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Nonalcoholic Fatty Liver Disease as a Risk Factor for Prolonged Corrected QT Interval in Apparently Healthy Korean Women

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ABSTRACT

Background & Aims: Nonalcoholic fatty liver disease (NAFLD) is clinically important because of its association with an increased risk of sudden cardiac death as well as liver-related mortality. Most cases of sudden cardiac death could be mediated by an arrhythmogenic process. Thus, we aimed to determine the association between NAFLD and corrected QT (QTc) interval in apparently healthy Korean women.

Methods: This cross-sectional study included 764 women aged 20 to 74 years old who underwent a health examination program between 2014 and 2015. The QTc interval was calculated using Bazett's formula (QTc = QT/√RR). Multiple linear and logistic regression analysis were performed to assess independent relationships between NAFLD and QTc interval and prolonged QTc (≥ 450 milliseconds) was calculated after adjusting for confounding variables.

Results: The overall prevalence of NAFLD was 23.5% in general healthy women. The standardized β coefficient (95% confidence interval) of the QTc increment in patients with NAFLD was 6.4 milliseconds (1.2–11.8) through multiple linear regression analysis after adjusting for age, body mass index, smoking status, and regular exercise as well as mean arterial pressure, fasting plasma glucose, triglycerides, high-density lipoprotein cholesterol, aspartate aminotransferase, alanine aminotransferase, calcium, potassium levels and menopause status. Similarly, the odds ratio (95% confidence interval) of NAFLD for prolonged QTc was 2.05 (1.13–3.71) according to multiple logistic regression analysis after adjusting for the same covariables in women aged 20 to 74 years old.

Conclusion: We demonstrated the arrhythmogenic potential of NAFLD, implying that careful monitoring of patient electrocardiograms is necessary to evaluate the possible arrhythmic risk in general healthy women with NAFLD.

Key words: nonalcoholic fatty liver disease – insulin resistance – QTc interval – arrhythmia

Abbreviations: BMI: body mass index; CI: confidence interval; DBP: diastolic blood pressure; ECG: electrocardiography; HDL: high-density lipoprotein; IQRs: interquartile ranges; ms: milliseconds; NAFLD: nonalcoholic fatty liver disease; NCEP-ATP III: National Cholesterol Education Program Adult Treatment Panel III; QTc: corrected QT; SBP: systolic blood pressure.

INTRODUCTION

The QT interval is the duration between depolarization and repolarization of the ventricular myocardium. Because the QT interval is highly influenced by the heart rate, a corrected QT (QTc) interval adjusted for the heart rate has been proposed from an electrophysiology perspective [1]. Prolonged QTc interval is well-known to be an arrhythmogenic parameter in electrocardiography (ECG) and is associated with electrical instability of the myocardium including ventricular tachycardia and fibrillation, which leads to sudden cardiac death [2, 3]. Prolonged QTc interval is a useful predictor for sudden cardiac death in patients after acute coronary syndrome and with heart failure and type 2 diabetes and even in apparently healthy adults [4].

Nonalcoholic fatty liver disease (NAFLD) is characterized by diffuse triglycerides accumulation in the liver not caused by excessive alcohol use and other causes of liver disease. With the growing epidemic of obesity, NAFLD is one of the most prevalent causes of chronic liver disease and encompasses a spectrum of clinical syndromes ranging from simple steatosis to nonalcoholic steatohepatitis that could progress

to advanced fibrosis, cirrhosis, and cirrhosis complicated by hepatocellular carcinoma [5]. More recently, accumulating evidence suggests that NAFLD is associated with an increased risk of cardiovascular disease, chronic kidney disease, and sudden cardiac death as well as liver related mortality [6, 7]. Because most cases of sudden cardiac death are related to severe ventricular arrhythmia, we expected that the link between NAFLD and sudden cardiac death may be mediated by an arrhythmogenic process. Although, several previous studies reported prolonged QTc intervals in subjects with NAFLD, most studies have been limited to Western populations with chronic medical conditions such as type 2 diabetes and admitted patients. Therefore, in the present study, we examined the association between NAFLD and QTc interval in apparently healthy Korean women.

