Predictive Value of Having Positive Family History of Cardiovascular Disorders, Diabetes Mellitus, Dyslipidemia, and Hypertension in Non-Alcoholic Fatty Liver Disease Patients

Mohammad Ebrahim Ghamar-Chehreh[1], Hossein Khedmat[1], Mohsen Amini[1], and Saeed Taheri[2]

[1] *Baqiyatallah Research Center for Gastroenterology and Liver Disease, Baqiyatallah University of Medical Sciences, Tehran, Iran*

[2] *Taheri Medical Research Group, Baqiyatallah University of Medical Sciences, Tehran, Iran*

Received: 21 Jun. 2012; Received in revised form: 25 Nov. 2012; Accepted: 5 Jan. 2013

Abstract- In the present study, we examined the relationship between family history of cardiovascular diseases (CVD), dyslipidemia, hypertension, and diabetes with laboratorial abnormalities and syndromes in Iranian patients with non-alcoholic fatty liver disease (NAFLD). A total of 332 NAFLD patients from our outpatient clinic were consecutively entered into analysis. Exclusion criteria were having diabetes mellitus and fasting blood glucose over 126, active hepatitis B virus infection, having HCV positive serology, and to be under corticosteroid therapy. Family history of CVD, diabetes, dyslipidemia, and hypertension were taken from patients and related to the study variables. Family history of cardiovascular diseases (CVD) was associated with low HDL levels (P=0.05). Patients with positive family history of diabetes mellitus were significantly more likely to have AST/ALT levels proportion of higher than one (P=0.044). Family history of dyslipidemia was a predictor for hypertriglyceridemia (P=0.02), higher prothrombin time levels (P=0.013), lower albumin (P=0.024) and T4 (P=0.043) levels. Family history of hypertension was associated with dysglycemia/diabetes (P=0.038), high ALT (P=0.008), and low TIBC (P=0.007) and albumin levels (P=0.001). Family history for CVD, diabetes, dyslipidemia, and hypertension were of clinical importance in the Iranian patients with NAFLD. We therefore recommend that physicians should precisely get family history of main disorders in all NAFLD patients; and to pay more attention to those having the mentioned family histories. Further studies with larger patient population and prospective approach are needed for confirming our findings.

Acta Medica Iranica, 2013; 51(5): 307-313.

Keywords: Family history; NAFLD, Non alcoholic fatty liver disease

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a term representing a wide range of liver diseases from non symptomatic simple steatosis to aggressive nonalcoholic steatohepatitis and cirrhosis (1). NAFLD characterizes the most frequent chronic liver disease in the general population of either developed (2) or developing (3) countries; and is anticipated to become even more prevalent in the future, due to the increasing proportion of people of older age, obesity and diabetes (4). NAFLD is a very important obstacle in public health due to its overwhelming amount of financial and health burden to the patients, their families and the society (7). The major health concern of NAFLD is the risk of progressing into liver failure, cirrhosis and neoplasms (8) which can considerably lower patients' survival. Many patients and practitioners view fat in the liver as just 'fat in the liver,' but some researchers believe that a diagnosis of fatty liver should raise an alarm for impending type 2 diabetes, arterial hypertension, and CAD. In recent years, fatty liver has become more appreciated as a sign of insulin resistance, being a further expression of the metabolic syndrome (low-grade chronic inflammation) (5,6).

The etiology of NAFLD is likely multifactorial, involving both hereditary and environmental factors as well as their interactions. As like other chronic liver

Corresponding Author: Mohsen Amini
Baqiyatallah Research Center for Gastroenterology and Liver Disease, Baqiyatallah University of Medical Sciences, Tehran, Iran
Tel: +98 21 81261, Fax: +98 21 88934125, E-mail: dr.mohsen.amini@gmail.com

diseases, heterogeneity in the clinical presentations and behavior of NAFLD and interfering factors seems to be specific among various ethnic groups and populations (9). It has been shown that NAFLD has quite heterogenic presentations in different racial and ethnic groups, suggestive of a major role for the underlying genetic factors (9). Familial studies on NAFLD patients have suggested the disease as a disorder of genetic etiology (10). Some types of polymorphisms have been suggested to predispose NAFLD patients to more aggressive forms of the disease including the steatohepatitis and hepatic fibrosis (11,12).

