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Cardiovascular Disease Risk Factors among Non-Alcoholic Fatty Liver Disease Patients at Makkah, Kingdom of Saudi Arabia

Ahmed Faisal[1], Mahmoud Elshahat[2], Reda Goweda[3], Arij Alzaidi[4], Bashaer Aldhawani[4] & Hibah Alharbi[4]

[1] Department of Infectious and Endemic Diseases, Faculty of Medicine, Suez Canal University, Egypt

[2] Cardiology Department, Faculty of Medicine, Al Azhar University, Egypt

[3] Department of Family Medicine, Faculty of Medicine, Suez Canal University, Egypt

[4] Medical Interns, Faculty of Medicine, Umm Al-Qura University, Makkah, KSA

Correspondence: Reda Goweda, Family Medicine Department, Faculty of Medicine, Suez Canal University, Egypt. E-mail: redagoweda@yahoo.com

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is one of the major health problems which is characterized by excessive fat accumulation in the liver. Worldwide, NAFLD has a reported prevalence of 6 to 35 percent in the general population. The prevalence of NAFLD has increased as more patients develop a sedentary lifestyle, metabolic syndrome, and obesity.

Aim and Objectives: To study cardiovascular disease risk factors among NAFLD patients aiming to reduce morbidity and mortality.

Methodology: This was a cross sectional study. Cardiovascular risk factors questionnaire including personal data, BMI, lipid profile and blood pressure was used to obtain the data from 150 patients with ultrasound diagnosed NAFLD and 150 patients with no evidence of NAFLD at Umm Al Qura University medical center, Makkah, Kingdom of Saudi Arabia.

Results: 54.7% out of 150 NAFLD patients were males, 91.3% were obese, 50.7% were diabetics, 28% hypertensive, 53.7% had high cholesterol level, 52.7 % had high triglycerides and 64.6% had high LDL level. Results showed significant high prevalence of most of CVD risk factors among NAFD patients in comparison to age matched group of patients without NAFLD.

Conclusion: NAFLD patients have a high risk of cardiovascular diseases more than non NAFLD.

Keywords: cardiovascular, risk, factors, NAFLD

1. Introduction

Nonalcoholic steatohepatitis (NASH) is characterized by deposition of fat inside liver cells accompanied by liver inflammation with no history of alcohol intake, this was described first by Dr. Ludwig 3 decades ago (Ludwig, Viggiano, McGill, & Oh BJ, 1889).

Nonalcoholic fatty liver disease (NAFLD) is a case of liver steatosis without secondary causes for hepatic fat accumulation. Liver cirrhosis may be a sequel of NAFLD which is considered as one of the most important causes of cryptogenic cirrhosis (Browning, Kumar, Saboorian, & Thiele, 2004). The prevalence of NAFLD is increasing quickly due to rising prevalence of Diabetes Mellitus and obesity (Chitturi et al., 2007).

In developed countries, NAFLD is considered the most common liver disease (Jump & Rinella, 2015). The prevalence of NAFLD is increasing and reported of 6 to 35%. In a prospective study of 400 participants, the prevalence of NAFLD by ultrasound was 46% and it was reported in the same study that factors correlating with NAFLD included obesity, male sex, diabetes, increasing age, and hypertension (Williams et al., 2011). Between 2011 and 2012, a new research in the United States depending on the National Health and Nutrition Examination Survey (NHANES) reported a 30% prevalence of NAFLD (Ruhl & Everhart, 2015).

In1988, NAFLD accounted for 47% of chronic liver diseases that rose to be 75% in 2008. This rise is most possibly due to increase in metabolic risk factors, also in the context of aging populations (Younossi et al., 2011).

Although the metabolic syndrome is a common factor among NAFLD's patients, NAFLD may be independently associated with cardiovascular disease. NAFLD was associated with cardiovascular diseases after controlling for male sex, older age, type 2 Diabetes, obesity, smoking, and family history of premature coronary heart disease, according to study that used data from NHANES (Stepanova & Younossi, 2012).

