



Nonalcoholic Fatty Liver Disease and the Risk of Atrial Fibrillation

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Abstract

Edited by: Mirko Spiroski
Citation: Abou Omar MA, Alaarag A, Abd-Elsalam S, El-Abgeegy M, Ahmed R, Mohamed AA, Khalil M, Abo-Amer YE, Elkadeem M, Yousef M. Nonalcoholic Fatty Liver Disease and the Risk of Atrial Fibrillation. Open Access Maced J Med Sci. 2020 May 20; 8(B):530-535. https://doi.org/10.3889/oamjms.2020.4319
Keywords: Atrial fibrillation; Nonalcoholic fatty liver disease; Liver disease; Obesity; Cardiac disease; Prevalence
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Received: 17-Jan-2020
Revised: 15-Mar-2020
Accepted: 14-Apr-2020
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Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors
Competing Interests: The authors have declared that no competing interests
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BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) is now the factor behind the development of liver cirrhosis, liver cell failure, and liver transplantation in many cases. However, its relation to atrial fibrillation (AF) could not be cleared up.

AIM: The purpose of the study was to evaluate prevalence of AF in the setting of NAFLD; the association between them, and to evaluate risk factors of AF in this category of patients.

METHODS: This cross-sectional study was performed on 400 patients between January 2018 and June 2019. These patients were analyzed for the presence of NAFLD and presence of persistent or chronic AF.

RESULTS: There were 138 patients with NAFLD, and 20 patients with persistent or permanent AF. Factors associated with AF were old age, male gender, and high values of aspartate aminotransferase, alanine-aminotransferase, γ -glutamyltranspeptidase, and serum uric acid. The participants with AF had a significantly greater prevalence of NAFLD than those without AF.

CONCLUSION: Incidence and prevalence of atrial fibrillation in NAFLD patients were high. Severity of liver disease was an important predictor of new-onset atrial fibrillation.

Introduction

Liver disease has an impact on autonomic nervous system through affecting circulating inflammatory peptides. This effect creates a proarrhythmic status [1], [2], [3], [4]. Autonomic dysfunction and inflammation seems to have a role in the development of atrial fibrillation (AF) [5].

There are few studies about AF in liver diseases, and these studied did not assess the severity of liver disease [6], [7], [8].

The prevalence of nonalcoholic fatty liver disease (NAFLD) could not be known accurately because of its variability in different people including age, gender, ethnicity, and various concomitant diseases. In addition, the different methods of NAFLD detection, including liver enzyme, imaging analysis (i.e., ultrasound or magnetic resonance imaging), and histological analysis make accurate detection of the prevalence too hard. Younossi *et al.*, 2018 [8] performed a meta-analysis, showing that 30–35% of adult North Americans had NAFLD (as detected

by ultrasonography), 20–30% [9], [10] of Europeans and the Middle Easterners had NAFLD, and the prevalence of NALFD among the Chinese and Japanese was from 15 to 30% and 20 to 30%, respectively [11], [12]. For Indian subcontinent populations, the prevalence was from 16% to 32% [13].

It is clear that the prevalence of NAFLD is much higher in special groups of populations (i.e., patients with dyslipidemia T2DM, obesity, or hypertension) [3], [14], NASH prevalence was reported to be from 30% to 70% in Type II DM population-based studies and from 45% to 75% in large hospital-based studies [14].

AF is the most common supraventricular arrhythmia seen in clinical practice in spite of improvement in management of cardiovascular disorders [15].

Käräjämäki *et al.*, 2016 [16] detected independent association between NAFLD and high incidence of AF. This study aimed to evaluate prevalence of AF in the setting of NAFLD; the association between them and to evaluate risk factors of AF in this category of patients.

Methods

This cross-sectional study included 400 patients who were received in outpatient clinics in the Cardiology and Hepatology Departments in a major university hospital in the period from January 2018 until June 2019 after taking consent from every one. The study protocol was reviewed and approved by the Ethics Committee (at Tanta Faculty of Medicine). All patients were informed and agreed to share in the study. Patients whose alcoholic history was unknown or known to be excessive alcoholic were excluded from the study.

Clinical examinations, including anthropometric and laboratory measurements, were performed. Weight and height were measured with basic clothing after shoes removal. Body mass index (BMI) was calculated ($Wt [kg]/height^2 [m^2]$). Blood pressure was measured by sphygmomanometer in a sitting position. Fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyltranspeptidase (GGT), serum uric acid, and albumin were measured using antecubital vein fasting blood samples. All values were measured using an Olympus AU640 autoanalyzer (Olympus, Kobe, Japan) and standard methods.