METHODS

Study participants

We retrospectively reviewed the medical records of 898 participants aged 20 years or older who underwent a medical examination at the Health Promotion Center, Seoul between 2014 and 2015. The subjects voluntarily visited the health promotion center to regularly undergo health assessment. Informed consent was obtained from each participant. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University College of Medicine, Seoul. We excluded participants who met one or more of the following criteria (n = 134): missing data; alcohol intake of 70 g/week or more, a positive test for hepatitis B antigens or hepatitis C antibodies; a history of cardiac arrhythmia, ischemic heart disease, stroke, cancer, thyroid, respiratory, renal, hepatobiliary, or rheumatologic disease; and failure to fast for 12h prior to testing. A total of 764 women aged 20 to 74 years old were included in the final analysis. A flow diagram of the study participants is showed in Fig. 1.

Data collection

Each participant completed a questionnaire about lifestyle and medical history. Self-reported cigarette smoking, alcohol consumption, and physical activity characteristics were gleaned from the questionnaires. The smoking statuses were nonsmoker, ex-smoker, and current smoker. Questions regarding alcohol intake included the frequency on a weekly basis. Regular alcohol consumption was defined as alcohol drinking two or more times per week. Participants were asked about their physical exercise on a weekly basis, and regular exercise was defined as exercise three times or more per week. Body mass and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with the participant in light indoor clothing without shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using the patient's right arm with a standard mercury sphygmomanometer (Baumanometer; W.A. Baum Co. Inc., Copiague, NY, USA). Mean arterial pressure was calculated using the equation (SBP + 2×DBP)/3. All blood samples were obtained from the antecubital vein after a 12-h overnight fast. Fasting plasma glucose, total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol levels were measured by enzymatic methods using a chemistry analyzer (Hitachi 7600-110; Hitachi, Ltd., Tokyo, Japan). The modified National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) was used to define metabolic syndrome. Because waist circumference was not measured, we defined obesity as a BMI 25 kg/m^2 or more, as suggested by the position statement of the American College of Endocrinology [8]. Therefore, metabolic syndrome was defined by the presence of

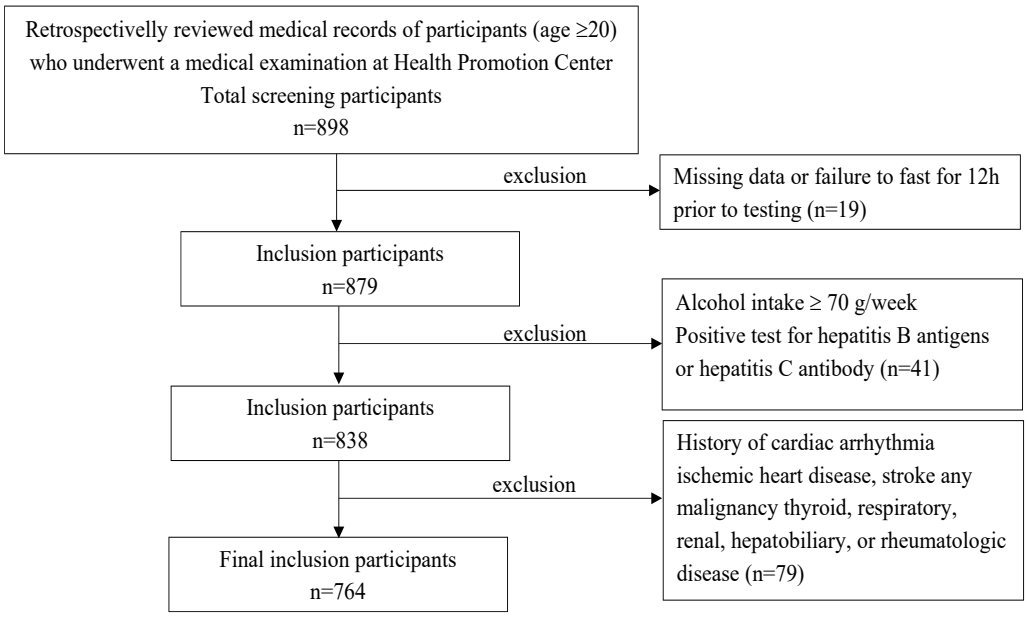

Fig. 1. Flow diagram of the study participants.

three or more of the following risk factors: obesity, with BMI 25.0 kg/m^2 or more; elevated systolic blood pressure (SBP) of 130 mmHg or more, elevated diastolic blood pressure (DBP) of 85 mmHg or more, or use of an antihypertensive medication; high fasting plasma glucose of 100 mg/dL or more or the use of an antidiabetic medication; high triglyceride level of 150 mg/dL or more; and low HDL cholesterol level of less than 40 mg/dL for men and less than 50 mg/dL for women, respectively.