Both environmental and genetic factors are involved in the pathogenesis of NAFLD and it was proven that the process of NAFLD pathogenesis is multifactorial (Kim & Younossi, 2008).

NAFLD is classified into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). In NAFL, the condition can be described as fatty liver without evidence of considerable inflammation, whereas in NASH, hepatic steatosis is associated with hepatic cells injury (Sheth, Gordon, & Chopra, 1997). NASH is considered as a major cause of hepatic cirrhosis of unknown cause after excluding alcohol intake, viral hepatitis and other causes of liver diseases (Jump, Clark, & Diehl, 2003). NASH will progress to cirrhosis in up to 20% of the patients that can progress to advanced liver disease, and hepatocellular carcinoma (Hashizume et al., 2013).

Most of the patients with NAFLD are diagnosed accidentally as most are symptomless (Lindor, 2003). Patients may complain of easy fatigability, malaise, and dull aching pain on the right-upper-quadrant of the abdomen (Adams & Angulo, 2006).

Although physical examination of the patients with NAFLD is usually unremarkable, some findings can be present as yellowish sclera and palpable liver (Loria et al., 2010).

No single laboratory test is diagnostic for nonalcoholic fatty liver disease. Liver enzyme levels have low sensitivity and specificity, and do not predict clinical outcomes (Musso, Gambino, Cassader, & Pagano, 2011). Abdominal ultrasonography is the first line for screening and diagnosis of steatosis and it is considered a reliable technique for evaluation and detection of steatosis (Musso et al., 2011).

Although liver biopsy is not routinely used for diagnosis of NAFLD, may not affect treatment decisions, and its routine use is controversial, it is still considered in patients with normal body weight and highly elevated liver enzymes (atypical clinical situations) (Ma et al., 2009).

The first-line therapeutic measures are healthy diet, weight reduction, and exercise to reduce insulin resistance (Musso et al., 2011).

Formerly, it was thought that NAFLD is a benign hepatic disease, but now it is considered as a greatly atherogenic disease as reported by studies when compared with control subjects who do not have NAFLD. Patients with NAFLD have a higher prevalence of atherosclerosis, which is independent of obesity and other established risk factors (Blackett & Sanghera, 2013) , moreover other studies have confirmed that cardiovascular disease is the single most important cause of mortality in this patient population (Misra , Khashab, & Chalasani, 2009).

2. Methodology

This was a cross sectional study conducted at Umm Al Qura University medical center, Makkah, Kingdom of Saudi Arabia, over patients attending both the Internal Medicine and Cardiology clinics.

Participants were classified into those with NAFLD (based on ultrasound analysis; n = 150) and those without NAFLD (absence of NAFLD or any other chronic liver diseases: controls n = 150).

All patients above 18 years of age who accepted to share in the study were included with exclusion of patients with alcohol consumption, chronic viral hepatitis, autoimmune liver disease and patients taking medications that can account for steatosis (e.g. tamoxifen, amiodarone, methotrexate) during the previous year.

2.1 Tools of the Study

2.1.1 Diagnosis of NAFLD

Subjects were included in the study according to the standard criteria accepted by the American Gastroenterology Association for diagnosis of NAFLD: a hyperechoic appearance of the liver parenchyma with fine, tightly packed echoes and posterior beam attenuation (Roti, Sunita, VK &, Sweta, 2008).

2.1.2 Patients' Data Used in this Study Included

2.1.2.1 Biographical Information

Age, Gender, Family History of CHD, Life Style Medical History such as DM and HTN Including Their Medications.

High risk age (men > 55 or women > 65), high risk age of relatives with CHD (men < 55 or women < 65).

2.1.2.2 Physical Examination

Weight, Height, BMI, Waist circumference and BP measurement.

BMI ranges are underweight: < 18.5 (kg/m2), normal weight: 18.5 to 25, overweight: 25 to 29.9, class I obesity: 30 to 34.9, class II obesity: 35 to 39.9 and class III obesity ≥ 40 (WHO expert consultation, 2004).

