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Non-alcoholic fatty liver disease may develop in individuals with normal body mass index

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Abstract

Background Although non-alcoholic fatty liver disease (NAFLD) is associated with obesity and metabolic syndrome (MS), it may also be present in lean individuals. We evaluated the characteristics of NAFLD patients, focusing on those with normal body mass index (BMI).

Methods One hundred and sixty-two of 185 consecutive NAFLD patients were included (23 were excluded due to missing data). NAFLD diagnosis required elevated ALT and/or GGT, hepatic steatosis on ultrasonography and no other cause of liver disease. Demographic, clinical, somatometric and laboratory characteristics were recorded. BMI <25 kg/m^2 was considered normal.

Results Normal BMI was present in 12% of patients. Patients with normal compared to those with increased BMI had numerically but not significantly lower prevalence of diabetes mellitus (6% vs. 15%, p=0.472), arterial hypertension (17% vs. 29%, p=0.276) and MS (20% vs. 41%, p=0.160). Normal BMI NAFLD patients met no criterion of MS more frequently (43% vs. 2%, p<0.0001) and had smaller waist circumference (94±6 vs. 108±10 cm, p<0.001), higher median levels of ALT (92 vs. 62 IU/L, p=0.032) and AST (45 vs. 37 IU/L, p=0.036) and relatively lower fasting glucose levels (98±22 vs. 106±29 mg/dL, p=0.052), but similar levels of HDL, LDL and triglycerides.

Conclusion Approximately 1 of 8 NAFLD patients coming to the tertiary liver center has normal BMI. These patients do not necessarily have insulin resistance associated metabolic disorders, but they have higher levels of ALT/AST than the overweight or obese NAFLD patients.

Keywords fatty liver, metabolic syndrome, insulin resistance

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Introduction

Non-alcoholic fatty liver disease (NAFLD) represents the most common cause of liver disease in industrialized countries [1,2]. In two large population-based cohort studies (the Dionysos Study from Italy and the Dallas Heart Study from the USA) its prevalence ranged between 25% and 30% [3,4]. In Greece, the prevalence of NAFLD in blood donors, based on elevated liver enzymes, was recently reported to be 18% [5]. The severity of NAFLD varies widely ranging from simple steatosis to steatohepatitis, advanced fibrosis and cirrhosis [6,7]. NAFLD is considered to be the hepatic manifestation of the metabolic syndrome [8]. Its prevalence increases with age and it is far more common among obese subjects (75%) and among subjects with type 2 diabetes mellitus (34-74%). In particular in obese subjects with type 2 diabetes, NAFLD is an almost universal finding [9,10]. Studies have also shown that the metabolic characteristics of NAFLD patients may be better predictors of the severity of NAFLD than the levels of alanine aminotransferase (ALT) [10,11]. Despite the higher prevalence of NAFLD in obese individuals and its association with the metabolic syndrome, the disease may also be present in the lean population [12]. Data from the Dionysos Study showed that the prevalence of NAFLD in the lean, non drinking population in Italy is around 16% [13]. Another study [14] reported that 22% of non-diabetic NAFLD patients had normal body mass index (BMI). However, the proportion of NAFLD patients with normal BMI among all NAFLD patients coming for evaluation in outpatient clinics and their characteristics in comparison with the overweight or obese NAFLD patients have not been completely clarified. Therefore, the aim of this study was to

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Conflict of Interest: None

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evaluate the characteristics of a large cohort of patients with NAFLD focusing on those with normal BMI.

Materials and Methods

In total, 185 adult patients with NAFLD were admitted to our outpatient liver clinics between 2002 and 2010. Of them, 23 patients were excluded because of missing data and 162 patients were included in this study.

