1.000 kcal	17.81 ± 5.54	16.81 ± 5.51	0.026
Fruits, g/1.000 kcal	217.44 ± 113.16	148.76 ± 76.29	< 0.001
Vegetables, g/1.000 kcal	390.03 ± 211.66	315.76 ± 182.69	< 0.001
Fructose, g	28.07 ± 13.83	22.70 ± 10.15	< 0.001
Sucrose, g	36.95 ± 20.71	31.05 ± 17.75	< 0.001

Abbreviations: BMI, body mass index; FBS, fasting blood sugar; HDL-C, high density lipoproteins-cholesterol; LDL-C, low density lipoproteins-cholesterol; MET, metabolic equivalent task; MUFA, mono-unsaturated fatty acid; NAFLD, nonalcoholic fatty liver disease; PUFA, poly-unsaturated fatty acid; SFA, saturated fatty acid.
[a] Values are expressed as mean ± SD or No. (%).
[b] Independent *t* test for quantitative variables and chi-square test for qualitative variables.

size and high participation rate. High participation rate reduces the inter-individual response bias. Using fibroscan for disease confirmation is another advantage of this study. Also, this study was conducted in a developing country, in where restricted income affects dietary food intakes. Cases were newly diagnosed patients, who possibly had not alternated their diet as a result of the disease diagnosis. Validated FFQ has been used for assessment of dietary intakes, which reduces risk of measurement error, and recall bias.

The study has some limitations. Although known risk factors have been adjusted in analysis, unknown confounders might affect our results. It was impossible to match for all of these variables because overmatching may cause loss of efficiency, and the matching effect may narrow the exposure range. Although case–control studies are efficient in terms of time and cost, both selection and recall biases are inevitable limitations of these studies.

In conclusion, our results suggest that higher intake of fructose is significantly associated with the higher risk of NAFLD; this association remained significant after adjustment for known confounding factors. Further studies are required to find the cut point for safe daily fructose consumption alone over in combination with dietary fiber sources.

Table 2. Basic Characteristics and Dietary Intakes of Study Participants by Quartiles of Total Dietary Fructose Intake[a]

	Quartiles of Total Dietary Fructose Intake				P Trend
	Quartile 1 (N = 257)	Quartile 2 (N = 238)	Quartile 3 (N = 238)	Quartile 4 (N = 226)	
Total dietary fructose intake, g/d	4 - 16	17 - 22	23 - 30	31 - 88	
Cases, N	27	42	54	60	
Age, y	41.31 ± 14.17	43.50 ± 13.24	43.26 ± 14.09	46.19 ± 14.69	< 0.001
Gender, %					< 0.001
Male	31	37	46	51	
Female	69	63	54	49	
BMI, kg/m^2	27.96 ± 5.57	28.79 ± 6.16	29.39 ± 6.09	28.45 ± 5.14	0.181
Physical activity, MET	34.14 ± 3.07	33.95 ± 3.03	33.61 ± 3.02	33.97 ± 3.04	0.311
Alcohol, N	20	18	24	28	0.229
Dietary factors					
Total energy intake, kcal	2324.82 ± 636.59	2500.07 ± 633.29	2854.45 ± 718.96	3237.39 ± 752.28	< 0.001
Carbohydrate, % of energy	54.60 ± 6.38	57.55 ± 6.94	58.81 ± 8.49	60.75 ± 8.35	< 0.001
Protein, % of energy	14.01 ± 2.58	14.36 ± 2.52	14.73 ± 2.19	14.38 ± 2.56	0.030
Total fat, % of energy	34.59 ± 6.49	32.94 ± 5.64	32.49 ± 5.47	32.31 ± 5.65	< 0.001
SFA, % of energy	11.49 ± 4.21	12.34 ± 6.54	12.37 ± 5.13	13.95 ± 7.42	< 0.001
MUFA, % of energy	11.14 ± 2.26	10.65 ± 1.98	10.29 ± 1.93	10.09 ± 1.95	< 0.001
PUFA, % of energy	11.36 ± 4.89	12.39 ± 4.84	13.41 ± 5.49	14.81 ± 7.26	< 0.001
Simple sugar, g	94.89 ± 36.25	117.23 ± 29.50	143.58 ± 39.39	176.48 ± 42.68	< 0.001
Dietary fiber, g/1.000 kcal	15.84 ± 5.32	17.48 ± 5.78	17.68 ± 5.53	17.07 ± 5.29	0.010
Fruits, g/1.000 kcal	108.27 ± 65.51	152.68 ± 75.09	173.73 ± 81.67	209.16 ± 100.76	< 0.001
Vegetables, g/1.000 kcal	102.63 ± 67.56	125.72 ± 78.64	139.46 ± 80.53	140.64 ± 72.18	< 0.001
Fructose, g	12.63 ± 2.74	19.38 ± 1.61	25.54 ± 2.19	38.99 ± 10.67	< 0.001
Sucrose, g	29.41 ± 17.33	30.25 ± 17.68	32.46 ± 19.52	37.11 ± 18.57	< 0.001