2.1.2.3 Laboratory Investigations Included (total cholesterol, LDL, HDL, TRIG, FBS).

Low risk HDL (men > 40 mg per dL or women > 50 mg per dL)

2.1.3 Risk Assessment

Estimating 10-year risk of having a heart attack was done and the risk was divided into High risk (> 20%), Intermediate risk (10% to 20%) and Low risk (< 10%) (CCHVI, 2015). This risk assessment tool depends on the Framingham Heart Study to calculate risk of having a heart attack or death from coronary disease in the next 10 years.

The risk factors included in the Framingham calculation included: age, cigarette smoking, total cholesterol, HDL cholesterol, blood pressure measurement and treatment for hypertension. Point values are calculated based on each of these risks.

A simple and clear explanation of the research aims and procedures was provided to each participant. Furthermore, written and verbal consent was obtained and confidentiality was assured. All the procedures of this study were approved by ethical committee of Faculty of Medicine, Umm Al Qura University, KSA.

SPSS Version 20 was used for statistical analysis. The chi-square test (Fisher's Exact) was used for categorical variables, while Student's t-test was used for continuous. Statistical significance was set at p-value < 0.05.

3. Results

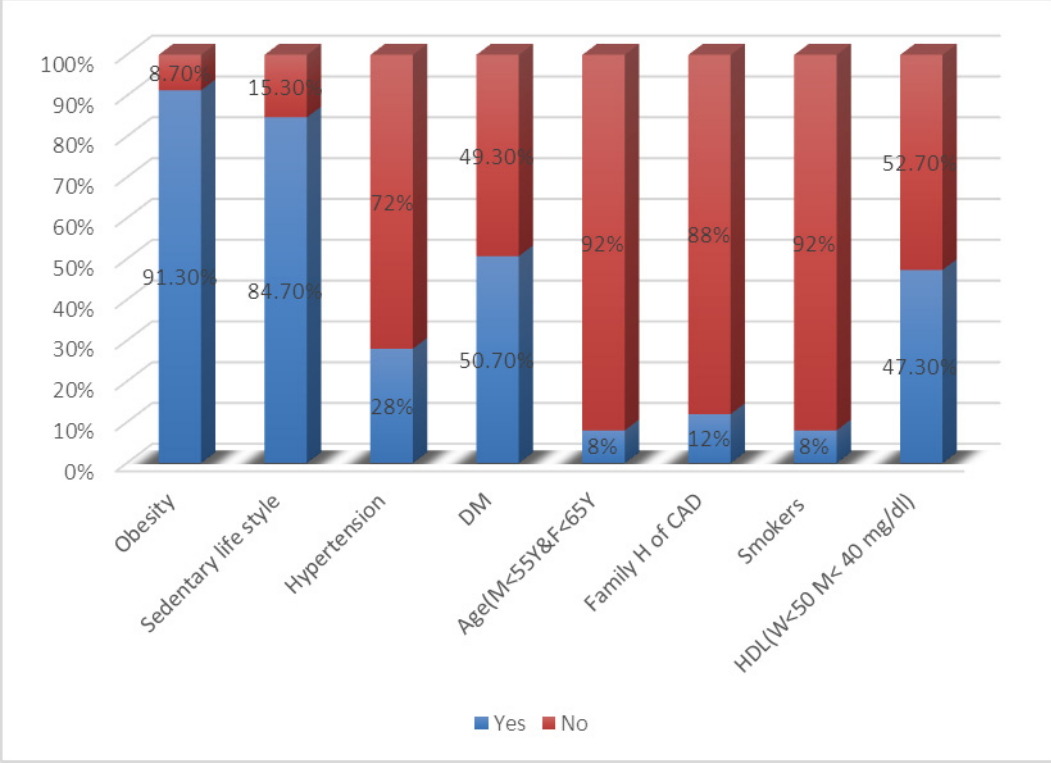

Figure 1. Patient's characteristics (NAFLD Group)

91.3% of NAFLD patients were obese, 50.7% were diabetics, 28% hypertensive, 12% had family history of premature coronary heart disease and 84.7% of them had sedentary lifestyle.