NAFLD was diagnosed in patients with abnormal ALT and/or gamma-glutamyl transferase (GGT) activity, evidence of liver steatosis at ultrasonography and/or liver histology and no other cause of liver steatosis or injury. In particular, all patients were negative for hepatitis B surface antigen (HBsAg), antibodies against hepatitis C virus (anti-HCV), antibodies against human immunodeficiency virus (anti-HIV), they reported no alcohol use or weekly alcohol use less than 210 g for males and 140 g for females, they did not use any potentially hepatotoxic drug or agent and did not have any systemic disease with potential liver involvement. The history of alcohol use was reported by the patients but also by relatives and/or friends, if possible.

Demographic characteristics, medical history data, anthropometrical measurements and laboratory data were recorded. The history of known arterial hypertension was recorded, while arterial blood pressure was also measured during the initial visit, with the patient being in a relaxed state. Presence of diabetes mellitus was recorded with diabetes being diagnosed in cases with a known history of anti-diabetic treatment use and/or fasting glucose >126 mg/dL on more than one occasion. Height was measured with the participants wearing no shoes and weight was measured with the participants wearing light clothing. Standing waist circumference was measured at the high point of the iliac crests and hip circumference at the maximum circumference of the buttocks.

Laboratory data recorded for all patients included complete blood count, prothrombin time, serum levels of fasting glucose, cholesterol [high (HDL) and low density (LDL)], triglycerides, uric acid, urea, creatinine, liver enzymes [ALT, aspartate aminotransferase (AST), alkaline phosphatase, GGT, total protein, albumin], copper, ceruloplasmin, iron and ferritin, as well as detection of HBsAg, anti-HBc, anti-HBs, anti-HCV, anti-HIV, liver autoantibodies (anti-nuclear, anti-smooth muscles, anti-microsomial, anti-mitochondrial).

Definitions

BMI was considered to be normal if it was less than 25 kg/m^2. Metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program: Adult Treatment Panel III [15]. In particular, patients were considered to have metabolic syndrome, if they met three or more of the following criteria a) increased waist circumference: >102 cm for males or >88 cm for females, b) high triglyceride levels: ≥150 mg/dL or specific medication, c) low HDL cholesterol levels: <40 mg/dL for males or <50 mg/dL for females, d) fasting plasma glucose ≥110 mg/dL or specific medication or previously diagnosed type 2 diabetes mellitus, e) elevated arterial pressure: systolic ≥135 mmHg and/or diastolic ≥85 mmHg or specific medication or previously diagnosed hypertension. In this study, the fulfillment of the criterion of arterial pressure was based on the patients' previous history and repeated measurements and not on the single arterial pressure measurement on the day of baseline evaluation. Patients were considered to have dyslipidemia, if they met at least one of the following criteria: 1) cholesterol >200 mg/dL, 2) LDL cholesterol >120 mg/dL, 3) triglycerides >150 mg/dL at the time of diagnosis or during follow up, or 4) on treatment for dyslipidemia.

Statistical analysis

All analyses were carried out using the SPSS Statistics 19.0 (SPSS Inc, an IBM Company). Quantitative data were expressed as mean values ± standard deviation or as median (range) values. The normality of distribution of continuous quantitative variables was tested using the Shapiro-Wilk test or the Kolmogorov-Smirnov test, as appropriate. Comparisons between groups of quantitative variables with normal or abnormal distribution were performed using the t-test or Mann-Whitney test, respectively. Comparisons of categorical variables were performed using the corrected chi-square or the Fisher's exact test, as appropriate. A two-tailed P value <0.05 was considered to be statistically significant.

Results

Patient characteristics

The main demographic, medical history, anthropometrical and laboratory characteristics of the 162 patients with NAFLD are presented in Table 1. The majority (59%) of the patients was male and their mean age at diagnosis was 47±14 years. Roughly half (52%) of the patients were non-smokers. Diabetes mellitus was present in 14%. Thirty percent of the patients had a history of arterial hypertension, whereas 71% of them were found to have increased arterial pressure (systolic pressure ≥135 mmHg and/or diastolic pressure ≥85 mmHg) at their initial visit. Dyslipidemia was very common (76%), while coronary artery disease was relatively uncommon (4%). Metabolic syndrome at diagnosis was present in 38% of the 162 patients. Of the patients with metabolic syndrome, 72% had increased waist circumference, 46% low HDL levels, 47% hypertriglyceridemia, 22% hyperglycemia and 28% hypertension. At least one criterion of metabolic syndrome was present in 93% of patients.

