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Original Article

Prevalence of Non-Alcoholic Fatty Liver Disease and Its Predictors in North of Iran

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is one of the aspects of metabolic syndrome (MetS). Due to the increase of MetS in Iran, this study was conducted to determine the prevalence of NAFLD, its potential predictors and their sex distribution in north of Iran, Amol.

Methods: In 2008 this population based cross-sectional study included 5023 adult individuals who were randomly selected from Amol healthcare centers. Blood analysis and hepatic sonography was performed for each individual and Clinical histories were reviewed. MetS was defined according to the National Cholesterol Education Program Adult Treatment Panel III. Chi-square test, univariate and multivariate logistic regression were used to analyze data.

Results: The prevalence of NAFLD and metabolic syndrome was 43.8% and 29.6% respectively. Both NAFLD and metabolic syndrome were significantly more prevalent in women. There was a stronger association between these two factors in women which may indicate MetS has a much more potency to result in NAFLD in women. The strongest predictors of NAFLD in men were waist circumference>102 cm, serum ALT ≥40 (U/L) and the age group of 40-60 years. The strongest predictors of NAFLD in women were waist circumference>88 cm, the age groups of 40-60 and >60 years.

Conclusions: The observed prevalence is alarming because almost 7out of 10 subjects with MetS had NAFLD. As high waist circumference was an important predictor of NAFLD in both sexes, health care policies to reduce the incidence of obesity in the country will have an important impact on the occurrence of NAFLD.

Keywords: Non-Alcoholic fatty liver disease (NAFLD), Metabolic syndrome, Risk factors

Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent types of liver diseases in western countries. It is defined as storage of triglycerides in hepatocytes more than 5% of liver weight, less than 20 g/d of alcohol consumption and exclusion of any other causes of chronic liver diseases (1-3). This disease has a wide spectrum of manifestations from simple hepatic steatosis to steatohepatitis with different grades of fibrosis to cirrhosis and in rare cases hepatocellular carcinoma (4). It is usually associated with visceral obesity, type 2 diabetes, dyslipidemia and other components of metabolic syndrome so it is considered to be one of the aspects of metabolic syndrome (1-3, 5-8). The prevalence of NAFLD in adults is 20-30% in western countries (9-13). In eastern

countries the disease did not used to be frequent but recent studies have shown an increasing rise in the prevalence of NAFLD and it has been associated with the change of life style (diet, physical activity) and increasing prevalence of obesity (14-15). The Third national surveillance of risk factors of non-communicable diseases (SuRFNCD-2007) in Iran reported a strikingly high prevalence of some metabolic abnormalities such as diabetes (8.7%), obesity (22.3%), hypertension (26.6%), hypertriglyceridemia (36.4%), hypercholesterolemia (42.9%) and central obesity (53.6%) in our country, as a developing country which was comparable, if not higher, to most developed countries (16). Since all these metabolic abnormalities are risk factors for NAFLD, these results predict a high prevalence of NAFLD in Iran.

To the best of our knowledge a few studies are available on the prevalence of NAFLD in Iran (17-19) and most of them have reported NASH prevalence in particular (not NAFLD) or has been conducted on a specific group such as diabetic patients (20). On the other hand there has been no study on the prevalence of NAFLD in Northern provinces of Iran. In fact the distribution of type 2 diabetes, central obesity, hypertension and dyslipidemia is not the same in different regions and it affects on the prevalence of NAFLD.

The aims of this study were to determine the prevalence of NAFLD, its potential predictors and their sex distribution in an adult population based study in Amol, northern Iran.

Material and Methods

Study design

This study was conducted within the framework of Amol health cohort study. From 2008, the Gastro Intestinal and Liver Disease Research Center (GILDRC) has conducted a multidisciplinary study on general population of Amol and surrounding areas. Total 6420 subjects were involved in this study by cluster random sampling. Details of the Amol cohort protocol have been published elsewhere (21).

This population based cross-sectional study was conducted on phase 1 of Amol cohort study and included 5023 adult individuals who had full relevant data.

Inclusion criteria

An adult population of 18-90 year old, who gave written informed consent, participated in the study.