Abbreviations: BMI: body mass index, MET: metabolic equivalent task; MUFA: mono-unsaturated fatty acid; PUFA: poly-unsaturated fatty acid; SFA: saturated fatty acid.
[a] Values are expressed as mean ± SD or No.
[b] Linear regression.

Table 3. Odds and 95% Confidence Interval for Occurrence of the NAFLD in Each Quartile Categories of Fructose Consumption

	Quartiles of Total Dietary Fructose Intake				P Trend [a]
	Quartile 1 (N = 257)	Quartile 2 (N = 238)	Quartile 3 (N = 238)	Quartile 4 (N = 226)	
Model 1[b]	1 (ref)	1.82 (1.08 - 3.07)	2.50 (1.51 - 4.13)	3.08 (1.87 - 5.06)	< 0.001
Model 2[c]	1 (ref)	1.79 (1.06 - 3.02)	2.35 (1.42 - 3.91)	2.88 (1.74 - 4.78)	< 0.001
Model 3[d]	1 (ref)	1.71 (0.95 - 3.09)	2.22 (1.21 - 4.06)	3.54 (1.81 - 6.93)	0.003

[a] Based on multiple logistic regression model
[b] Model 1: Crude.
[c] Model 2: Adjustment for age, sex.
[d] Model 3: Adjustment for age, sex, body mass index (kg/m^2), physical activity (MET-h/wk), alcohol, energy intake (kcal/d), simple sugar , and dietary food groups.

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Footnotes

Authors' Contribution: Mina Darand and Azita Hekmatdoost designed the study. Zahra Yari analyzed the data. Zahra Darabi wrote the primary draft of the manuscript.

Azita Hekmatdoost supervised the study and revised the manuscript.

Conflict of Interests: The authors declare that they have no competing interests.

Ethical Approval: The study protocol was approved at our local ethics committee.