Diagnosis of NAFLD was based according to abdominal ultrasonography performed by well-trained operators who were blind to the laboratory and clinical data, and after excluding other etiology. The apparatus used was a Toshiba Nemio 20 sonography machine with a 3.5-MHz probe (Toshiba, Tokyo, Japan) [15].

Diagnostic criteria of fatty liver included: (1) Increased liver brightness; (2) diffuse hyperechogenicity of the liver compared to the kidneys; (3) deep attenuation of hepatic echo; and (4) intrahepatic vessel borders and diaphragm [16]. This study used ultrasonography also for evaluation of intra-abdominal organs (liver, spleen gallbladder, and pancreas).

AF was diagnosed using a 12-lead electrocardiogram (ECG) showing irregularly irregular ventricular rate and absent discrete P waves.

Statistical analysis

The collected data were tabulated and statistically analyzed using Prism 5 software statistical computer package version 5. Range, mean, standard deviation, number, and percent were calculated. Chi-square and Fisher exact test were used as a test of significance. Continuous variables between the two groups were compared with the t-test. $p < 0.05$ was considered significance.

Results

Clinical characteristics of the included patients: Of the 400 participants included in this study, 138 met the diagnostic criteria for NAFLD (34.5%, 98 males and 40 females). Of the entire sample, 20 participants (5.0%, 16 males and 4 females) had persistent or permanent AF. The clinical characteristics of patients are shown in Table 1. Patients with AF were older, more likely to be male, and had significantly higher values of AST, ALT, GGT, serum uric acid. BMI, blood pressure, lipid profile, albumin, and FPG did not significantly differ between the two groups. As shown in Table 1, the participants

Table 1: Baseline clinical, demographic, and characteristics of studied patients stratified by AF status

Characteristic	All pts (n=400)	Pts without AF (n=380)	Pts with AF (n=20)	t value	p value*
Age (years): Mean \pm SD	60.5 \pm 9.2	59.2 \pm 8.0	64.6 \pm 9.5	2.015	0.0093
Gender, No. (M/F)	291/109	276/104	16/4	2.08	0.08
BMI (kg/m)	24.90 \pm 2.70	23.60 \pm 3.00	23.70 \pm 2.80	0.145	0.88
Systolic BP	135.10 \pm 15.00	134.30 \pm 15.10	136.10 \pm 14.60	0.520	0.60
Diastolic BP	73.40 \pm 11.60	72.60 \pm 11.80	73.40 \pm 12.10	0.292	0.768
FPG (mg/dl)	108.50 \pm 12.30	110.40 \pm 11.90	105.8 \pm 12.70	1.67	0.09
Total chol. (mg)	176.50 \pm 19.80	175.40 \pm 19.60	165.50 \pm 20.70	1.28	0.198
HDL (mg/dl)	40.96 \pm 4.58	40.26 \pm 4.64	38.64 \pm 3.70	1.53	0.125
LDL (mg/dl)	131.65 \pm 19.50	130.60 \pm 19.20	128.50 \pm 18.90	0.477	0.633
TG (mg/dl)	164.50 \pm 22.10	162.70 \pm 21.0	157.30 \pm 19.80	1.124	0.260
AST (U/L)	32.10 \pm 3.72	31.80 \pm 3.70	33.90 \pm 3.91	2.40	0.014
ALT (U/L)	24.82 \pm 3.94	24.50 \pm 3.90	26.30 \pm 4.10	2.01	0.045
γ -GTP (U/L)	22.49 \pm 3.60	22.41 \pm 3.50	24.20 \pm 4.00	2.20	0.0275
Albumin (g/L)	44.83 \pm 2.80	44.54 \pm 2.70	45.28 \pm 2.90	1.190	0.234
Serum UA (mg/dL)	5.23 \pm 1.64	5.10 \pm 1.60	5.90 \pm 2.85	2.33	0.020
NAFLD (%)	33.4	33.2	44.4		

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GTP: Glutamyltranspeptidase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, FPG: Fasting plasma glucose, TG: Triglycerides, BMI: Body mass index, M/F: Male/female, BP: Blood pressure, AF: Atrial fibrillation, NAFLD: Nonalcoholic fatty liver disease.

with AF had a significantly greater prevalence of NAFLD than those without AF. As regards NAFLD status (Table 2), the group of NAFLD contained more males and was slightly older than the group without NAFLD. The values for SBP, DBP, BMI, LDL, TG, AST, ALT, GGT, FPG, albumin, and serum UA were higher among the participants with NAFLD; but, they had lower values of HDL. Furthermore, as shown in Table 2, there was a marked difference in the prevalence of AF among participants with or without NAFLD.