Exclusion criteria

The exclusion criteria were patients with chronic liver diseases, the presence of hepatitis B virus surface antigen or hepatitis C virus antibodies, known cases of autoimmune hepatitis or Wilson disease, an alcohol consumption more than 30 g/day in men and more than 20 g/day in women, patients with cognitive diseases and individuals who were incapable of communicating.

Procedure

Details of the Amol cohort health study have been published elsewhere (21) but briefly, after signing a detailed informed consent, a standardized questionnaire was administered to determine the clinical histories, past medical histories, alcohol consumption and the use of any drugs including hepatotoxic drugs in all the participants. Then a physical examination was performed to measure weight (kg), height (m) and waist circumference [WC (cm)] according to the standard protocol (22). Body mass index (BMI) was calculated as body weight in kilogram divided by square of height in meter. Blood pressure was measured by mercury sphygmometer three times at 1-min intervals, with the patient in a sitting position; the average of the second and third measurements was reported.

Then a 12-h fasting venous blood sample was taken from each participant to measure biochemical parameters [Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), triglyceride (TG), Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), total cholesterol (T-Chol), fasting serum glucose (FSG), fasting serum insulin, hepatitis B virus surface antigens and hepatitis C virus antibodies.

AST, ALT, triglyceride, LDL, HDL and T-Chol and FSG were measured by auto-analyzer (Bio system kits). Fasting serum Insulin was measured by ELIZA (Monobind kit), hepatitis B virus surface antigens and hepatitis C virus antibodies were measured by ELIZA (Acon kit). Insulin resistance was assessed by HOMA-IR index as follows:
HOMA-IR = fasting serum glucose (mg/dl) × fasting serum insulin (mU/l)/405.
Finally, all subjects underwent abdominal sonography (by Esaote May lab number 15) for evaluation of fatty liver or other abnormal findings. All sonographies were done by one expert sonographist.

Definition of Fatty liver

In sonography, fatty liver was diagnosed with an increase in hepatic echogenicity using renal echogenicity as a reference, the presence of enhancement and a lack of differentiation of periportal and bile duct walls reinforcement because of great hyperechogenicity of the parenchyma (23).

Definition of Metabolic Syndrome

Metabolic syndrome was defined according to National Cholesterol Education Program Adult Treatment Panel III criteria (ATPIII) (24). ATPIII defines Metabolic Syndrome, as presence of any three out of five risk factors:

- Fasting Glucose ≥100 mg/dl
- Waist Circumference: (i) Men: >102 cm (40 in); (ii) Women: >88 cm (35 in)
- TG ≥150 mg/dl
- HDL-C: (i) Men: < 40 mg/dl; (ii) Women: < 50 mg/dl
- Blood Pressure ≥130/ or ≥85 mm Hg

Statistical analysis

Data were analyzed by SPSS ver. 16 J for Windows. Variables were categorized according to the definition of metabolic syndrome and standard protocols (Table 1) and were described by frequency tables in the total population and in each sex separately. Chi-square test was used to compare the frequency of these variables between two sexes.

Table 1: The prevalence of NAFLD and its potential predictors in the study population

Parameters	Men n (%)	Women n (%)	Total n (%)	*P* value
Waist Circumference (cm) >102 in males and >88 in females	505 (17.7)	1361 (62.6)	1866 (37.1)	<0.001*
Fasting Serum Glucose (mg/dl) ≥ 100	782 (27.5)	709 (32.6)	1491 (29.7)	<0.001*
Hypertension (mm Hg) (SBP≥130 or DBP≥85)	1128 (39.6)	814 (37.4)	1942 (38.7)	0.116
Triglycerides (mg/dl) ≥ 150	984 (34.6)	710 (32.6)	1694 (33.7)	0.157
HDL (mg/dl)<40 in males and <50 in females	1534 (53.9)	764 (35.1)	2298 (45.7)	<0.001*
Total cholesterol (mg/dl) >200	853 (30.0)	885 (40.7)	1738 (34.7)	<0.001*
ALT(U/L) ≥40	403 (14.2)	119 (5.5)	522 (10.40	<0.001*
AST (U/L) ≥40	140 (4.9)	57 (2.6)	197 (3.9)	<0.001*
HOMA Index ≥3.8	354 (12.4)	453 (20.8)	807 (16.1)	<0.001*
BMI (kg/m²)				
<25	1039 (36.6)	411 (18.9)	1450 (28.9)	<0.001*
≥25 -<30	1155 (40.7)	685 (31.6)	1840 (36.7)	
≥30	647 (22.8)	1073 (49.5)	1720 (34.3)	
Metabolic syndrome (ATPIII)	570 (20.0)	917 (42.2)	1487 (29.6)	<0.001*
Age groups (years)				
<40	1072 (37.6)	826 (38.0)	1898 (37.8)	0.113
40-60	1198 (42.1)	972 (44.7)	2170 (43.2)	
Above 60	578 (20.3)	377 (17.3)	955 (19.0)	
Fatty liver	1203 (42.2)	996 (45.8)	2199 (43.8)	0.012*

