The relationship between Dyspepsia and Non-Alcoholic Fatty Liver Disease: A case-control study

Rasoul Shafiezadeh[1], Seyed Saeid Esmaeili Saber[2✉], Seyed Moayed Alavian[3], Mohammad Gholamiphesharaki[4], Asie Poorasar[5]

[1]MD, Department of Traditional Medicine, Faculty of Traditional Medicine, Shahed University of Medical Sciences, Teheran, Iran
[2]PhD, Department of Traditional Medicine, Faculty of Traditional Medicine, Shahed University of Medical Sciences, Teheran, Iran
[3]Professor of Gastroenterology and Hepatology, Baqiatallah Research Center for Gastroenterology and liver disease, Baqiatallah University of Medical Science, Tehran, Iran
[4]PhD, Assistant Professor of Biostatistics, Biostatistics Department, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Islamic Republic of Iran
[5]MD, Department of Traditional Medicine, Faculty of Traditional Medicine, Tehran University of Medical Sciences, Teheran, Iran

✉Corresponding author
PhD, Department of Traditional Medicine, Faculty of Traditional Medicine, Shahed University of Medical Sciences,
Teheran, Iran
Email: seyedsaeidesmaeilisaber@gmail.com

Citation
Rasoul Shafiezadeh, Seyed Saeid Esmaeili Saber, Seyed Moayed Alavian, Mohammad Gholamiphesharaki, Asie Poorasar. The relationship between Dyspepsia and Non-Alcoholic Fatty Liver Disease: A case-control study. *Medical Science*, 2020, 24(102), 587-593

General Note
Article is recommended to print as color digital version in recycled paper.

ABSTRACT

Background and Objective: Non-alcoholic fatty liver is one of the most common non-infectious diseases in the liver, which is currently increasing prevalence in Iran and in the world. According to WHO recommendations for liver and related diseases, as well as identification of factors affecting non-alcoholic fatty liver, this study was conducted to investigate the association of Dyspepsia with non-alcoholic fatty liver. *Material and Methods:* This case-control study was conducted on patients referred to an ultrasound center in Isfahan, Iran during January to May 2018. In this study, ultrasound was used to diagnose non-alcoholic fatty liver and ROMEIII questionnaire for Dyspepsia diagnosis, and SPSS 21 software was used to analyze the data. *Results:* This study was performed on 190 subjects including 70 (37%) women and 120 (63%) men with an average age of 40 years with a standard deviation of 15 years. The results of this study showed that bloating (OR = 3.5, P-value = 0.001) and Dyspepsia (OR = 2.7, P-value = 0.002) is related to non-alcoholic fatty liver. Further analysis based on the decision tree showed that at the age of 29 years, having dyspepsia is a sign of a significant in the incidence of non-alcoholic fatty liver. This means that at the age of 29, Dyspepsia can be a sign of non-alcoholic fatty liver. *Conclusion:* Given that the results of this study showed that dyspepsia is very effective in predicting non-alcohol fatty liver, especially at the age of 29 years, it can be used as a quick, inexpensive and effective method for identifying or Suspecting non-alcoholic fatty liver and also treating it.