Each participant underwent resting standard supine 12-lead ECG at a paper speed of 25 mm/s and amplitude of 10 mm/mv using a Marquette MAC 12 (Marquette Medical Systems, Inc., Milwaukee, WI, USA). The QT and R–R intervals were measured over three consecutive cycles on leads V2 or V3. The QT intervals were measured from the beginning of the QRS complex of the ECG to the end of the T-wave and were corrected according to Bazett's formula (QTc = QT/√RR) [1].

Diagnosis of nonalcoholic fatty liver disease

A diagnosis of fatty liver was based on abdominal ultrasonography with a 3.5-MHz transducer (HDI 5000; Philips, Bothell, WA, USA). Ultrasonography was performed by two experienced radiologists who were unaware of the aims of the study and blinded to laboratory findings. We analyzed the linear weighted kappa statistics to analyze agreement between the two radiologists because the outcome encompasses ordinal scoring, and the kappa index (95% CI) was 0.809 (0.782–0.867). The presence of hepatic steatosis was determined according to the findings of high hepatorenal echo contrast, bright liver, or attenuation of ultrasound in a deep area of the liver. Hepatic steatosis was graded according to criteria previously described: mild, slight diffuse increase in bright homogeneous echoes in liver parenchyma, with normal visualization of the diaphragm and portal and hepatic vein borders, and normal hepatorenal contrast; moderate, diffuse increase in bright echoes in liver parenchyma, with slightly impaired visualization of the peripheral portal and hepatic vein borders; and severe, marked increase in bright echoes at a shallow depth, with deep attenuation and impaired visualization of the diaphragm and marked vascular blurring [9]. Liver with any degree of hepatic steatosis was considered as having NAFLD in this study.

Statistical analysis

Normal distribution was evaluated with determination of skewness using a Kolmogorov–Smirnov test. Serum triglycerides, aspartate aminotransferase, and alanine aminotransferase levels have skewed distributions, so these variables were expressed as medians (interquartile ranges; IQRs) in descriptive analysis and log-transformed prior to simple correlation and multiple regression analysis. The clinical characteristics of the study population according to the presence of NAFLD were compared using an independent two-sample Student's t-test for continuous variables and the chi-squared test for categorical variables. Continuous data are presented as means (standard deviations; SDs) or medians (IQRs), and categorical data are presented as frequencies. The Pearson's correlation coefficients were determined for QTc versus age, BMI, blood pressure, fasting plasma glucose, total cholesterol, log-transformed triglycerides, HDL cholesterol, aminotransferase, calcium, and potassium levels. Prolonged QTc interval was defined as one of 450 milliseconds (ms) or more in women according to a previous Korean epidemiologic study [10]. Multiple linear regression analysis was performed to assess independent relationships between NAFLD and QTc interval. Also, the odds ratios (ORs) and 95% confidence intervals (95% CIs) for prolonged QTc (≥ 450 ms) were calculated after adjusting for confounding variables using multiple logistic regression analysis. All analyses were conducted using the SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided, and statistical significance was determined at $p < 0.05$.

RESULTS

Table I shows the clinical characteristics of the study population according to the presence of NAFLD (23.4%). The mean values of BMI, blood pressures, fasting plasma glucose, total cholesterol, and triglyceride levels and the median values of triglycerides and aminotransferases were higher in individuals with NAFLD than in individuals without. The prevalence rates of hypertension, type 2 diabetes, and metabolic

Table I. Clinical characteristics of the study population according to the presence of nonalcoholic fatty liver disease (NAFLD).

	NAFLD (-)	NAFLD (+)	p
No. or patients	585	179	
Age (years)	45.7 (8.2)	50.1 (7.6)	<0.001
Body mass index (kg/m^2)	22.9 (2.5)	26.0 (2.9)	<0.001
Systolic blood pressure (mmHg)	118.2 (16.0)	128.1 (14.4)	<0.001
Diastolic blood pressure (mmHg)	73.1 (9.6)	79.7 (9.0)	<0.001
Mean arterial pressure (mmHg)	88.1 (11.4)	95.8 (10.4)	<0.001
Fasting plasma glucose (mg/dL)	87.2(113.7)	95.5 (16.5)	<0.001
Triglycerides (mg/dL)	99 (72-137)	152 (110-214)	<0.001
HDL-cholesterol (mg/dL)	59.3 (12.4)	50.6 (9.3)	<0.001
Aspartate aminotransferase (U/L)	19 (16-22)	22 (19-28)	<0.001
Alanine aminotransferase (U/L)	16 (13-21)	26 (20-39)	<0.001
Calcium (mEq/L)	9.22 (0.37)	9.32 (0.40)	0.001
Potassium (mEq/L)	4.02 (0.35)	4.03 (0.36)	0.913
QTc (ms)	429.0 (21.2)	439.8 (22.1)	<0.001
Leukocyte count (cells/μL)	5686 (1452)	6503 (1675)	<0.001
Current smoking (%)	6.9	1.9	0.014
Regular exercise (%)[a]	35.8	30.4	0.206
Hypertension (%)[b]	14.4	38.7	<0.001
Type 2 diabetes (%)[c]	1.0	7.3	<0.001
Metabolic syndrome (%)[d]	8.0	44.1	<0.001