Abbreviations: NAFLD: Nonalcoholic fatty liver disease, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, BMI: Body Mass Index/ *Statistically significant: $P<0.05$

Univar ate regression analysis was performed to find the association of NAFLD with its potential predictors for each sex separately. Then all the factors with *P*_value ≥ 0.2 were used in multivariate logistic regression (forward LR) analysis. *P*_value < 0.05 was used to identify significant level in statistical tests.

Ethics approval

This study received ethics approval from the Human Research Ethics Committee of Iran University of Medical Science.

Results

Descriptive analysis

This study included 5023 participants (56.7% men and 43.3% women) with a mean age of 45.35 ± 15.87 years (age range: 18 to 90 years). The prevalence of NAFLD and metabolic syndrome (as one of the most important predictors of NAFLD) in the study group was 43.8% and 29.6% respectively. NAFLD was significantly more prevalent in women than men (45.8% vs. 42.2%, *P*= 0.01). The prevalence of metabolic syndrome was also significantly more prevalent in women than men (42.2% vs. 20%, *P*<0.001) (Table 1). The distribution of age groups between the two sexes was not significantly different (*P*=0.113) (Table 1).

NAFLD was significantly more prevalent in the age group of 40-60 years in comparison to the other two groups of <40 and > 60 years in total population (55.3% vs. 26.4% and 52% respectively, *P* < 0.001). This result was the same in men (51.8% vs. 30.2% and 44.6% respectively, *P* < 0.001) but in women NAFLD was most prevalent in the age group of >60 years (63.4% vs. 21.5% for<40 year old and 59.6% for 40-60 year old, *P* < 0.001)

As the prevalences of metabolic syndrome and NAFLD were significantly different between the two sexes, the prevalences of potential predictors of NAFLD (metabolic syndrome components and some other related biochemical and anthropometric parameters) were assessed for each sex separately.

The frequency of high WC, FSG, T-Chol, HOMA index, BMI and low HDL were significantly more in women than men (all *P* <0.001). The only two components of metabolic syndrome which were not significantly different between the two sexes were TG and Blood Pressure. At the same time women had significantly lower serum AST and ALT level (all *P* <0.001) (Table 1).

Univariate analysis

The risk of having NAFLD in participants with metabolic syndrome was significantly more than the participants without metabolic syndrome (OR: 4.328, CI (95%):3.08-4.92) and the risk was higher in women than men [OR: 5.9, CI (95%): 4.9-7.12 vs. OR:3.43, CI (95%): 2.83-4.16] (Table 2).

All components of metabolic syndrome (High Waist Circumference (cm), Fasting Serum Glucose, Triglycerides, hypertension and low HDL), high total cholesterol, high HOMA Index, serum ALT and AST ≥40 U/L, age ≥ 40 years and BMI ≥25 significantly increased the risk of NAFLD in both sexes (Table 3) so all these variables were used in Multivariate logistic regression except for BMI. Because of the significant correlation between BMI and WC, BMI was not included in the model.

Table 2: Association of metabolic syndrome with NAFLD

		NAFLD n(%)					
		Men		Women		Total	
		Yes	No	Yes	No	Yes	No
Metabolic syndrome	Yes	377 (66.1)	193 (33.9)	641 (69.9)	276 (30.1)	1018 (68.5)	469 (31.5)
	No	826 (36.3)	1452 (63.7)	355 (28.2)	903 (71.8)	1181 (33.4)	2355 (66.6)
OR (CI)		3.43 (2.83-4.16)		5.9 (4.9-7.12)		4.328 (3.08-4.92)	

Abbreviations: NAFLD: Nonalcoholic fatty liver disease.