Keywords: Non-alcoholic fatty liver, Traditional Iranian Medicine, Dyspepsia

1. INTRODUCTION

Non-alcohol fatty liver is the most common chronic liver disorder in the world. The prevalence of this disease in adult populations in western societies is reported to be 34% to 46%, with an incidence of 70-80% in obese subjects (Browning et al., 2004 and Chen et al., 2008 and Brunt et al., 2015 and Williams et al., 2011). In Iran, the prevalence of this disease has been reported from 21.5% to 31.5% (Jamali et al., 2008 and Sohrabpour et al., 2010 and Lankarani et al., 2013). Non-alcoholic fatty liver disease refers to a condition of the liver that triglycerides accumulate in the liver cells of people who have not had a history of alcohol or low alcohol consumption (Harte et al., 2010). In fact, non-alcoholic fatty liver disease (NAFLD) occurs when more than 5-10% of the liver is fat (Vajro et al., 2012 and Festi et al., 2004 and Mensink et al., 2008) and has recently been considered as an important cause of cirrhosis and liver failure (Savadkouhi et al., 2003). The high prevalence and chronic nature of the disease affects people's quality of life and imposes a heavy economic burden on the community (Baumeister et al., 2008 and Zivkovic et al., 2007). Most patients with NAFLD are asymptomatic, but some complain of weakness and fatigue, nausea, and abnormal pain. So diagnosis usually follows the incidental finding of abnormal liver enzymes or steatosis on imaging (Duvnjak et al., 2009 and Promrat et al., 2010 and Zelber-Sagi et al., 2011). Nonalcoholic fatty liver is currently treated in two general categories of medicinal and non-pharmacological treatments. Drug therapy is in cases where the disease is active and progressive and non-pharmacological treatment includes lifestyle modification with nutrition and exercise (Kani et al., 2014 and Ahmed, 2015). At the moment, diet and exercise are the most effective way to control and reverse the symptoms of the disease. However, many improvements have been made in the field of drug manufacturing; however, there are no effective and reliable medications so far (Than and Newsome, 2015). According to the WHO, the best treatment is prevention (Treerutkuarkul and Gruber, 2015). Therefore, the recognition of simple symptoms that has the potential to detect non-alcoholic fatty liver disease in early stage is very important. In classical medicine, the role of the gastrointestinal system has been raised in the formation of fatty liver in several ways: unhealthy nutrition and the use of high-fat and high-calorie foods, gastric helicobacter pylori infection and gastrointestinal microbiota (Akhavan et al., 2015 and Lambert et al., 2015 and Lomonaco et al., 2013).

From the viewpoint of Iranian Traditional Medicine (ITM), liver is one of the most three important organs of human body along with two other organs, brain and heart. Liver produces not only whole body nutrition; but also, four fundamental bodily humors including blood, yellow bile, black bile, and phlegm. To produce healthy blood, liver needs primary high quality nutrient which should be provided by stomach, according to ITM scientists. Therefore, if gastric digestion impaired, other organs like liver, blood vessels, and tissues which are involved in digestive processes will be weakened and malfunctioned due to lack of proper nutrition. This actually may cause fatty liver. Hence, the hypothesis is that gastrointestinal abnormalities due to digestive disorder in this organ can play an important role in the occurrence of fatty liver. The stomach is the target organ in treating these patients. If the first step in dealing with these patients is the treatment of gastrointestinal disorders, it will be possible that improved digestion will play a

very important and effective role in the treatment of these patients (Shah, 1966). Considering the importance of this issue, this study was conducted to determine the relationship between dyspepsia and non-alcoholic fatty liver disease (NAFLD).

2. MATERIALS AND METHODS

The present case-control study was conducted within a 5-month period on 190 patients referred to ultrasound unit in a semi-public health center in Isfahan, Iran. In this study, the participants were selected using a random sampling method and enrolled in a study based on inclusion criteria, including willingness to participate in the study, over 20 years of age, no pregnancy and breastfeeding, no past or recent use of alcohol, no history of cirrhosis, heart failure, liver failure, renal failure, and neoplasms.

In this study, all patients who referred to the clinic for various reasons from February 2017 to May 2018 completed the ROMEIII questionnaire after obtaining consent, and then underwent liver ultrasonography by a certified radiologist. On the basis of ultrasound findings, the subjects with a fatty liver grade 1 to 3 were assigned to the case group as NAFLD patients, and those with normal liver were selected as the control group.

Dyspepsia is defined as having one or more of the primary symptoms, including Bothersome postprandial fullness (an unpleasant feeling of completeness after a normal meal), Early satiation (inability to complete a typical meal) and epigastric pain or burning (feeling pain or burning in the middle of the abdomen), which can be presented by Supportive criteria including Upper abdominal bloating or postprandial nausea or excessive belching. In this study, ROMIII questionnaire was used to investigate dyspepsia and abdominal bloating. However, the symptoms associated with bloating such as stomach growling, excessive flatulence and intestinal gas incontinence were also included in the questionnaire.

The ROME III questionnaire used in this study has been provided by the Rome Foundation Board for the diagnosis of gastrointestinal dysfunction. The latest version was published by a group of experts in the field of gastrointestinal disorders in 2006 (Esmaillzadeh et al., 2013) and has been evaluated and approved in various research (Sorouri et al., 2010) .

The current study was approved by the Medical Ethics Committee of Shahed University on 8/01/2018 with code of IR.Shahed.REC.1396.82, and also registered on the Iranian Registry of Clinical Trials with registration code of IRCT20171102037178N2 on 11/03/2018.