As expected, the majority (143/162 or 88%) of patients had

Table 1 Demographic, clinical, anthropometrical and laboratory characteristics of 162 patients with non-alcoholic fatty liver disease

Gender, males (%)	96 (59)
Age on diagnosis, years	47±14
Body mass index, kg/m2	30 ±5
Waist circumference, cm	106±11
Increased waist circumference*, n/N (%)	71/99 (72)
Waist-to-hip ratio	0.96±0.61 (0.85-1.13)
Smoking habits, n/N (%)	
Never smokers	75/145 (52)
Previous smokers	35/145 (24)
Current smokers	35/145 (24)
Diabetes mellitus, n/N (%)	22/162 (14)
Family history of diabetes mellitus, n/N (%)	33/79 (42)
Arterial hypertension, yes	47/162 (29)
Coronary artery disease, yes	6/162 (4)
Dyslipidemia, n/N (%)	118/155 (76)
ALT, IU/L (ULN= 40)	65 (14-701)
Normal ALT, n/N (%)	34/162 (21)
AST, IU/L (ULN= 40)	38 (12-296)
GGT, IU/L (ULN= 50)	70 (13-1483)
Total cholesterol, mg/dL	218±44 (88-364)
HDL cholesterol, mg/dL	47±12 (11-75)
Low# HDL, n/N (%)	53/122 (43)
LDL cholesterol, mg/dL	138±34 (62-232)
Triglycerides, mg/dL	165±82 (46-590)
Triglycerides ≥150 mg/dL, n/N (%)	67/151 (44)
Serum glucose (fasting state), mg/dL	106±29 (70-275)
Serum glucose ≥ 110 mg/dL, n/N (%)	41/145 (28)
Uric acid, mg/dL	5.8±1.6 (2.2-10.8)
Metabolic syndrome, yes (≥3 criteria)	44/116 (38)
At least one criterion of metabolic syndrome, n/N (%)	132/142 (93)

**Waist circumference >102 cm for males or >88 cm for females*

#HDL <40 mg/dL for males or <50 mg/dL for females

increased BMI (≥25 kg/m^2), but there were 19 (12%) NAFLD patients with normal BMI (<25 kg/m^2). Waist circumference was increased in 71 (72%) of 99 patients with available data. In particular, waist circumference was increased in all (35/100%) female and 36 of 64 (56%) male patients (p<0.001).

Patients with normal or increased BMI

Table 2 shows the comparisons in the main characteristics between patients with normal and increased BMI. The gender distribution as well as the age of diagnosis did not differ significantly between these two groups. However, 79% (15/19) of the normal BMI patients did not have any comorbidity compared to 37% (49/143) of the patients with increased BMI (p=0.001). The prevalence of diabetes (normal vs. increased BMI group: 6% vs. 15%, p= 0.472) or family history for diabetes (33% vs. 43%, p=0.520) and the prevalence of arterial hypertension (17% vs. 29%, p=0.276) were numerically but not significantly lower in the normal BMI group. The prevalence of dyslipidemia was similar in the two groups (71% vs. 77%, p=0.556).

As anticipated, patients with normal BMI had significantly smaller waist circumference compared to those with elevated BMI (94±6 vs. 108±10 cm, p<0.001). However, one third of the normal BMI patients had increased waist circumference. The waist-to-hip ratio, another indirect marker of visceral adiposity, was also significantly lower in the normal than increased BMI patients (0.93±0.06 vs. 0.97±0.06, p=0.024).