Multivariate analysis

In both sexes WC, FSG, TG, HDL, Blood Pressure, age, ALT and HOMA Index were significantly associated with NAFLD (all, *P*<0.001). The association of T- Chol with NAFLD was significant only in men (*P*<0.001) (Table 3).

The strongest predictors of NAFLD in men were WC (OR: 7.99, CI (95%): 6.09-10.48), serum ALT (OR: 3.59, CI (95%): 2.76-4.69) and age 40-60 years old (OR: 2.56, CI (95%): 2.07-3.15).

The strongest predictors of NAFLD in women were WC (OR: 5.93, CI (95%): 4.66-7.55), age 40-60 years old (OR: 3.09, CI (95%): 2.41-3.97) and age>60 years (OR: 2.8, CI (95%): 2.01-3.88).

Table 3: Association between NAFLD and potential risk factors according to sex

Variables	Men		Women	
	Crude OR (CI)	Adjusted OR* (CI)	Crude OR (CI)	Adjusted OR* (CI)
Waist Circumference (cm) >102 in males and >88 in females	10.868 (8.422-14.025)	7.991 (6.090-10.485)	10.722 (8.566-13.421)	5.935 (4.661-7.556)
Fasting Serum Glucose (mg/dl) ≥ 100	2.181 (1.845-2.578)	1.536 (1.254-1.883)	3.933 (3.250-4.759)	1.449 (1.138-1.846)
Hypertension (mm Hg) (SBP≥130 or DBP≥85)	2.252 (1.931-2.626)	1.545 (1.287-1.855)	2.945 (2.460-3.525)	1.528 (1.224-1.907)
Triglycerides (mg/dl) ≥ 150	3.036 (2.587-3.562)	1.955 (1.588-2.406)	3.767 (3.115-4.554)	1.896 (1.506-2.388)
HDL (mg/dl)<40 in males and <50 in females	2.149 (1.847-2.500)	1.255 (1.034-1.5240	2.151 (1.791-2.582)	1.264 (1.005-1.590)
Total cholesterol (mg/dl) >200	1.976 (1.679-2.324)	1.263 (1.036-1.539)	2.157 (1.812-2.568)	1.048 (0.840-1.307)
ALT(U/L) ≥40	3.599 (2.871-4.511)	3.598 (2.761-4.690)	1.945 (1.331-2.841)	1.674 (1.047-2.676)
AST (U/L) ≥40	2.065 (1.461-2.917)	.793 (0.505-1.245)	2.629 (1.494-4.625)	1.634 (0.733-3.639)
HOMA Index ≥3.8	3.828 (3.005-4.876)	1.821 (1.353-2.451)	2.890 (2.326-3.592)	1.850 (1.401-2.444)
age 40-60 years	2.485 (2.091-2.953)	2.563 (2.079-3.159)	5.363 (4.349-6.614)	3.095 (2.412-3.971)
>60 years	1.861 (1.510-2.295)	1.835 (1.417-2.378)	6.305 (4.826-8.236)	2.800 (2.017-3.887)

Abbreviations: NAFLD: Nonalcoholic fatty liver disease, ALT: Alanine Aminotransferase.
*Each OR is adjusted according to other variables in the table.

Discussion

In this study, the prevalence of NAFLD in Amol, a city in north of Iran, diagnosed by sonography, was 43.8% which is more than the reported prevalence of 20-30% in western countries. This result can be due to the high prevalence of metabolic syndrome in Iran which has been reported to have one of the highest prevalences of metabolic syndrome worldwide. In this study the prevalence of metabolic syndrome was 29.6% which was is in close agreement with the results of Tehran Lipid and Glucose Study (TLGS) which found total age-standardized prevalence of 33.7% in the adult population (24).

In the current study NAFLD was significantly more prevalent in women than a man which was in accordance with the significantly higher preva-

lence of metabolic syndrome in women (42.2%) than men (20%). This is in close agreement with the results of Tehran Lipid and Glucose Study (TLGS) which found metabolic syndrome in 42% of women and 24% of men (25). The initial epidemiologic studies reported the same results (26-27) but some recent studies have reported a higher prevalence of NAFLD in men (28-30).