Statistical analysis and sample size

In this study, the attained data were analyzed by SPSS version 21 software using descriptive statistics (mean, standard deviation, correlation, frequency and ratio) and inferential statistics (Chi-square test, independent t-test, Mann-Whitney test) proportional to normal or non-normal distribution of the response variable using KS test, as well as logistic regression and decision tree at a significance level of 5%. In this study, the sample size was calculated to be 196 people using the equation of $n = \left(Z_{\frac{\alpha}{2}} + Z_\beta \right)^2 /$ δ^2 .$\delta^2 = (p_1 - p_2)^2/(p_1(1 - p_1) + p_2(1 - p_2))$ and considering α = 0.05, β = 0.1 and δ = 0.35. Including 15% dropout, 14 samples were added to this number. Finally, 210 subjects were considered in this study.

3. RESULT

The current study examined 203 people, of which 13 were excluded, and finally 190 were enrolled and analyzed. The demographic characteristics of the participants of the two groups are presented in Table 1. According to the results reported in this table, the majority of NAFLD patients were male, and had a higher age compared to the healthy people. The heterogeneity of the distribution of the age and gender of the participants caused these two variables to be considered as a moderator variable in the logistic regression in the final analysis. Based on the results reported in Table 2, feelings of abdominal bloating and dyspepsia were strongly correlated with the NAFLD. In the results of logistic regression analysis with age and gender, these two variables were effective on the NAFLD. For further analysis and obtaining a more predictive contribution by using the decision tree and entering the variables that influence the logistic regression, namely age, gender, abdominal bloating and dyspepsia, the two variables of age and dyspepsia were significant in the decision tree. According to the findings from decision tree (Figure 1), it can be said that if a person is under the age of 29 years, the dyspepsia will not contribute much to the diagnosis of fatty liver, and only there will be a 30% risk of having a fatty liver if having dyspepsia. If there is dyspepsia at the age of 29 years, it will probably show a 70% risk of NAFLD. If there is no dyspepsia, the person will suffer from NAFLD with a probability of 45%. Finally, the results showed that the decision tree model mentioned in Figure 1 has a predictive value of approximately 70%.

Table 1 The demographical variables according to the normal and non-alcoholic fatty liver group

		Group				P-value
		Normal		NAFLD		
		N	%	N	%	
Sex	Female	41	44.6%	29	29.6%	0.036
	Male	51	55.4%	69	70.4%	
		Mean	SD	Mean	SD	
Age	year	36.71	16.01	43.77	13.92	0.001

SD: Standard Deviation
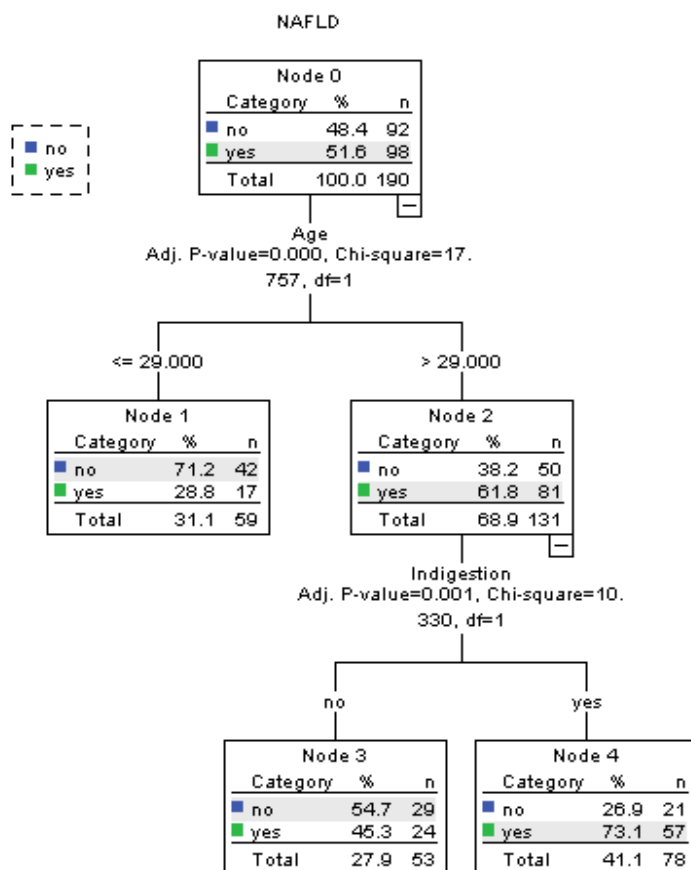
Figure 1 Decision tree of variables affecting non-alcoholic fatty liver disease