Overwhelming data has demonstrated a strong epidemiological link between NAFLD and several metabolic disorders from which diabetes mellitus and coronary heart disease (CHD) has been well demonstrated (13); moreover, most of these morbidities are well known to have genetic and familial origins or strong associations. So, it would be logical if one assumes family history as a strong interfering factor in NAFLD development. Evidence suggests a strong family clustering of NASH (14). The genetic background of type 2 diabetes needs no description. It has been long known that healthy offspring of parents with Type 2 diabetes are at a higher risk of developing diabetes, and they have abnormal levels of fatty acids in their blood. Effects of genetic factors on the behavior of NAFLD have also been demonstrated with a relatively higher incidence of cirrhosis attributed to NASH in Hispanics than that in African-Americans despite similar levels of Type 2 diabetes in both groups (9,15). Surprisingly, this observation was despite a better lipids profile (low triacylglycerols and high HDL-cholesterol) in African-Americans. Another study focusing on the epidemiology of having positive family history of cardiovascular diseases in the general population showed that NAFLD is more prevalent among patients with such a positive history (16). In the present study, we examined the relationship between family history of coronary heart disease (CHD), hypertension, and diabetes with the epidemiology of disease presentations and syndromes in our Iranian NAFLD patient population.

Materials and Methods

The study was conducted cross-sectionally in the outpatients Clinic of Gastroenterology and Hepatology of Baqiyatallah University of Medical Sciences, Tehran, Iran. Overall 332 patients consecutively attended to our clinic, giving informed consent and were diagnosed as NAFLD entered into the study. NAFLD diagnosis was performed based on ultrasonographic evaluations which was prescribed due to clinical or biochemical suspicion (especially abnormal liver enzymes) to NAFLD, and exclusion of other diseases by medical history and/or laboratorial and physical evaluations. Exclusion criteria were having diabetes mellitus and fasting blood glucose over 126, active hepatitis B virus infection, having HCV positive serology, and to be under corticosteroid therapy. The study participants comprised a full range of socioeconomic levels. Family histories of hypertension, dyslipidemia, cardiovascular diseases, and diabetes mellitus were evaluated. The study was approved by the local Ethics Committee of the Baqiyatallah University of Medical Sciences; and written informed consent for participation was obtained from all the participants.

Study variables

The following data were achieved from each patient and entered into a database: gender, age, weight, height, waist circumstance, hip circumstance, serology test for HBs IgG, fasting blood glucose, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride, systolic and diastolic blood pressure, glucose tolerance test, serum insulin, C. peptide, HbA1C, total and direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombin time (PT), albumin, thyroid stimulating hormone (TSH), thyroid hormone (T4), ferritin, iron, and total iron binding capacity (TIBC). Metabolic syndrome, insulin resistance, and body mass index were calculated according to formulas described later in methods. A positive family history was diagnosed when the history was present in the first or second degree family members. The prevalence of a positive family history for diabetes mellitus was 125 (37.7%), cardiovascular diseases (CVD) 110 (33.1%), dyslipidemia 147 (44.3%), and hypertension 111 (33.4%).

Anthropometrical measures

Anthropometrical measurements (height, weight, blood pressure, and waist/hip diameter) were collected by experienced nurses while patients wore light clothing and no shoes. Waist circumference was measured - with the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared (kg/m^2).