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References

1. Rinella ME. Nonalcoholic fatty liver disease: A systematic review. *JAMA*. 2015;**313**(22):2263–73. doi: 10.1001/jama.2015.5370. [PubMed: 26057287].
2. Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. *Dig Dis*. 2010;**28**(1):155–61. doi: 10.1159/000282080. [PubMed: 20460905].
3. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: Trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol*. 2018;**15**(1):11–20. doi: 10.1038/nrgastro.2017.109. [PubMed: 28930295].
4. Younossi ZM, Henry L. Economic and quality-of-life implications of non-alcoholic fatty liver disease. *Pharmacoeconomics*. 2015;**33**(12):1245–53. doi: 10.1007/s40273-015-0316-5. [PubMed: 26233836].
5. Ghaemi A, Taleban FA, Hekmatdoost A, Rafiei A, Hosseini V, Amiri Z, et al. How much weight loss is effective on nonalcoholic fatty liver disease? *Hepat Mon*. 2013;**13**(12). e15227. doi: 10.5812/hepatmon.15227. [PubMed: 24358045]. [PubMed Central: PMC3867211].
6. Lim JS, Mietus-Snyder M, Valente A, Schwarz JM, Lustig RH. The role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. *Nat Rev Gastroenterol Hepatol*. 2010;**7**(5):251–64. doi: 10.1038/nrgastro.2010.41. [PubMed: 20368739].
7. Eslamparast T, Poustchi H, Zamani F, Sharafkhah M, Malekzadeh R, Hekmatdoost A. Synbiotic supplementation in nonalcoholic fatty liver disease: A randomized, double-blind, placebo-controlled pilot study. *Am J Clin Nutr*. 2014;**99**(3):535–42. doi: 10.3945/ajcn.113.068890. [PubMed: 24401715].
8. Rahimlou M, Yari Z, Hekmatdoost A, Alavian SM, Keshavarz SA. Ginger supplementation in nonalcoholic fatty liver disease: A randomized, double-blind, placebo-controlled pilot study. *Hepat Mon*. 2016;**16**(1). e34897. doi: 10.5812/hepatmon.34897. [PubMed: 27110262]. [PubMed Central: PMC4834197].
9. Yari Z, Rahimlou M, Eslamparast T, Ebrahimi-Daryani N, Poustchi H, Hekmatdoost A. Flaxseed supplementation in non-alcoholic fatty liver disease: A pilot randomized, open labeled, controlled study. *Int J Food Sci Nutr*. 2016;**67**(4):461–9. doi: 10.3109/09637486.2016.1161011. [PubMed: 26983396].
10. Schwarz JM, Noworolski SM, Wen MJ, Dyachenko A, Prior JL, Weinberg ME, et al. Effect of a high-fructose weight-maintaining diet on lipogenesis and liver fat. *J Clin Endocrinol Metab*. 2015;**100**(6):2434–42. doi: 10.1210/jc.2014-3678. [PubMed: 25825943]. [PubMed Central: PMC4454806].
11. Zhang DM, Jiao RQ, Kong LD. High dietary fructose: Direct or indirect dangerous factors disturbing tissue and organ functions. *Nutrients*. 2017;**9**(4). doi: 10.3390/nu9040335. [PubMed: 28353649]. [PubMed Central: PMC5409674].
12. Jegatheesan P, De Bandt JP. Fructose and NAFLD: The multifaceted aspects of fructose metabolism. *Nutrients*. 2017;**9**(3). doi: 10.3390/nu9030230. [PubMed: 28273805]. [PubMed Central: PMC5372893].
13. Chiu S, Sievenpiper JL, de Souza RJ, Cozma AI, Mirrahimi A, Carleton AJ, et al. Effect of fructose on markers of non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of controlled feeding trials. *Eur J Clin Nutr*. 2014;**68**(4):416–23. doi: 10.1038/ejcn.2014.8. [PubMed: 24569542]. [PubMed Central: PMC3975811].
14. Alwahsh SM, Gebhardt R. Dietary fructose as a risk factor for non-alcoholic fatty liver disease (NAFLD). *Arch Toxicol*. 2017;**91**(4):1545–63. doi: 10.1007/s00204-016-1892-7. [PubMed: 27995280].
15. Ouyang X, Cirillo P, Sautin Y, McCall S, Bruchette JL, Diehl AM, et al. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. *J Hepatol*. 2008;**48**(6):993–9. doi: 10.1016/j.jhep.2008.02.011. [PubMed: 18395287]. [PubMed Central: PMC2423467].