4. DISCUSSION

According to the teachings of ITM, nutrients take four digestive stages from the time of entering into the mouth until being ready for cellular use, including digestion in the stomach, liver, blood vessels and organs, respectively (Shah, 1966). Accordingly, each of the four stages of digestion consists of certain processes and actions that must be done on the food to provide the ability to exploit the products in the body. In fact, two factors are effective in digestion in the liver: 1 - the liver health and 2 - the raw materials sent from the stomach to the liver. Therefore, traditional medicine suggests the assumption that gastric abnormalities can play an important role in the development of fatty liver due to digestive disorder in this organ and that the stomach is the target organ in the treatment of these patients and If the first step in dealing with these patients is the treatment of gastrointestinal disorders, it will be possible that improved digestion will play a very important and effective role in the treatment of these patients. Gastrointestinal

symptoms can also be used to suspect fatty liver and diagnostic follow-up. On the other hand, digestive improvement can also have a preventative effect on the development of fatty liver. Given the importance of this issue, this study was conducted with the aim of linking dyspepsia with NAFLD.

Table 2 Frequency and percent of sign of Dyspepsia between two groups, in addition crude and adjusted OR

	Group				Crude		Adjusted	
	Normal		Non-alcoholic fatty liver		OR 95% CI	P-value	OR 95% CI	P-value
	N	%	N	%				
Abdomen growling	62	67.4%	71	72.4%	1.3 (0.7-2.4)	0.527	1.6 (0.8-3.2)	0.150
flatulence	66	71.7%	80	81.6%	1.8 (0.9-3.5)	0.127	1.9 (0.9-3.8)	0.088
gas incontinence	38	41.3%	46	46.9%	1.3 (0.7-2.2)	0.467	1.4 (0.7-2.5)	0.320
sensation of fullness after eating	37	40.2%	55	56.1%	1.9 (1.1-3.4)	0.031	1.7 (0.9-3.1)	0.082
early satiation	42	45.7%	54	55.1%	1.5 (0.8-2.6)	0.245	1.6 (0.9-2.9)	0.131
postprandial nausea	28	30.4%	26	26.5%	0.8 (0.4-1.6)	0.630	1 (0.5-1.9)	0.961
excessive belching	63	68.5%	79	80.6%	1.9 (1.0-3.7)	0.066	1.9 (0.9-3.8)	0.072
abdominal bloating	59	64.1%	82	83.7%	2.9 (1.4-5.7)	0.003	3.5 (1.7-7.3)	0.001
Dyspepsia	41	44.6%	67	68.4%	2.7 (1.5-4.9)	0.001	2.7 (1.5-5.0)	0.002

The results of this study showed that the NAFLD is more prevalent in older ages and males. In this regard, the results of this study were similar to those of Ishiba et al. (Ishiba et al., 2018) and Ballestri et al. (Ballestri et al., 2017), and inconsistent with the study by Cuthbertson et al. (Cuthbertson et al., 2019), Yang et al. (Yang et al., 2018).

The results of this study by controlling confounding variables showed that the abdominal bloating and the dyspepsia could be associated with the NAFLD. The odds ratio of NAFLD in patients with the abdominal bloating was 3.5 times higher than in those without the abdominal bloating. The odds ratio of NAFLD for people with the dyspepsia was 2.7 times higher than in those without the dyspepsia. In this regard, the results of this study were similar to those of Emtiazi et al., who showed a relationship between gastric abnormalities and liver disease (Emtiazy et al., 2011). Some studies also documented the association between the presence of Helicobacter pylori (as a cause of gastrointestinal and duodenal diseases) and the outbreak of NAFLD (Ahmed, 2015 and Abdel-Razik et al., 2018 and He et al., 2018 and Kang et al., 2018 and Okushin et al., 2018). Fujiwara et al. showed the association between obesity, dyspepsia and gastroesophageal reflux disease (GERD) with NAFLD (Fujiwara et al., 2015).

Further analysis based on the decision tree showed that dyspepsia over 29 years of age showed a high incidence of fatty liver disease. In other words, dyspepsia over the age of 29 can be a sign of the NAFLD. Some of the strengths of this study are the diagnosis of NAFLD using ultrasound, the use of decision tree method, the appropriate sample size and the control of confounding variables.