Normal compared to increased BMI patients had higher median ALT [92 (17-164) vs. 62 (14-704) IU/L, p=0.032] and AST levels [45 (18-121) vs. 37 (12-295), p=0.036], but the two groups did not differ significantly in total cholesterol, HDL and LDL cholesterol or triglycerides levels. Glucose and uric acid serum levels tended to be lower in the normal than increased BMI subgroup, but the differences did not reach statistical significance (glucose: 98±22 vs. 106±29 mg/dL, p=0.052, uric acid: 5.1±0.9 vs. 5.9±1.6 mg/dL, p=0.061). Similarly, metabolic syndrome tended to be less common in patients with normal BMI (20% vs. 41%, p=0.160), while at least one criterion of metabolic syndrome was significantly less frequent in patients with normal than increased BMI (57% vs. 98%, p<0.001).

Discussion

Our data show that approximately one of 8 NAFLD patients admitted to the outpatient liver clinics of a tertiary Greek center have normal BMI. The inclusion of all patients with NAFLD followed at our clinics over a 9-year period suggests that the population of this study safely represents the patients with NAFLD coming for evaluation at the outpatient liver clinics of tertiary centers in Greece. Although lifestyle and diet modifications can result in BMI changes, the possibility of such modifications due to the diagnosis of NAFLD is very small in our patients, since we used data recorded at the patients' initial visit and before or at NAFLD diagnosis. NAFLD in non-obese patients has also been reported by others [8,14,16,17], even in children [18].

The associations of NAFLD with obesity [6,9] and the metabolic syndrome are well established in both Caucasians [14,19,20] and Asians [21], but the definition of metabolic

Table 2 Characteristics of patients with non-alcoholic fatty liver disease and normal or increased body mass index (BMI, kg/m^2)

	BMI <25 N=19	BMI ≥ 25 N=143	P
Gender, males (%)	11 (58)	85 (59)	0.897
Age at diagnosis, years	44±16	47±14	0.328
Comorbidities, n/N (%)	4/19 (21)	90/143 (63)	0.001
Smoking habits, n/N (%)			0.307
Never smokers	12/18 (67)	63/127(50)	
Previous smokers	4/18 (22)	31/127 (24)	
Current smokers	2/18 (11)	33/127 (26)	
Waist-to-hip ratio	0.93±0.06	0.97±0.06	0.024
Waist circumference, cm	94±5	108±10	<0.001
Increased waist circumference*, n/N (%)	5/15 (33)	66/84(79)	<0.001
Diabetes mellitus (DM), n/N (%)	1/19 (5)	21/143 (15)	0.475
Family history of DM, n/N (%)	4/12 (33)	29/67 (43)	0.520
Coronary artery disease, n/N (%)	0 (0)	6 (4)	>0.90
Arterial hypertension, n/N (%)	3/19 (16)	44/143 (31)	0.281
Dyslipidemia, n/N (%)	12/17 (71)	106/138 (77)	0.570
ALT, IU/L (ULN= 40)	92 (17-164)	62 (14-701)	0.032
Normal ALT, n/N (%)	2/19 (11)	32/143 (22)	0.369
AST, IU/L (ULN= 40)	45 (18-121)	37 (12-295)	0.036
GGT, IU/L (ULN= 50)	136 (15-482)	66 (13-1483)	0.226
Total cholesterol, mg/dL	223±48	218±44	0.566
HDL cholesterol, mg/dL	51±11	46±12	0.144
Low HDL#, n/N (%)	4/15 (27)	49/107 (46)	0.266
LDL cholesterol, mg/dL	145±38	137±34	0.343
Triglycerides, mg/dL	148±92	166±85	0.178
Triglycerides ≥150 mg/dL, n/N (%)	4/15 (27)	63/136 (46)	0.178
Serum glucose (fasting state), mg/dL	98±22	106±29	0.052
Serum glucose ≥110 mg/dL, n/N (%)	2/17 (12)	39/128 (31)	0.153
Uric acid, mg/dL	5.1±0.9	5.9±1.6	0.061
Metabolic syndrome, n/N (%)	3/15 (20)	41/101 (41)	0.160
At least one criterion of metabolic syndrome, n/N (%)	8/14 (57)	124/127 (98)	<0.001