16. Hekmatdoost A, Shamsipour A, Meibodi M, Gheibizadeh N, Eslamparast T, Poustchi H. Adherence to the dietary approaches to stop hypertension (DASH) and risk of nonalcoholic fatty liver disease. *Int J Food Sci Nutr*. 2016;**67**(8):1024–9. doi: 10.1080/09637486.2016.1210101. [PubMed: 27436528].
17. Mokhtari Z, Poustchi H, Eslamparast T, Hekmatdoost A. Egg consumption and risk of non-alcoholic fatty liver disease. *World J Hepatol*. 2017;**9**(10):503–9. doi: 10.4254/wjh.v9.i10.503. [PubMed: 28443155]. [PubMed Central: PMC5387362].
18. FAO . *Dietary assessment: A resource guide to method selection and application in low resource settings*. Rome: Food and Agriculture Organization of the United Nations; 2018.
19. Esfahani FH, Asghari G, Mirmiran P, Azizi F. Reproducibility and relative validity of food group intake in a food frequency questionnaire developed for the Tehran Lipid and Glucose Study. *J Epidemiol*. 2010;**20**(2):150–8. doi: 10.2188/jea.JE20090083. [PubMed: 20154450]. [PubMed Central: PMC3900814].
20. Mirmiran P, Esfahani FH, Mehrabi Y, Hedayati M, Azizi F. Reliability and relative validity of an FFQ for nutrients in the Tehran lipid and glucose study. *Public Health Nutr*. 2010;**13**(5):654–62. doi: 10.1017/S1368980009991698. [PubMed: 19807937].
21. Food and Nutrition Information Center. *Composition of foods raw, processed, prepared USDA national nutrient database for standard reference, release 27 documentation and user guide*. Beltsville, Maryland: US Department of Agriculture: Food composition table (FCT); 2009.
22. Jensen T, Abdelmalek MF, Sullivan S, Nadeau KJ, Green M, Roncal C, et al. Fructose and sugar: A major mediator of non-alcoholic fatty liver disease. *J Hepatol*. 2018;**68**(5):1063–75. doi: 10.1016/j.jhep.2018.01.019. [PubMed: 29408694]. [PubMed Central: PMC5893377].
23. Basaranoglu M, Basaranoglu G, Bugianesi E. Carbohydrate intake and nonalcoholic fatty liver disease: fructose as a weapon of mass destruction. *Hepatobiliary Surg Nutr*. 2015;**4**(2):109–16. doi: 10.3978/j.issn.2304-3881.2014.11.05. [PubMed: 26005677]. [PubMed Central: PMC4405421].
24. Abdelmalek MF, Suzuki A, Guy C, Unalp-Arida A, Colvin R, Johnson RJ, et al. Increased fructose consumption is associated with fibrosis severity in patients with nonalcoholic fatty liver disease. *Hepatology*. 2010;**51**(6):1961–71. doi: 10.1002/hep.23535. [PubMed: 20301112]. [PubMed Central: PMC2922495].
25. Nier A, Brandt A, Conzelmann IB, Ozel Y, Bergheim I. Non-alcoholic fatty liver disease in overweight children: Role of fructose intake and dietary pattern. *Nutrients*. 2018;**10**(9). doi: 10.3390/nu10091329. [PubMed: 30235828]. [PubMed Central: PMC6165138].
26. Jin R, Welsh JA, Le NA, Holzberg J, Sharma P, Martin DR, et al. Dietary fructose reduction improves markers of cardiovascular disease risk in Hispanic-American adolescents with NAFLD. *Nutrients*. 2014;**6**(8):3187–201. doi: 10.3390/nu6083187. [PubMed: 25111123]. [PubMed Central: PMC4145302].
27. Kanerva N, Sandboge S, Kaartinen NE, Mannisto S, Eriksson JG. Higher fructose intake is inversely associated with risk of nonalcoholic fatty liver disease in older Finnish adults. *Am J Clin Nutr*. 2014;**100**(4):1133–8. doi: 10.3945/ajcn.114.086074. [PubMed: 25099548].
28. Saadati S, Hekmatdoost A, Hatami B, Mansour A, Zahra Z, Hedayati M, et al. Comparing different non-invasive methods in assessment of the effects of curcumin on hepatic fibrosis in patients with non-alcoholic fatty liver disease. *Gastroenterol Hepatol Bed Bench*. 2018;**11**(Suppl 1):S8–S13. [PubMed: 30774801]. [PubMed Central: PMC6347983].