5. CONCLUSION

Given that the results of this study showed that the dyspepsia is very effective in predicting the NAFLD, especially at the age of 29 years and over, the dyspepsia can be used as a rapid, inexpensive and effective strategy to identify or suspect the NAFLD. Improved nutrition and digestion is suggested to prevent this symptom.

Conflicts of Interest:

The authors declare no conflict of interest.

REFERENCE

1. Abdel-Razik A, Mousa N, Shabana W, Refaey M, Elhelaly R, Elzehery R, et al. Helicobacter pylori and non-alcoholic fatty liver disease: A new enigma? Helicobacter 2018; 23:12537.

2. Ahmed M. Non-alcoholic fatty liver disease in 2015. World journal of hepatology 2015; 7:1450-9.

3. Akhavan Rezayat K, Afkhamizadeh M, Chachi K, Salehi M. Evaluation of effect of helicobacter pylori treatment on insulin resistance in patients with nonalcoholic fatty liver disease. medical journal of mashhad university of medical sciences 2015;58:425-31.

4. Ballestri S, Nascimbeni F, Baldelli E, Marrazzo A, Romagnoli D, Lonardo A. NAFLD as a Sexual Dimorphic Disease: Role of Gender and Reproductive Status in the Development and Progression of Nonalcoholic Fatty Liver Disease and Inherent Cardiovascular Risk. Adv Ther 2017; 34:1291-326.

5. Baumeister SE, Völzke H, Marschall P, John U, Schmidt CO, Flessa S, et al. Impact of fatty liver disease on health care utilization and costs in a general population: a 5-year observation. Gastroenterology 2008; 134:85-94.

6. Browning JD, Szczepaniak LS, Dobbins R, Horton JD, Cohen JC, Grundy SM, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004; 40:1387-95.

7. Brunt EM, Wong VW, Nobili V, Day CP, Sookoian S, Maher JJ, et al. Nonalcoholic fatty liver disease. Nat Rev Dis Primers 2015; 1:80.

8. Chen Z-w, Chen L-y, Dai H-l, Chen J-h, Fang L-z. Relationship between alanine aminotransferase levels and metabolic syndrome in nonalcoholic fatty liver disease. Journal of Zhejiang University Science B 2008; 9:616-22.

9. Cuthbertson DJ, Brown E, Koskinen J, Magnussen CG, Hutri-Kahonen N, Sabin M, et al. Longitudinal analysis of risk of Non-Alcoholic Fatty Liver Disease (NAFLD) in adulthood. Liver Int 2019; 39:1147-54.

10. Duvnjak M, Gomerčić M, Tomašić V, Duvnjak LS, Baršić N, Lerotić I. Therapy of nonalcoholic fatty liver disease: current status. Journal of physiology and pharmacology 2009; 60:57-66.

11. Emtiazy M, Nazem E, Keshavarz M, Kamalinejad M, Gooshehgir SA, Hashem Dabbaghian F, et al. Avicenna Medicine and Hyperlipidemia. Journal of Islamic and Iranian Traditional Medicine 2011; 2:155-60.

12. Esmaillzadeh A, Keshteli A, Feizi A, Zaribaf F, Feinle-Bisset C, Adibi P. Patterns of diet-related practices and prevalence of gastro-esophageal reflux disease. Neurogastroenterology & Motility 2013; 25:831-638.

13. Festi D, Colecchia A, Sacco T, Bondi M, Roda E, Marchesini G. Hepatic steatosis in obese patients: clinical aspects and prognostic significance. Obesity reviews 2004; 5:27-42.

14. Fujiwara M, Eguchi Y, Fukumori N, Eguchi H, Tomonaga M, Yoshioka T, et al. The symptoms of gastroesophageal reflux disease correlate with high body mass index, the aspartate aminotransferase/alanine aminotransferase ratio and insulin resistance in Japanese patients with non-alcoholic fatty liver disease. Internal Medicine 2015; 54:3099-104.

15. Harte AL, da Silva NF, Creely SJ, McGee KC, Billyard T, Youssef-Elabd EM, et al. Elevated endotoxin levels in non-alcoholic fatty liver disease. Journal of inflammation 2010; 7:15.

16. He C, Cheng D, Wang H, Wu K, Zhu Y, Lu N. Helicobacter pylori infection aggravates diet-induced nonalcoholic fatty liver in mice. Clin Res Hepatol Gastroenterol 2018; 42:360-7.