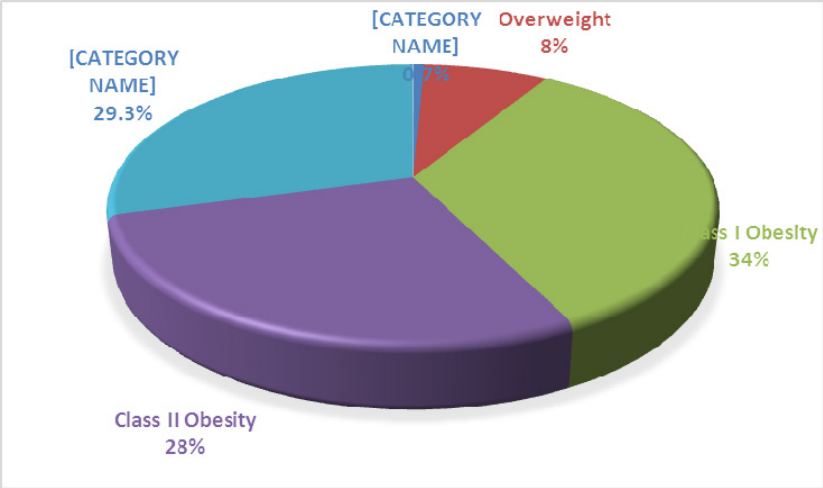

Figure 2. Distribution of NAFLD patients according to BMI

According to BMI; 12 (8%) of NAFLD patients were overweight and 137 (91.3%) were obese, 51 (34%) of obese patients had Class I obesity obese, 42 (28%) had Class II obesity and 44 (29.3) had Class III obesity.

Table 1. Comparison between NAFLD and non NAFLD patients regarding demographic characteristics

	NAFLD	**Non NAFLD**	**Test**	**P value**
Gender				
Male	103 (68.7%)	99 (66%)	Chi-Square	0.712
Female	47 (31.3%)	51 (34.0%)		
Age				
High risk **(males>55 or females>65 years)**	12(8.0%)	10(6.7%)	Chi-Square	0.825
Low risk	138 (92.0%)	140 (93.3%)		
	μ 45.38±8.43	**μ 44.08±10.12**	T test	0.228
Life style				
Sedentary	127 (84.7%)	75 (50%)	Chi-Square	0.000
Regular exercise	23 (15.3%)	75 (50%)		
Family history of premature CAD				
Yes	18(12.0%)	6(4.0%)	Chi-Square	0.018
No	132 (88.0%)	144 (96.0%)		
Smoking				
Non-smoker	131 (87.3 %)	132 (88 %)		
current smoker	12 (8 %)	18 (10%)	Fisher's Exact	0.011
Ex- smoker	7 (4.7 %)	0 (0.0%)		
DM				
Yes	76 (50.7%)	6 (4%)	Chi-Square	0.000
No	74 (49.3%)	146 (96%)		
Hypertension				
Yes	42 (28.0%)	15 (10.0%)	Chi-Square	0.000
No	108 (72%)	135 (90%)		
Obesity				
Yes	137 (91.3%)	24 (16%)	Fisher's Exact	0.000
No	13 (8.7%)	126 (84%)		

Mean age in NAFLD group was 45.38 ± 8.43 while in Non NAFLD group it was 44.08 ± 10.12 with no significant difference, furthermore there was no significance among the two groups regarding gender. Regarding lifestyle there was significant difference between NAFLD and Non NAFLD as shown; most of NAFLD group (84.7%) had sedentary lifestyle. Additionally, there was a significant difference between NAFLD and Non NAFLD group regarding obesity, hypertension, diabetes, smoking and family history of premature coronary heart diseases.