Blood samples

Blood samples were taken in 0.1% EDTA in morning and after 12 hours overnight fast. Blood tubes were immediately stored at 4ºC and shielded from light. Blood tubes were centrifuged within 6 h at 2500 rpm for 20 min to separate plasma. Plasma concentrations of total cholesterol, fasting triglycerides, glucose, LDL- and HDL-cholesterol (LDL-C, HDL-C plus 2nd generation, direct quantification) were determined by using enzymatic kits from Roche Diagnostics with an autoanalyzer. Cholesterol measurements were standardized according to the program specified by the Centers for Disease Control and the National Heart, Lung and Blood Institute.

Homeostatic model assessment (HOMA) was calculated with the following formula: insulin (mIU/L) x glucose (mmol/L)/22.5. ALT levels were considered pathologically high when it was over 30 for men and over 19 for women.

Metabolic syndrome

As detailed in the third report of the Adult Treatment Panel (ATP III), subjects having three or more of the following criteria were defined as having the metabolic syndrome (17): 1) waist circumstance over 102 cm in men or 88 cm in women; (2) hypertriglyceridemia: serum triglycerides over 150 mg/dl; 3) low high-density lipoprotein cholesterol: serum HDL cholesterol below 40 mg/dl in men or 50 mg/dl in women; 4) high blood pressure: blood pressure over130/85 mmHg; 5) high fasting glucose: blood glucose levels exceeding 100 mg/dl. Subjects using antihypertensive medication were considered to meet the criteria for high blood pressure.

Data analysis

For descriptive data, student's t test was used. Chi-square test was used for categorical analysis. A value of $P<0.05$ on the two-tail test was considered statistically significant. All data were re-analyzed after excluding smokers, but it made no change to the study results. Statistical analyses were performed using SPSS-17.0 (SPSS Corp.; IL; Chicago; USA) for Windows.

Results

Tables 1 and 2 show demographic and laboratorial tests data of the study population. There were 211 (63.6%) males and 121 (36.4%) females. Mean ± SD age of the study population was 43.5±11.7 years. Self-rated socioeconomic levels were 325 (97.9%) intermediate and 4 (1.2%) low and 3 (0.9%) high. Educational levels of the study participants were 184 (55.8%) high school diploma, 97 (29.4%) under diploma, 1 (0.3%) illiterate, and 48 (14.5%) bachelor of science or more. 25 (7.5%) were smokers and 7 (2.1%) reported alcohol consumers.

Table 3 summarizes significant associations between the study variables and the evaluated histories. None of the demographic data were different between the two groups. Positive family history of CVD was associated with low HDL levels ($P=0.05$). Patients with positive family history of diabetes mellitus were significantly more likely to have AST/ALT levels proportion of higher than one ($P=0.044$). Family history of dyslipidemia was a predictor for hypertriglyceridemia ($P=0.02$), higher PT levels ($P=0.013$), lower albumin ($P=0.024$) and T4 ($P=0.043$) levels. Family history of hypertension was associated with dysglycemia/diabetes ($P=0.038$), high ALT ($P=0.008$), and low TIBC ($P=0.007$) and albumin levels ($P=0.001$).

Table 1. Categorical demographic and laboratorial data (%) of the study participants.

Variables	Result*
Age-year (SD)	43.5 (11.7)
Gender (male) (%)	211 (63.6)
Obesity (%)	192 (65.8)
HBS IgG positive (%)	242 (73.3)
Metabolic syndrome (%)	99 (42.7)
Hyperglycemia** (%)	96 (37.8)
High blood pressure or treatment (%)	70 (28.7)
Low HDL (%)	94 (37.9)
Hypertriglyceridemia (%)	160 (63)
Metabolic syndrome (%)	87 (27.7)
Insulin resistance (%)	163 (54.7)

* Percentages are derived from the available data for each item;** Defined by FBS>100 mg/dl or to be under antihyperglycemic treatment.

Table 2. Continuous laboratorial data of the study participants.