17. Ishiba H, Sumida Y, Tanaka S, Yoneda M, Hyogo H, Ono M, et al. Correction to: The novel cutoff points for the FIB4 index categorized by age increase the diagnostic accuracy in NAFLD: a multi-center study: J Gastroenterol 2018; 53:1216-24.

18. Jamali R, Khonsari M, Merat S, Khoshnia M, Jafari E, Bahram Kalhori A, et al. Persistent alanine aminotransferase elevation among the general Iranian population: prevalence and causes. World journal of gastroenterology 2008; 14:2867-71.

19. Kang SJ, Kim HJ, Kim D, Ahmed A. Association between cagA negative Helicobacter pylori status and nonalcoholic fatty liver disease among adults in the United States. PLoS One 2018; 13.

20. Kani AH, Alavian SM, Haghighatdoost F, Azadbakht L. Diet macronutrients composition in nonalcoholic Fatty liver disease: a review on the related documents. Hepatitis monthly 2014; 14:10939.

21. Lambert JE, Parnell JA, Eksteen B, Raman M, Bomhof MR, Rioux KP, et al. Gut microbiota manipulation with prebiotics in patients with non-alcoholic fatty liver disease: a randomized controlled trial protocol. BMC gastroenterology 2015; 15:169.

22. Lankarani KB, Ghaffarpasand F, Mahmoodi M, Lotfi M, Zamiri N, Heydari ST, et al. Non alcoholic fatty liver disease in southern Iran: a population based study. Hepatitis monthly 2013; 13:9248.

23. Lomonaco R, Sunny NE, Bril F, Cusi K. Nonalcoholic fatty liver disease: current issues and novel treatment approaches. Drugs 2013; 73:1-14.

24. Mensink RP, Plat J, Schrauwen P. Diet and nonalcoholic fatty liver disease. Current opinion in lipidology 2008; 19:25-9.

25. Okushin K, Tsutsumi T, Ikeuchi K, Kado A, Enooku K, Fujinaga H, et al. Helicobacter pylori infection and liver diseases: Epidemiology and insights into pathogenesis. World J Gastroenterol 2018; 24:3617-25.

26. Promrat K, Kleiner DE, Niemeier HM, Jackvony E, Kearns M, Wands JR, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. Hepatology 2010; 51:121-9.

27. Savadkouhi F, HOSSEINI TS, Shahabi NS. The frequency of fatty liver in sonography of patients without liver diseases background and its correlation with blood cholesterol and triglyceride 2003; 5:177-83.

28. Shah MH. The general principles of Avicenna's Canon of Medicine: Naveed Clinic 1966.

29. Sohrabpour A, Rezvan H, Amini-Kafiabad S, Dayhim M, Merat S, Pourshams A. Prevalence of Nonalcoholic Steatohepatitis in Iran: A Population based Study. Middle East journal of digestive diseases 2010; 2:14-9.

30. Sorouri M, Pourhoseingholi MA, Vahedi M, Safaee A, Moghimi-Dehkordi B, Pourhoseingholi A, et al. Functional bowel disorders in Iranian population using Rome III criteria. Saudi journal of gastroenterology: official journal of the Saudi Gastroenterology Association 2010; 16:154-160.

31. Than NN, Newsome PN. A concise review of non-alcoholic fatty liver disease. Atherosclerosis 2015; 239:192-202.

32. Treerutkuarkul A, Gruber K. Prevention is better than treatment. World Health Organization Bulletin of the World Health Organization 2015; 93:594.

33. Vajro P, Lenta S, Socha P, Dhawan A, McKiernan P, Baumann U, et al. Diagnosis of nonalcoholic fatty liver disease in children and adolescents: position paper of the ESPGHAN Hepatology Committee. Journal of pediatric gastroenterology and nutrition 2012; 54:700-13.

34. Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology 2011; 140:124-31.

35. Yang H, Li D, Song X, Liu F, Wang X, Ma Q, et al. Joint associations of serum uric acid and ALT with NAFLD in elderly men and women: a Chinese cross-sectional study. J Transl Med 2018; 285.

36. Zelber-Sagi S, Ratziu V, Oren R. Nutrition and physical activity in NAFLD: an overview of the epidemiological evidence. World journal of gastroenterology: WJG 2011; 17:3377-3389.

37. Zivkovic AM, German JB, Sanyal AJ. Comparative review of diets for the metabolic syndrome: implications for nonalcoholic fatty liver disease. The American journal of clinical nutrition 2007; 86:285-300.