**Waist circumference >102 cm for males or >88 cm for females*
#HDL <40 mg/dL for males or <50 mg/dL for females

syndrome may not be fulfilled in the majority of NAFLD patients, at least of Caucasian origin [2,14]. Similarly, most of the patients (62%) did not have metabolic syndrome. However, the vast majority of NAFLD patients (93%) fulfilled at least one criterion. This is also in agreement with data reported in other studies [14]. Our NAFLD patients with normal BMI

seem to have metabolic disorders less frequently compared to overweight or obese NAFLD patients, since the prevalence of metabolic syndrome, diabetes, elevated glucose levels, arterial hypertension and low HDL or high triglycerides levels were all found to be numerically higher in the latter group. The absence of statistical significance in these comparisons might be due to type II statistical errors because of the relatively small number of cases in the normal BMI group. In any case, diabetes mellitus, dyslipidemia, arterial hypertension and ischemic heart disease are strongly associated with obesity in the general population [22] and therefore they are expected to be more common among the overweight or obese than in the normal BMI NAFLD patients.

Almost all (98%) our patients with increased BMI had at least one criterion of metabolic syndrome compared to only 57% of the normal BMI cases ($p<0.001$). The most common feature of the metabolic syndrome was increased waist circumference, found in 72% of our patients and being significantly more frequent by definition in the increased than normal BMI group. The relationship of increased waist circumference with NAFLD is very prominent in Asians [17,23] and relatively variable in Caucasians [24,25]. However, in a recent study [26] increased waist circumference was reported to be present in only one third of NAFLD patients. Such a low prevalence of increased waist circumference in NAFLD patients may be related to the different anatomical area used for the measurement of waist circumference (at the level of the umbilicus in the study by Fracanzani instead of the midpoint between the lower border of the rib cage and the iliac crests in the Asian studies or the level of the iliac crests in the other studies) [27].

Arterial hypertension has been associated with a greater risk of NAFLD in the general population [24,28]. The prevalence of arterial hypertension did not differ significantly between our patients with normal and increased BMI, but the proportion of cases with increased arterial pressure at the initial visit was higher and significantly greater among the overweight and obese than in normal BMI patients (76% vs. 40%, $p=0.004$). Recent data [29,30] suggest that white coat hypertension is not an innocent condition, since it is related to structural changes in the left ventricle and therefore could be associated with increased cardiovascular risk [30]. NAFLD patients have been reported to have early left ventricular diastolic dysfunction [31] and impaired myocardial metabolism even in the absence of hypertension or diabetes [32].

The causes of NAFLD development in patients with normal BMI and no metabolic risk factor have not been completely clarified. Given the multi-factorial pathogenesis of this disease [6] genetic factors and/or specific dietary habits might be responsible for the development of NAFLD in lean individuals, even in the absence of metabolic disorders [33-36]. An increased intake of dietary fat has been suggested to lead to increased accumulation of lipids in the liver, thus leading to hepatic steatosis [37]. More specifically, a higher nutritional intake of cholesterol and a lower intake of polyunsaturated fatty acids has been reported by non-obese NAFLD patients compared to controls in a Japanese study [38], while a higher intake of soft drinks and meat has been shown to be associated with an increased risk of NAFLD, independently of BMI [36].