The prevalence of high WC, FSG, T-Chol, HOMA index, BMI and low HDL was significantly more in women than men which were in accordance with higher prevalence of NAFLD in women. As the distribution of age groups between the two sexes was not significantly different, the higher prevalence of NAFLD and its risk factors in women can not be related to age. This result confirms the existence of gender difference in the prevalence of NAFLD, which has also been shown in previous studies (31-32).

Despite the high prevalence of NAFLD in the study population (43.8%), high serum AST (≥40 U/L) and ALT (≥40 U/L) were only present in 3.9% and 10.4% of them respectively. This result was the same in another study where almost half of the patients with NAFLD had normal transaminases (33) or the studies based on liver biopsy that reported normal transaminases in patients with severe lesions (34-35). This is clinically important and several authors have suggested redefining the normal value of transaminases (12, 36-38). On the other hand, despite the higher prevalence of NAFLD and its risk factors in women, high serum AST and ALT were significantly more prevalent in men. This may be the result of more severe injuries of NAFLD in men despite the lower prevalence of NAFLD in them.

In both sexes WC, FSG, TG, HDL, Blood Pressure, age, ALT and HOMA Index were significantly associated with NAFLD. The association of T-Chol with NAFLD was significant only in men. The close association between different components of metabolic syndrome and NAFLD supports the theory that NAFLD is the hepatic manifestation of metabolic syndrome (39). These results are in agreement with the results of other studies which have reported that metabolic syndrome is an important risk factor for NAFLD (27). But the interesting point is that the association of metabolic syndrome and NAFLD is much stronger in women than men (Table 2) that means metabolic syndrome has a much more potency to result in NAFLD in women than men. More well designed studies are needed to clear the association between sex and the degree of injuries in NAFLD over time.

In this study, the strongest predictors of NAFLD in men were high WC, serum ALT and the age group of 40-60 years old and the strongest predictors of NAFLD in women were high WC, the age groups of 40-60 years old and older than 60 years respectively.

In both sexes the risk of having NAFLD in the age group of 40-60 years old was more than the group who were older than 60 years. This could be related to the difference of dietary habits in these two groups. Usually in Iran older people avoid consuming fast food and prefer traditional food.

This result is in accordance with Italian and Taiwanese studies which showed that an age of above 66 years and 65 years were inversely associated with the prevalence of NAFLD(12, 14). In fact the association of age with NAFLD has been controversial in different studies. In one study, age, especially of above 60 years, was an independent risk factor for NAFLD (33) and in another study it did not present any association between age and NAFLD (13).

This study also has its limitations. The first limitation is that although abdominal sonography is a good diagnostic tool for NAFLD it is not useful when fat accumulation is less than 30% of liver volume(9-10, 12-13, 40-41) or in morbid obesity (42) so this could underestimate the prevalence of NAFLD. The second limitation is that except for insulin resistance and metabolic syndrome components there are many factors such as genetic background, environmental factors and gut microbiota that may lead to the development of NAFLD (43) thus further studies are needed to evaluate the association of these potential risk factors and NAFLD in different communities.

Conclusion

This study showed a high prevalence of NAFLD and metabolic syndrome in Amol and its suburbs with a strong association between these two disorders. The prevalence of both disorders was significantly higher and their association significantly stronger in women but at the same time lower serum AST and ALT level in women may be an indicator of lower severity of NAFLD in this group. The strongest predictors of NAFLD in men were high WC, serum ALT and the age group of 40-60 years old and in women were high WC, the age groups of 40-60 years old and older than 60 years.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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References