Variables	N	Mean ± SD
Systolic blood pressure	319	122 ± 14
Diastolic blood pressure	319	80 ± 8
Weight (kg)	323	84 ± 16
Height (cm)	322	167 ± 15
Waist circumstance (cm)	292	103 ± 11
Hip circumstance (cm)	292	104 ± 11
Body mass index	286	30 ± 4
Fasting blood sugar	332	97 ± 10
Glucose tolerance test	301	121 ± 73
Serum insulin	298	12 ± 7
C. peptide	279	6 ± 47
HbA1C	304	6 ± 2
Cholesterol	329	199 ± 42
Triglyceride	329	208 ± 119
High density lipoprotein	322	46 ± 11
Low density lipoprotein	320	114 ± 35
Total bilirubin	302	1 ± 0.6
Direct bilirubin	299	0.4 ± 0.2
Uric acid	275	6 ± 1.4
ALP	311	190 ± 69
AST	330	32 ± 18
ALT	330	47 ± 35
Albumin	250	5 ± 0.4
PT	125	13 ± 2
TSH	302	2.4 ± 2.9
T4	287	87 ± 24
Ferritin	270	182 ± 459
Iron	287	127 ± 308
TIBC	276	322 ± 60

Table 3. Significant associations of positive family history for diabetes mellitus, hypertension, dyslipidemia, and cardiovascular diseases with the study variables in NAFLD patients.

Variables	Positive family history	Negative family history	*P* value
Low HDL (%)	37 (45.7)	57 (34.1)	0.05*
AST/ALT>1 (%)	3 (3.3)	0	0.044**
Triglyceride (mg/dl)	226 ± 130	195 ± 107	0.02***
PT	13.2 ± 2.2	12.3 ± 1.9	0.013***
Albumin (mg/dl)	4.5 ± 0.49	4.6 ± 0.37	0.024***
T4	83.8 ± 26.5	89.6 ± 21.5	0.043***
Hyperglycemia*****/Diabetes (%)	46 (32.2)	50 (45)	0.038****
High ALT levels (%)	120 (78.9)	71 (64)	0.008****
TIBC	310 ± 66	332 ± 55	0.007****
Albumin (mg/dl)	4.5 ± 0.4	4.7 ± 0.3	0.001****

Note. Significant association for *family history of CVD; **family history of diabetes mellitus; ***family history of dyslipidemia; ****family history of hypertension; *****Defined by FBS>100 mg/dl or to be under antihyperglycemic treatment;

Discussion

Liver disease is associated with several other disorders including diabetes mellitus, CHD and heart diseases, quite more intensively than can be expected only by accident. Several risk factors have been associated with the development of new onset diabetes mellitus which are highly shared with those of NAFLD; an association between NAFLD and the insulin resistance (IR) syndrome has been observed (18). Familial clustering of insulin resistance supports a genetic predisposition to NAFLD (19). In the Iranian population, assessment of genetic polymorphisms has shown several genetic susceptibilities to NAFLD development (20). There is also evidence that single nucleotide polymorphisms (SNPs) in the gene for peroxisome proliferator-activated receptor-gamma (PPAR-γ), but not its co-activator-1a (PGC-1a), are associated with individual susceptibility to NAFLD (21). In the present study we have shown that family histories for CVD, diabetes mellitus, dyslipidemia, and hypertension in NAFLD patients are associated with important factors and can predict some critical abnormalities of utmost importance which can be used in the clinical practice.

There is overwhelming data on the cardiovascular diseases and their ominous consequences in diabetic or non-diabetic patients (22,23). It has also been shown that NAFLD has very strong relationships with cardiovascular disorders (24). On the other hand, it has been demonstrated that positive family history for CVD is associated with enhanced risk for NAFLD development in the general population (16). However, despite a comprehensive search of the current literature, no data was found about the relevance of having family history of CVD in NAFLD patients; so, this study can be considered the first evidence providing data on this issue. Among all the demographic and laboratorial data and syndromes evaluated in this study (listed in table 1&2), family history of CVD was associated with low HDL cholesterol levels in our NAFLD population. Since low HDL level is one of the best known factors associated with heart events (25), our finding would be of a highly important clinical prospect, alerting us to pay more attention to NAFLD patients who have a positive family history for CVD.