Table 2: Baseline clinical, demographic, and characteristics of studied patients stratified by NAFLD status

Characteristic	Pts without NAFLD (n=272)	Pts with NAFLD (n=138)	t value	p value*
Age (years): Mean \pm SD	61.20 \pm 8.80	62.20 \pm 8.60	1.09	0.273
Gender, No. (M/F)	170/102	98/40	1.4	0.294
BMI (kg/m)	24.00 \pm 2.800	23.90 \pm 2.90	0.337	0.7358
Systolic BP	133.40 \pm 16.80	138.20 \pm 18.30	2.82	0.005
Diastolic BP	72.70 \pm 12.00	75.90 \pm 11.80	2.56	0.0106
FPG (mg/dl)	112.30 \pm 11.80	118.40 \pm 13.20	4.6	0.001
Total chol. (mg)	154.30 \pm 12.40	160.25 \pm 11.60	1.32	0.203
HDL (mg/dl)	42.20 \pm 6.40	38.10 \pm 4.6	6.534	0.001
LDL (mg/dl)	120.40 \pm 17.80	126.20 \pm 19.30	3.03	0.0026
TG (mg/dl)	150.20 \pm 22.80	170.30 \pm 26.8	2.30	0.025
AST (U/L)	28.60 \pm 4.60	32.10 \pm 5.8	6.60	0.0013
ALT (U/L)	24.80 \pm 3.40	30.20 \pm 3.80	4.58	0.001
γ -GTP (U/L)	21.400 \pm 2.800	24.60 \pm 4.10	9.20	0.001
Albumin (g/L)	44.500 \pm 2.900	46.20 \pm 2.60	1.41	0.150
Serum UA (mg/dL)	5.00 \pm 2.100	5.6 \pm 3.00	2.23	0.019
AF (%)	2.1	3.8		

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GTP: Glutamyltranspeptidase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, FPG: Fasting plasma glucose, TG: Triglycerides, BMI: Body mass index, M/F: Male/female, BP: Blood pressure, AF: Atrial fibrillation.

The association between AF and NAFLD remained statistically significant even after adjustment for age and gender. Further adjustment for SBP, FPG, GGT, HDL, and TG did not remarkably change the study group's status. Age and GGT were independent predictors of AF.

AST and ALT were calculated according to normal values up to 45 U/L. GGT was calculated with the upper limit 50 U/L for males and 32 U/L for females. There was an increasing trend of the prevalence rate of AF as serum liver enzyme increased. The prevalence rates of AF in normal and elevated serum AST groups were 2.1% and 9.8% ($p < 0.001$). The rates in normal and elevated serum ALT groups were 2.0% and 8.2% ($p = 0.003$). Meanwhile, the rates in GGT groups were 1.7% and 7.8% with significant result as well ($p < 0.001$). These results showed that participants with higher serum liver enzyme are more likely to develop AF than those with lower one.

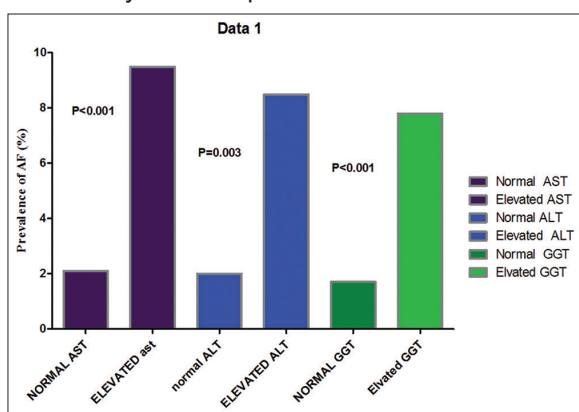


Figure 1: Prevalence of atrial fibrillation in patients stratified by normal or elevated serum liver enzyme concentration

As regards the relationship between NAFLD and AF, participants were classified into three groups: Group without NAFLD, group with NAFLD and normal AST/ALT/GGT, and group with NAFLD and elevated AST/ALT/GGT. AF was significantly higher among patients with elevated liver enzymes; also, in those with hepatic steatosis, irrespective of liver enzymes. However, the presence of AF among those without hepatic steatosis on ultrasound was not significant (Figures 1 and 2).