1. Alba L, Lindor K (2003). Non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*,17 (8): 977-86.
2. Angulo P (2007). GI epidemiology: nonalcoholic fatty liver disease. *Aliment Pharmacol Ther*, 25 (8): 883-9.
3. Clark JM, Brancati FL, Diehl AM (2002). Nonalcoholic fatty liver disease. *Gastroenterology*, 122 (6): 1649-57.
4. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. (2005). Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology*, 41 (6): 1313-21.
5. Lattuada G, Ragogna F, Perseghin G (2011). Why Does NAFLD Predict Type 2 Diabetes? *Curr Diab Rep*, 11 (3): 167-72.
6. FAN JGAO, Zhu J, LI XJ, Chen L, LU YSAN, Li L, et al. (2005). Fatty liver and the metabolic syndrome among Shanghai adults. *J Gastroenterol Hepatol* , 20 (12): 1825-32.
7. Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, et al. (2005). The Metabolic Syndrome as a Predictor of Nonalcoholic Fatty Liver Disease. *Ann Intern Med*, 143 (10): 722-28.
8. Jeong SK, Kim YK, Park JW, Shin YJ, Kim DS (2008). Impact of visceral fat on the metabolic syndrome and nonalcoholic fatty liver disease. *J Korean Med Sci*, 23 (5): 789-95.
9. Neuschwander-Tetri BA, Caldwell SH (2003). Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology*, 37 (5): 1202-19.
10. Bedogni G, Bellentani S (2004). Fatty liver: how frequent is it and why. *Ann Hepatol*, 3 (2): 63-5.
11. Lee JY, Kim KM, Lee SG, Yu E, Lim YS, Lee HC, et al. (2007). Prevalence and risk factors of non-alcoholic fatty liver disease in potential living liver donors in Korea: a review of 589 consecutive liver biopsies in a single center. *J Hepatol*, 47 (2): 239-44.
12. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S (2005). Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology*, 42 (1): 44-52.
13. Zelber-Sagi S, Nitzan-Kaluski D, Halpern Z, Oren R (2006). Prevalence of primary non-alcoholic fatty liver disease in a population-based study and its association with biochemical and anthropometric measures. *Liver Int*, 26 (7): 856-63.
14. Chen CH, Huang MH, Yang JC, Nien CK, Yang CC, Yeh YH, et al. (2006). Prevalence and risk factors of nonalcoholic fatty liver disease in an adult population of Taiwan: metabolic significance of nonalcoholic fatty liver disease in nonobese adults. *J Clin Gastroenterol*, 40 (8): 745-52.
15. Fan JG, Saibara T, Chitturi S, Kim BI, Sung JJY, Chutaputti A (2007). What are the risk factors and settings for non-alcoholic fatty liver disease in Asia–Pacific? *J Gastroenterol Hepatol*, 22 (6): 794-800.
16. Esteghamati A, Meysamie A, Khalilzadeh O, Rashidi A, Haghazali M, Asgari F, et al (2009). Third national surveillance of risk factors of

non-communicable diseases (SuRFNCD-2007) in Iran: methods and results on prevalence of diabetes, hypertension, obesity, central obesity, and dyslipidemia. *BMC Public Health*, 29 (9): 167.

17. Rogha M, Najafi N, Azari A, Kaji M, Pourmoghaddas Z, Rajabi F, et al. (2011). Non-alcoholic Steatohepatitis in a Sample of Iranian Adult Population: Age is a Risk Factor. *Int J Prev Med*, 2 (1): 24–7.

18. Jamali R, Khonsari M, Merat S, Khoshnia M, Jafari E, Bahram Kalhori A, et al (2008). Persistent alanine aminotransferase elevation among the general Iranian population: Prevalence and causes. *World J Gastroenterol*, 14 (18): 2867-71.

19. Sohrabpour A, Rezvan H, Amini-Kafiabad S, Dayhim MR, Merat Shahin, Pourshams A (2010). Prevalence of nonalcoholic steatohepatitis in Iran: A population based study. *Mid East J Dig Dis*, 2 (1): 14 –9.

20. Hosseinpanah F, Rambod M, Sadeghi L (2007). Predictors of Non-Alcoholic Fatty Liver Disease in Type 2 Diabetese. *Int J Endocrinol Metab*, 2: 61-9.

21. Zamani F, Sohrabi M, Poustchi H, Keyvani H, Saeedian FS, Ajdarkosh H. (2013). Prevalence and Risk Factors of Hepatitis C Virus Infection in Amol City, North of Iran: A Population-Based Study (2008-2011). *Hepat Mon*, 13 (12): e13313.

22. McDowell MA (2005). Statistics NCfH, Control CfD, Prevention. Anthropometric reference data for children and adults: US population, 1999-2002: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics.