Regardless of dietary habits, NAFLD has been repeatedly shown to be associated with insulin resistance independently of BMI [8,25,39]. In particular in non-obese subjects, dysglycemia was found to be an independent risk factor for NAFLD [16]. The absence of the evaluation of serum insulin levels and insulin resistance is a limitation of our study, but other studies have reported that insulin resistance is frequently present in lean NAFLD patients even without other metabolic disorders [17,39,40]. It has also been shown that NAFLD patients, compared to healthy controls, have a higher degree of insulin resistance, even if they have fasting plasma glucose, fasting insulin levels and serum lipids within the normal range [40]. Since the degree of insulin resistance and prevalence of metabolic syndrome may increase from lean to overweight and obese NAFLD patients [14,17,40], it could be assumed that NAFLD often develops in the early phases of insulin resistance before the development of clinically evident metabolic disorders.

Although NAFLD has been shown to be closely associated with insulin resistance, this may not be the case for all NAFLD patients. A recent review by Tilg and Moschen [37] implies that inflammation may precede hepatic steatosis. In that context, the authors implied that steatosis is a "by-stander phenomenon" and not necessarily the cause of inflammation, adopting a multiple hits hypothesis in order to explain the pathogenesis of NAFLD. This is in agreement with the results of a study by Sanyal [41], which showed significant improvement in liver histology of NAFLD patients receiving vitamin E, an anti-oxidant agent, without any change in the degree of insulin resistance. These data give insight into the mechanisms involved in the development of hepatic steatosis and inflammation, which might also apply to the lean individuals.

An interesting finding was that our NAFLD patients with normal BMI were found to have significantly higher

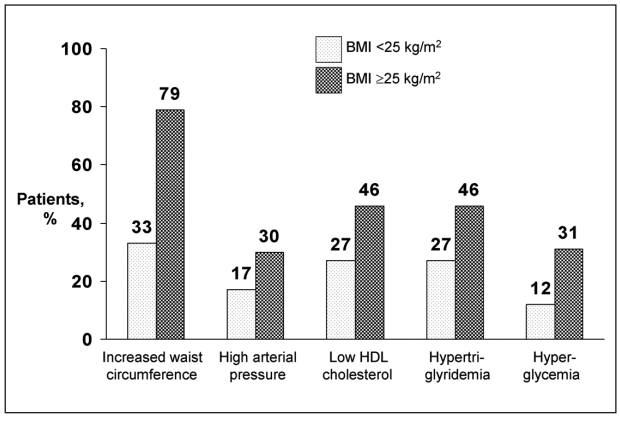

Figure 1 Prevalence of each criterion of the metabolic syndrome among NAFLD patients in relation to their body mass index (BMI). *HDL-c: high density lipoprotein cholesterol*

serum ALT and AST levels, compared to the overweight or obese patients. This finding might be related to a lower clinical suspicion of NAFLD in normal BMI individuals, in whom higher or persistently abnormal aminotransferase levels may be required before the admission to liver clinics and the initiation of diagnostic work-up. In contrast, mild or transient elevations of aminotransferases are often considered enough to raise the suspicion and justify further diagnostic procedures in individuals with increased BMI [42]. In addition, only GGT elevations can raise the suspicion of NAFLD in obese individuals [42] resulting in the diagnosis of NAFLD in patients with increased BMI and even normal ALT levels. Higher prevalence of normal ALT in obese patients with NASH has also been reported in another study including 97 patients with morbid obesity [43]. It should be noted, however, that the development of NASH and the severity of fibrosis are not necessarily associated with the levels of aminotransferases [10,11], but with the presence of obesity and diabetes mellitus, underlining the importance of the metabolic disorders in NAFLD.

In conclusion, more than 10% of patients with NAFLD referred to tertiary liver centers have normal BMI. These patients may have clinically evident metabolic disorders, but at a lower prevalence compared to overweight or obese NAFLD patients. Whether all NAFLD patients with normal BMI are at increased risk for subsequent development of metabolic disorders should be prospectively evaluated.