Table 2. Comparison between NAFLD and non NAFLD patients regarding lipid profile and 10-year risk of having a heart attack

	NAFLD	**Non NAFLD**	**Test**	**P value**
Triglycerides				
<150 mg/dL	65(43.3%)	114 (76.0%)	Chi square	0.000
150-250	60 (40 %)	30 (20.0%)		
250-500	23 (15.3 %)	6 (4.0%)		
>500	2 (1.3 %)	0 (0.0%)		
	µ179.98± 82.53	**µ139.00± 57.45**	t test	0.000
Total cholesterol				
less than 200	68 (45.3 %)	93 (62.0%)	Chi- square	0.000
200-239	52 (34.7 %)	39 (26.0%)		
more than 240	30 (20 %)	18 (12.0%)		
	µ205.74± 49.85	**µ195.90±24.86**	t test	0.031
HDL				
Low risk	79(52.7%)	123 (82.0%)	Chi-- square	0.000
High risk	71 (47.3%)	27 (18%)		
	µ47.85±16.37	**µ44.30±5.75**	t test	0.013
LDL				
<100 mg/dL	50 (33.3 %)	126(84%)	Chi- square	0.000
100-130	38 (25.3 %)	12 (8.0%)		
130-160	35 (23.3 %)	12 (8.0%)		
≥190	27 (18 %)	0 (0.0%)		
	µ122.66±44.26	**µ107.36±33.08**	t test	0.002
10-year Risk of Having a Heart Attack				
Low risk	128 (85.3 %)	141 (94.0%)	Chi- square	0.033
Intermediate	20 (13.3 %)	9 (6.0%)		
High	2 (1.3 %)	0 (0.0%)		
	µ4.2133±4.25	**µ2.80±3.53**	t test	0.022

23 (15.3 %) of NAFLD had triglycerides of 250-500 while 71 (47.3%) had bad HDL. Low risk (women < 50 and men < 40 mg per dL) and 27 (18 %) had HDL of ≥ 190 mg /dL. There was statistical significance between NAFLD and Non NAFLD patients regarding all parameters of lipid profile (HDL, LDL, Triglycerides, and total cholesterol). 20 (13.3 %) of NAFLD patients had intermediate risk for having heart attack while 128 (85.3 %) had low risk as well as a statistical significance when comparing the two groups regarding 10-year risk of having a heart attack.

4. Discussion

Nonalcoholic fatty liver disease is a hepatic condition that may progress to hepatic cirrhosis and liver failure.

(Vernon, Baranova, & Younossi, 2011).

Coronary artery disease is considered the most common cause of death in patients with NAFLD, not end stage liver disease. Cardiovascular risk among NAFLD is increased by multiple mechanisms (Nseir, Shalata, Marmor, & Assy, 2011). Many studies showed increased prevalence of cardiovascular disease in individuals with NAFLD, showing that NAFLD might be an independent risk factor for cardiovascular disease (Targher et al., 2006).

In this study there was no significance difference between NAFLD and non NAFLD regarding age and gender (p value > 0.05). After assessment of a 10- year risk of having heart attack for both NAFLD and non NAFLD group, it was found that there is a statistical significance difference between the two means (NAFLD 4.21 ± 4.25 non NAFLD 2.80±3.53). Furthermore, it was found that 13.3% of the NAFLD group have an intermediate risk while 96.7% of non NAFLD have a low risk, with high significance (p value 0.033). This is in agreement with several longitudinal studies which established that cardiovascular disease is the most common cause of death in patients with NAFLD (Söderberg et al., 2010).

Results from a study done by Rargher reported that increase of cerebrovascular stroke (17.2% vs. 10.2%) , prevalence of coronary artery disease (23 % vs. 15.5%) and peripheral vascular disease (12.8% vs. 7%) in people with type 2 diabetes and NAFLD as compared to diabetic patients without NAFLD (Targher et al., 2007).

Ioannou et al., found that patients with NAFLD had significantly higher Framingham risk score (FRS) than those without when comparing the 10-year risk of cardiovascular events based on the FRS after excluding excessive alcohol intake and viral hepatitis (Ioannou et al., 2006).