Other than laboratorial abnormalities, a number of clinical conditions have also been identified as risk factors for NAFLD development, including diabetes mellitus (26). In one study on an Iranian population, no significant relationship was found between having a family history for diabetes and GGT level alterations (27). However, that study was only on a male population whereas ours included both genders. The prevalence of diabetes mellitus in Iran is extremely high, notably in young population (28); and there is no need to explain that diabetes mellitus is associated with morbidity to almost all vital organs including the liver (29). As well, the existing evidence on the association of diabetes mellitus and NAFLD is extremely definite. Several studies have shown that NAFLD is highly prevalent among diabetic patients (30,31). On the other hand, in NAFLD patients, insulin resistance and diabetes mellitus is highly common (32-35). Previous studies have also mentioned potential association of having family history of diabetes with NAFLD development (36). Moreover, AST, ALT, and GGT levels had positive associations with having a family history of liver diseases (27). However, to the best of our knowledge, no major study exists about the family history of diabetes mellitus and its clinical and laboratorial relevance in non-diabetic NAFLD patients. As the first study, our survey showed that family history of diabetes mellitus is associated with elevated AST to ALT levels ratios in NAFLD patients. This finding is of utmost importance because AST/ALT>1 is usually considered as the determinant of progressed liver damage and cirrhosis (37). Moreover, it must be emphasized that this fact was found in NAFLD patients who had not diabetes or elevated serum glucose levels at the time of evaluations.

Dyslipidemia is one of the basic predictors of developing NAFLD in the general population (38). But alike the previously evaluated family histories, no study was found to show any association between having family history of dys- or hyper-lipidemias and laboratorial factors or specific syndromes in NAFLD patients; so we believe that our study provides the first data on. The associations of having a positive family history of dyslipidemia in NAFLD patients, as it was expected, was quite more extended than that the previously described disorders. Higher PT levels, as well as lower serum albumin and T4 levels were the laboratorial disorders found in NAFLD patients who had family history of dyslipidemia. Hypothyroidism has previously been associated with dyslipidemias in the general population (39). But this is the first study showing that a positive family history of dyslipidemias is associated with low T4 levels and disturbed liver function tests, in NAFLD patients.

Among the four disorders whose family histories were evaluated in our NAFLD patient population, family history of hypertension is the most investigated one in the literature. Even though, we found no study

which has investigated this in a NAFLD population. Evidence on general population has showed a higher incidence of lipid metabolism abnormalities as well as insulin resistance in people with a positive family history of hypertension (40). In the current study, we found that having a family history of hypertension is significantly associated with having lower TIBC and serum albumin levels. The observed lower serum albumin levels in NAFLD patients with a family history of hypertension shows that these patients are at risk for developing higher grades of liver damage.

This study has some limitations. The diagnosis of NAFLD in this study population was performed using ultrasonographic evaluations which might be a controversial definition method for some scientists. However, we should mention that we used this method due to ethical concerns over a liver biopsy for symptom-free patients of a non-life threatening illness. Finally, in conclusion, we found that family history for CVD, diabetes, dyslipidemia, and hypertension are of clinical importance in NAFLD patient population; so, we recommend physicians and most especially health authorities to pay more attention to children and youngsters with positive family histories for the mentioned diseases concomitant with clinical and laboratorial vulnerability to NAFLD development. Further studies with larger patient population and prospective approach are needed for confirming our findings.