Summary Box

What is already known:

- Non-alcoholic fatty liver disease (NAFLD), the most common cause of liver disease in industrialized countries, is considered to be the hepatic manifestation of the metabolic syndrome
- NAFLD is much more common in obese than lean subjects
- NAFLD may also be present in the lean population, but the proportion and the characteristics of NAFLD patients with normal body mass index (BMI) have not been completely clarified

What the new findings are:

- Approximately 1 of 8 NAFLD patients coming to tertiary liver centers has normal BMI
- NAFLD patients with normal BMI:
  a. do not necessarily have insulin resistance associated metabolic disorders
  b. have higher levels of ALT/AST than the overweight or obese NAFLD patients

References

1. Argo CK, Caldwell SH. Epidemiology and natural history of non-alcoholic steatohepatitis. *Clin Liver Dis* 2009;**13**:511-531.
2. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004;**40**:1387-1395.
3. Bellentani S, Tiribelli C, Saccoccio G, et al. Prevalence of chronic liver disease in the general population of northern Italy: the Dionysos Study. *Hepatology* 1994;**20**:1442-1449.
4. Szczepaniak LS, Nurenberg P, Leonard D, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. *Am J Physiol Endocrinol Metab* 2005;**288**:E462-E468.
5. Papatheodoridis GV, Goulis J, Christodoulou D, et al. High prevalence of elevated liver enzymes in blood donors: associations with male gender and central adiposity. *Eur J Gastroenterol Hepatol* 2007;**19**:281-287.
6. Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med* 2002;**346**:1221-1231.
7. Rector RS, Thyfault JP, Wei Y, Ibdah JA. Non-alcoholic fatty liver disease and the metabolic syndrome: an update. *World J Gastroenterol* 2008;**14**:185-192.
8. Marchesini G, Brizi M, Bianchi G, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes* 2001;**50**:1844-1850.
9. Bellentani S, Marino M. Epidemiology and natural history of non-alcoholic fatty liver disease (NAFLD). *Ann Hepatol* 2009;**8 Suppl 1**:S4-S8.
10. Fracanzani AL, Valenti L, Bugianesi E, et al. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. *Hepatology* 2008;**48**:792-798.
11. Wong VW, Wong GL, Tsang SW, et al. Metabolic and histological features of non-alcoholic fatty liver disease patients with different serum alanine aminotransferase levels. *Aliment Pharmacol Ther* 2009;**29**:387-396.
12. Youssef WI, McCullough AJ. Steatohepatitis in obese individuals. *Best Pract Res Clin Gastroenterol* 2002;**16**:733-747.
13. Bellentani S, Saccoccio G, Masutti F, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. *Ann Intern Med* 2000;**132**:112-117.
14. Marchesini G, Bugianesi E, Forlani G, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology* 2003;**37**:917-923.
15. 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**:2486-2497.
16. Das K, Das K, Mukherjee PS, et al. Nonobese Population in a Developing Country Has a High Prevalence of Nonalcoholic Fatty Liver and Significant Liver Disease. *Hepatology* 2010;**51**:1593-1602.
17. Kim HJ, Kim HJ, Lee KE, et al. Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. *Arch Intern Med* 2004;**164**:2169-2175.
18. Manco M, Alisi A, Real JMF, et al. Early interplay of intra-hepatic iron and insulin resistance in children with non-alcoholic fatty liver disease. *Journal of Hepatology* 2011;**55**:647-653.
19. Caballeria L, Pera G, Auladell MA, et al. Prevalence and factors associated with the presence of nonalcoholic fatty liver disease in an adult population in Spain. *Eur J Gastroenterol Hepatol* 2010;**22**:24-32.
20. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006;**43**:S99-S112.