Coronary imaging for acute coronary syndrome found in NAFLD a higher risk for significant coronary artery disease, after controlling for other risk factors, as seen in a Turkish study on 92 patients who underwent coronary angiogram (Ua et al., 2007).

Obesity, hyperinsulinemia, hypertriglyceridemia and hypertension, which are features of metabolic syndrome are associated with NAFLD. Obesity is considered the single most common feature associated with NAFLD as it was found in 50.1% of obese patients (Kwon et al., 2012).

In our study, 91.3% of NAFLD patients were found to be obese with a high significance (p value < 0.05) compared to the non NAFLD group that showed an obesity rate of 16%.

An autopsy study of 351 patients by Wanless found that 70% of obese patients had liver steatosis, and the degree of steatosis was proportional to the degree of obesity (Wanless & Lentz, 1990). This was reported by other studies that concluded that the prevalence of NAFLD increased to approximately 60–70% in obese patients (Angulo, 2002).

It has been recognized that NAFLD represents an important burden of disease for patients with diabetes (Day CP, 2006).

Diabetes mellitus and NAFLD are closely associated in the current study. The prevalence of DM among the NAFLD group was 50%, being highly significant from the non NAFLD group with 4% (p value < 0.05). This is in agreement with a study done by Leite which found that the prevalence of NAFLD in 180 patients with DM was 69.4%; furthermore NAFLD was associated with obesity and hypertriglyceridemia. The authors concluded that the progression of NAFLD is independent of diabetes progression (Leite, Salles, Araujo, Villela, & Cardoso, 2009).

In the present study 42 of 150 (28.0%) of patients with NAFLD had hypertensive disease. Another study reported by Bajaj et al found hypertensive disease proportion to be 48 (72%). This difference may be due to our group of patients having additionally DM besides NAFLD (Bajaj et al., 2009).

NAFLD patients usually have a lipid derangement besides other features of metabolic syndrome such as diabetes mellitus, hypertension, and obesity. Dyslipidemia is in the form of high level of serum triglycerides and low-density lipoprotein (LDL), and with low level of high-density lipoprotein (HDL) cholesterol (Chatrath , Vuppalanchi, & Chalasani, 2012). This is parallel to our results when a comparison of the mean values between the groups with NAFLD (122.6600 ± 44.26064) and without NAFLD (107.3600 ± 33.08973) regarding LDL was insignificant (P value 0.002).

In the current study, 71 (47.3%) patients of the NAFLD group had low HDL levels (< 40 mg/dl in males and < 50 mg/dl in females) while in the non-NAFLD group low HDL accounts for 27 (18%) patients. Bajaj et al described 66.7% of NAFLD patients having low HDL levels (Bajaj et al., 2009).

The results of the current study correspond to findings by Kantartzis et al, who reported that fatty liver is significantly and independently associated with lower levels of high density lipoprotein cholesterol in a study of

16 patients with fatty liver and 24 control (Kantartzis et al., 2008).

Historically, hypertriglyceridemia and low HDL are the lipid fraction disorders most often associated with the presence of steatosis (Angelico et al., 2003); this is in agreement with the current study that demonstrates most of NAFLD patients with a high level of triglyceridemia and low HDL.

Indeed, the impact of NAFLD on cardiovascular disease deserves particular attention in view of the implications for screening/surveillance strategies in the growing number of patients with NAFLD.

5. Conclusion

Most of NAFLD patients were obese, diabetics, and most of them showed lipid profile abnormalities. There was a significant high prevalence of most of CVD risk factors among NAFD patients in comparison to age matched group of patients without NAFLD. So NAFLD patients have a high risk of cardiovascular diseases more than non NAFLD.

Recommendations

Currently there are no recommendations at all regarding screening for NAFLD. In this study and in the literature, there is a strong association of NAFLD with diabetes. Therefore, the authors recommend annual ultrasound screening of diabetic patients for NAFLD.

This study has revealed a significant association between patients with NAFLD and dyslipidemia. Therefore, the authors recommend that NAFLD patients receive close follow up with a screening lipid profile, and subsequent treatment as needed.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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