References

1. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatology 2006; 43(2 Suppl 1):S99-S112.
2. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol 2003;98(5):960-7.
3. Kojima S, Watanabe N, Numata M, Ogawa T, Matsuzaki S. Increase in the prevalence of fatty liver in Japan over the past 12 years: analysis of clinical background. J Gastroenterol 2003;38(10):954-61.
4. Lazo M, Clark JM. The epidemiology of nonalcoholic fatty liver disease: a global perspective. Semin Liver Dis 2008;28(4):339-50.
5. Tarantino G. Should nonalcoholic fatty liver disease be regarded as a hepatic illness only? World J Gastroenterol 2007;13(35):4669-72.
6. Tarantino G, Colicchio P, Conca P, Finelli C, Di Minno MN, Tarantino M, Capone D, Pasanisi F. Young adult obese subjects with and without insulin resistance: what is the role of chronic inflammation and how to weigh it non-invasively? J Inflamm (Lond) 2009;6:6.
7. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2005;129(1):113–21.
8. Baumeister SE, Völzke H, Marschall P, John U, Schmidt CO, Flessa S, Alte D. Impact of fatty liver disease on health care utilization and costs in a general population: a 5-year observation. Gastroenterology 2008;134(1):85–94.
9. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004;40(6):1387–95.
10. Willner IR, Waters B, Patil SR, Reuben A, Morelli J, Riely CA. Ninety patients with nonalcoholic steatohepatitis: insulin resistance, familial tendency, and severity of disease. Am J Gastroenterol 2001;96(10):2957—61.
11. Valenti L, Fracanzani AL, Dongiovanni P, Santorelli G, Branchi A, Taioli E, Fiorelli G, Fargion S. Tumor necrosis factor alpha promoter polymorphisms and insulin resistance in nonalcoholic fatty liver disease. Gastroenterology 2002;122(2):274-80.
12. Dixon JB, Bhathal PS, Jonsson JR, Dixon AF, Powell EE, O'Brien PE. Pro-fibrotic polymorphisms predictive of advanced liver fibrosis in the severely obese. J Hepatol 2003;39(6):967-71.
13. Gupte P, Amarapurkar D, Agal S, Baijal R, Kulshrestha P, Pramanik S, Patel N, Madan A, Amarapurkar A, Hafeezunnisa. Non-alcoholic steatohepatitis in type 2 diabetes mellitus. J Gastroenterol Hepatol 2004;19(8):854-8.
14. Struben VM, Hespenheide EE, and Caldwell SH. Nonalcoholic steatohepatitis and cryptogenic cirrhosis within kindreds. Am J Med 2000;108(1):9-13.
15. Browning JD, Kumar KS, Saboorian MH, Thiele DL. Ethnic differences in the prevalence of cryptogenic cirrhosis. Am J Gastroenterol 2004;99(2):292-8.
16. Zhanga L, Pua K, Chaib Z, Dixon JB. Family history of coronary heart disease is associated with a higher incidence of nonalcoholic fatty liver disease: Central obesity the likely link. Obes Res Clin Pract 2007;1:125-31.
17. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285(19):2486-97.