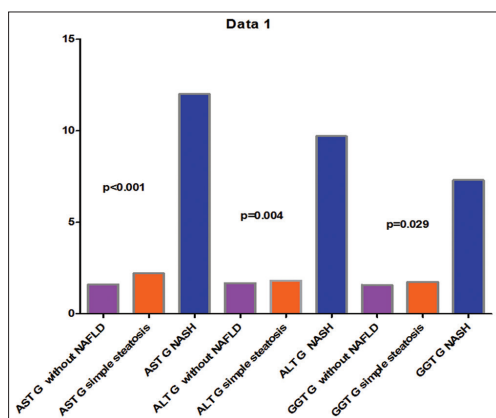


Figure 2: Prevalence of atrial fibrillation in patients stratified by nonalcoholic fatty liver disease status on ultrasound combined with normal or elevated serum aspartate aminotransferase/alanine aminotransferase/ γ -glutamyltranspeptidase concentration

Discussion

Till now, multiple similar risk factors can lead to both AF and NAFLD. As a result, there were many studies about the association between AF and NAFLD [17], [18], [19], [20], [21]. However, they were limited. A study made by Targher *et al.* [20] was restricted on subjects with type II diabetes mellitus and the OPERA study focused on middle-aged patients [16].

AF is prevalent in patients with liver disease. Furthermore, incidence of AF is proportional to the severity of liver disease, which is independently associated with new-onset AF, in spite of adjustment of other AF risk factors. This finding may explain additional mechanistic insight into the pathogenesis of AF, which shares the underlying link of inflammation and autonomic dysfunction, known to play a role in development of AF. Both cardiologists and hepatologists consider AF screening in patients with liver disease [21], [22], [23].

Our study revealed the association between NAFLD and AF. The serum transaminase levels were significantly associated with high risk of AF. It is not known whether the association between them is causative relationships or these two diseases share common pathophysiologic mechanisms. As it is reasonable to deduce that there may be a causal link between them because NAFLD is known to be a risk factor for many cardiovascular diseases.

Our finding could be explained by the following: First, liver transaminases may link NAFLD and AF which was in agreement with The Framingham Heart Study which detected the independent relationship between liver transaminase concentrations and the risk of new-onset AF in the general adult population [24]. Targher *et al.*'s [18] study detected that GGT was the only liver enzyme significantly associated with the prevalence of AF in Type II diabetes patients [18]. A similar result was found in our studied patients. GGT is also a systemic marker of NAFLD so that the development of the two diseases may be parallel. Furthermore, it has been proven that the most specific marker of liver pathology (ALT) is also associated with an increased risk of cardiovascular-related mortality [25], [26], [27], [28], [29].

As regards AST, it is produced in the both liver and myocardium, increases in either NAFLD or AF patients, or in patients with both conditions. This is similar to our results. Therefore, control of liver transaminase concentrations may have a role in reduction of the mortality in patients with AF.

Second, NAFLD leads to accumulation of lipids in the liver, impaired lipoprotein metabolism, increased oxidative stress, and release of inflammatory factors [30], which are important risk factors for

AF [32], [33], [34]. Furthermore, it was reported that AF could trigger inflammatory environment [33], creating a vicious cycle.

Persistent low levels of LDL and HDL cause further lipoprotein consumption [31]. These conclusions were consistent with our results where HDL cholesterol, LDL cholesterol, and TG were all lower in group with AF than in the group without AF.

Third, since NAFLD carries multiple cardiovascular complications, it may induce AF direct through several mechanisms including left ventricular diastolic dysfunction [35], and alteration of atrial conduction properties [36]. Fat does not accumulate only in the liver tissue but also in other organs and viscera including cardiac tissue (myocardium, pericardium, and atrial septum) so that the diastolic function of the atria or the ventricle, and electrical activity may be affected [36], [37].

Finally, many studies have reported that NAFLD is an independent risk factor for autonomic dysfunction [38], [39], [40] which has a role in development of AF [40], [41].

There were some limitations to our study. First, NAFLD was not diagnosed histologically but through ultrasound which was non-invasive and cost-effective. Second, the sample was small. Third, AF was diagnosed according to resting ECG without 24 h dynamic ECG which was more precise but more difficult. Fourth, the cross-sectional nature of our study did not enable us to know the most recent mean levels of some lab results of every patient. As formal cohort studies have shown, NAFLD is associated with an increased risk of prevalent AF [18], [19], [42].

Conclusion

NAFLD is an independent risk factor for AF mainly with the progression of liver disease. NAFLD patients should be examined for arrhythmia symptoms, and evaluated ECGs and ambulatory monitors. Future studies are needed to evaluate risks and benefits of anticoagulation in the setting of liver disease.

Acknowledgments

The authors acknowledge all patients participated in this study and take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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