23. Sanyal AJ (2002). AGA technical review on nonalcoholic fatty liver disease. *Gastroenterology*, 123 (5): 1705-25.

24. Grundy SM, Hansen B, Smith Jr SC, Cleeman JI, Kahn RA (2004). Clinical management of metabolic syndrome. *Circulation*, 109 (4): 551-6.

25. Azizi F, Salehi P, Etemadi A, Zahedi-Asl S (2003). Prevalence of metabolic syndrome in an urban population: Tehran Lipid and Glucose Study. *Diabetes Res Clin Pract*, 61(1): 29-37.

26. Ludwig J, Viggiano TR, McGill DB, Oh BJ (1980). Nonalcoholic steatohepatitis. Mayo Clinic experiences with a hitherto unnamed disease: *Mayo Clin Proc*, 55 (7): 434-8.

27. Falck-Ytter Y, Younossi ZM, Marchesini G, McCullough AJ (2001). Clinical features and natural history of nonalcoholic steatosis syndromes. *Semin Liver Dis*, 21 (1): 17-26.

28. Bugianesi E, Manzini P, D'Antico S, Vanni E, Longo F, Leone N, et al. (2004). Relative contribution of iron burden, HFE mutations, and insulin resistance to fibrosis in nonalcoholic fatty liver. *Hepatology*, 39 (1): 179-87.

29. Harrison SA, Torgerson S, Hayashi PH (2003). The natural history of nonalcoholic fatty liver disease: a clinical histopathological study. *Am J Gastroenterol*, 98 (9): 2042-7.

30. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, et al. (2003). Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology*, 37 (4): 917-23.

31. Fraser A, Longnecker MP, Lawlor DA (2007). Prevalence of elevated alanine aminotransferase among US adolescents and associated factors: NHANES 1999–2004. *Gastroenterology*, 133 (6): 1814-20.

32. Tominaga K, Kurata JH, Chen YK, Fujimoto E, Miyagawa S, Abe I, et al (1995). Prevalence of fatty liver in Japanese children and relationship to obesity. *Dig Dis Sci*, 40 (9): 2002-9.

33. Caballería L, Pera G, Auladell MA, Torán P, Muñoz L, Miranda D, et al. (2010). Prevalence and factors associated with the presence of nonalcoholic fatty liver disease in an adult population in Spain. *Eur J Gastroenterol Hepatol*, 22 (1): 24-32.

34. Park JW, Jeong G, Kim SJ, Kim MK, Park SM (2007). Predictors reflecting the pathological severity of non-alcoholic fatty liver disease: Comprehensive study of clinical and immunohistochemical findings in younger Asian patients. *J Gastroenterol Hepatol*, 22 (4): 491-7.

35. Mofrad P, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, et al. (2003). Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology*, 37 (6): 1286-92.

36. Prati D, Taioli E, Zanella A, Torre ED, Butelli S, Del Vecchio E, et al. (2002). Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med*, 137 (1): 1-10.

37. Browning JD, Szczepaniak LS, Dobbins R, Horton JD, Cohen JC, Grundy SM, et al. (2004). Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology*, 40 (6): 1387-95.
38. Ekstedt M, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al. (2006). Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology*, 44 (4): 865-73.
39. Loria P, Lonardo A, Carulli N (2005). Should nonalcoholic fatty liver disease be renamed? *Dig Dis*, 23(1):72-82.
40. Caballería L, Auladell MA, Torán P, Miranda D, Aznar J, Pera G, et al. (2007). Prevalence and factors associated with the presence of non alcoholic fatty liver disease in an apparently healthy adult population in primary care units. *BMC Gastroenterol*, 7(1):41.
41. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, et al. (2002). The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology*, 123 (3): 745-50.
42. Mottin CC, Moretto M, Padoin AV, Swarowsky AM, Toneto MG, Glock L, et al. (2004). The role of ultrasound in the diagnosis of hepatic steatosis in morbidly obese patients. *Obes Surg*, 14(5): 635-7.
43. Burcelin R, Serino M, Chabo C, Blasco-Baque V, Amar J (2011). Gut microbiota and diabetes: from pathogenesis to therapeutic perspective. *Acta Diabetol*, 48 (4): 257-73.