21. Chen SH, He F, Zhou HL, Wu HR, Xia C, Li YM. Relationship between nonalcoholic fatty liver disease and metabolic syndrome. *J Dig Dis* 2011;**12**:125-130.
22. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 1999;**341**:1097-1105.
23. Sung KC, Ryan MC, Kim BS, Cho YK, Kim BI, Reaven GM. Relationships between estimates of adiposity, insulin resistance, and nonalcoholic fatty liver disease in a large group of nondiabetic Korean adults. *Diabetes Care* 2007;**30**:2113-2118.
24. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology* 2005;**42**:44-52.
25. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. *Gastroenterology* 2003;**124**:71-79.
26. Fracanzani AL, Valenti L, Bugianesi E, et al. Risk of nonalcoholic steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease and low visceral adiposity. *J Hepatol* 2011;**54**:1244-1249.
27. Bosy-Westphal A, Booke CA, Blocker T, et al. Measurement site for waist circumference affects its accuracy as an index of visceral and abdominal subcutaneous fat in a Caucasian population. *J Nutr* 2010;**140**:954-961.
28. Donati G, Stagni B, Piscaglia F, et al. Increased prevalence of fatty liver in arterial hypertensive patients with normal liver enzymes: role of insulin resistance. *Gut* 2004;**53**:1020-1023.
29. Pall D, Lengyel S, Komonyi E, et al. Impaired cerebral vasoreactivity in white coat hypertensive adolescents. *Eur J Neurol* 2011;**18**:584-589.
30. Shehab A, Abdulle A. Cognitive and autonomic dysfunction measures in normal controls, white coat and borderline hypertension. *BMC Cardiovasc Disord* 2011;**11**:3.
31. Goland S, Shimoni S, Zornitzki T, et al. Cardiac abnormalities as a new manifestation of nonalcoholic fatty liver disease: echocardiographic and tissue Doppler imaging assessment. *J Clin Gastroenterol* 2006;**40**:949-955.
32. Perseghin G, Lattuada G, De Cobelli F, et al. Increased mediastinal fat and impaired left ventricular energy metabolism in young men with newly found fatty liver. *Hepatology* 2008;**47**:51-58.
33. Daly AK, Ballestri S, Carulli L, Loria P, Day CP. Genetic determinants of susceptibility and severity in nonalcoholic fatty liver disease. *Expert Rev Gastroenterol Hepatol* 2011;**5**:253-263.
34. Solga S, Alkhuraishe AR, Clark JM, et al. Dietary composition and nonalcoholic fatty liver disease. *Dig Dis Sci* 2004;**49**:1578-1583.
35. Valenti L, Al Serri A, Daly AK, et al. Homozygosity for the patatin-like phospholipase-3/adiponutrin I148M polymorphism influences liver fibrosis in patients with nonalcoholic fatty liver disease. *Hepatology* 2010;**51**:1209-1217.
36. Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, et al. Long term nutritional intake and the risk for non-alcoholic fatty liver disease (NAFLD): a population based study. *J Hepatol* 2007;**47**:711-717.
37. Tilg H, Moschen AR. Evolution of Inflammation in Nonalcoholic Fatty Liver Disease: The Multiple Parallel Hits Hypothesis. *Hepatology* 2010;**52**:1836-1846.
38. Yasutake K, Nakamuta M, Shima Y, et al. Nutritional investigation of non-obese patients with non-alcoholic fatty liver disease: The significance of dietary cholesterol. *Scandinavian Journal of Gastroenterology* 2009;**44**:471-477.
39. Marchesini G, Brizi M, Morselli-Labate AM, et al. Association of nonalcoholic fatty liver disease with insulin resistance. *Am J Med* 1999;**107**:450-455.
40. Bugianesi E, Gastaldelli A, Vanni E, et al. Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. *Diabetologia* 2005;**48**:634-642.
41. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis. *New England Journal of Medicine* 2010;**362**:1675-1685.
42. Clark JM, Brancati FL, Diehl AM. Nonalcoholic fatty liver disease. *Gastroenterology* 2002;**122**:1649-1657.
43. Gholam PM, Flancbaum L, Machan JT, Charney DA, Kotler DP. Nonalcoholic fatty liver disease in severely obese subjects. *Am J Gastroenterol* 2007;**102**:399-408.