18. Moscatiello S, Manini R, Marchesini G. Diabetes and liver disease: an ominous association. Nutr Metab Cardiovasc Dis 2007;17(1):63-70.
19. Abdelmalek MF, Liu C, Shuster J, Nelson DR, Asal NR. Familial aggregation of insulin resistance in first-degree relatives of patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2006;4(9):1162-9.
20. Hashemi M, Eskandari-Nasab E, Fazaeli A, Bahari A, Hashemzehi NA, Shafieipour S, Taheri M, Moazeni-Roodi A, Zakeri Z, Bakhshipour A, Ghavami S. Association of Genetic Polymorphisms of Glutathione-S-Transferase Genes (GSTT1, GSTM1, and GSTP1) and Susceptibility to Nonalcoholic Fatty Liver Disease in Zahedan, Southeast Iran. DNA Cell Biol 2011;31(5):672-7.
21. Kallwitz ER, McLachlan A, Cotler SJ. Role of peroxisome proliferators-activated receptors in the pathogenesis and treatment of nonalcoholic fatty liver disease. World J Gastroenterol 2008 Jan 7;14(1):22-8.
22. Dagogo-Jack S, Egbuonu N, Edeoga C. Principles and practice of nonpharmacological interventions to reduce cardiometabolic risk. Med Princ Pract 2010;19(3):167-75.
23. Saad H, Sawan S, Rashed W, Zubaid M. Influence of diabetes on the outcome of acute coronary syndrome in Kuwait. Med Princ Pract 2010;19(2):113-7.
24. Schindhelm RK, Diamant M, Heine RJ. Nonalcoholic fatty liver disease and cardiovascular disease risk. Curr Diab Rep 2007;7(3):181-7.
25. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. Circulation 1998;97(20):2007-11.
26. Fan JG, Farrell GC. Epidemiology of non-alcoholic fatty liver disease in China. J Hepatol 2009;50(1):204-10.
27. Khedmat H, Fallahian F, Abolghasemi H, Hajibeigi B, Attarchi Z, Alaeddini F, Holisaz MT, Pourali M, Sharifi S, Zarei N. Serum gamma-glutamyltransferase, alanine aminotransferase, and aspartate aminotransferase activity in Iranian healthy blood donor men. World J Gastroenterol 2007;13(6):889-94.
28. Azizi F, Salehi P, Etemadi A, Zahedi-Asl S. Prevalence of metabolic syndrome in an urban population: Tehran Lipid and Glucose Study. Diabetes Res Clin Pract 2003;61(1):29-37.
29. Al-Saeedi F, Loutfi I. (99m)Tc sulfur colloid and (99m)Tc mebrofenin hepatobiliary functional liver imaging in normal and diabetic rats. Med Princ Pract 2011;20(2):129-32.
30. Prashanth M, Ganesh HK, Vima MV, John M, Bandgar T, Joshi SR, Shah SR, Rathi PM, Joshi AS, Thakkar H, Menon PS, Shah NS. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus. J Assoc Physicians India 2009;57:205-10.
31. Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, Day C, Arcaro G. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care 2007;30(5):1212-8.
32. Younossi ZM, Gramlich T, Matteoni CA, Boparai N, McCullough AJ. Nonalcoholic fatty liver disease in patients with type 2 diabetes. Clin Gastroenterol Hepatol 2004;2(3):262-5.
33. Adams LA, Waters OR, Knuiman MW, Elliott RR, Olynyk JK. NAFLD as a risk factor for the development of diabetes and the metabolic syndrome: an eleven-year follow-up study. Am J Gastroenterol 2009;104(4):861-7.
34. Sargin M, Uygur-Bayramiçli O, Sargin H, Orbay E, Yayla A. Association of nonalcoholic fatty liver disease with insulin resistance: is OGTT indicated in nonalcoholic fatty liver disease? J Clin Gastroenterol 2003;37(5):399-402.
35. Chitturi S, Farrell GC. Fatty liver now, diabetes and heart attack later? The liver as a barometer of metabolic health. J Gastroenterol Hepatol 2007;22(7):967-9.
36. Johanson EH, Jansson PA, Lönn L, Matsuzawa Y, Funahashi T, Taskinen MR, Smith U, Axelsen M. Fat distribution, lipid accumulation in the liver, and exercise capacity do not explain the insulin resistance in healthy males with a family history for type 2 diabetes. J Clin Endocrinol Metab 2003;88(9):4232-8.
37. Giannini E, Botta F, Fasoli A, Ceppa P, Risso D, Lantieri PB, Celle G, Testa R. Progressive liver functional impairment is associated with an increase in AST/ALT ratio. Dig Dis Sci 1999;44(6):1249-53.
38. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999;116(6):1413-9.
39. Liberopoulos EN, Elisaf MS. Dyslipidemia in patients with thyroid disorders. Hormones (Athens) 2002;1(4):218-23.
40. Facchini F, Chen YD, Clinkingbeard C, Jeppesen J, Reaven GM. Insulin resistance, hyperinsulinemia, and dyslipidemia in nonobese individuals with a family history of hypertension. Am J Hypertens 1992;5(10):694-9.