Data are expressed as the mean (SD), median (interquartile range) or percentage. P values were calculated using independent two-sample test, Wilcoxon-Rank sum test, or chi-square test. [a] Regular exercise ≥ three times /week. [b] Hypertension was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or a current use of hypertension medication. [c] Type 2 diabetes was defined as a fasting plasma glucose ≥126 mg/dL or a current use of diabetes medication. [d]Metabolic syndrome was defined by the presence of three or more of the following risk factors: obesity with BMI ≥25.0 kg/m^2, high triglycerides ≥150 mg/dL, low HDL cholesterol <50 mg/dL, elevated systolic blood pressure ≥130 mmHg, elevated diastolic blood pressure ≥85 mmHg, or a current use of hypertension medication, and high fasting plasma glucose ≥100 mg/dL or a current use of diabetes medication.

syndrome were higher, whereas the smoking rate was lower in individuals with NAFLD than in individuals without.

The Pearson correlation results are listed in Table II. The QTc interval positively correlated with age and BMI as well as blood pressure, fasting plasma glucose, and triglycerides levels and negatively correlated with potassium and HDL cholesterol levels.

Table II. Correlation between QTc interval and clinical variables.

	r	p
Age (year)	0.108	0.002
Body mass index (kg/m^2)	0.159	<0.001
Systolic blood pressure (mmHg)	0.238	<0.001
Diastolic blood pressure (mmHg)	0.196	<0.001
Mean arterial pressure (mmHg)	0.221	<0.001
Fasting plasma glucose (mg/dL)	0.121	<0.001
Triglycerides[a] (mg/dL)	0.199	<0.001
HDL-cholesterol (mg/dL)	-0.034	0.354
Aspartate aminotransferase (U/L)[a]	0.106	<0.001
Alanine aminotransferase (U/L)[a]	0.134	<0.001
Calcium, mEq/L	-0.007	0.856
Potassium, mEq/L	-0.157	0.012

p-values were calculated using Pearson's correlation analysis for continuous variables and Spearman-rank correlation analysis for current smoking and regular exercise. [a] Indicates log-transformed values.

Table III shows the results of multiple linear and logistic regression analysis to assess independent relationships between the NAFLD and QTc interval. The standardized β coefficient (95% CI) of the QTc increment in patients with NAFLD was 6.4 ms (1.2–11.8) according to multiple linear regression analysis after adjusting for age, BMI, smoking status, and regular exercise as well as mean arterial pressure, fasting plasma glucose, triglycerides, HDL cholesterol, aspartate aminotransferase, alanine aminotransferase, calcium, potassium levels and menopause status. Similarly, the OR (95% CI) of NAFLD for the prolonged QTc was 2.05 (1.13–3.71) based on multiple logistic regression analysis after adjusting for the same covariables, in total women aged 20 to 74 years old. When stratified by menopause, the standardized β coefficient (95% CI) of the QTc increment in NAFLD group and the OR (95% CI) of NAFLD for the prolonged QTc was 7.7 ms (0.9-15.4) and 2.87 (1.15-7.12) after adjusting for age, BMI, smoking status, and regular exercise as well as mean arterial pressure, fasting plasma glucose, triglycerides, HDL cholesterol, aspartate aminotransferase, alanine aminotransferase, calcium, and potassium levels. However, this positive association between NAFLD and QTc prolongation was not found in premenopausal women.

DISCUSSION

In this cross-sectional study, we found a positive association between NAFLD and QTc prolongation in apparently healthy women after adjusting for potential confounding variables. Our findings are consistent with previous studies on the association between NAFLD and arrhythmogenic potentials [11-14]. In another case-control retrospective study of 700 admitted patients in the United States, Magni et al. [13] reported a positive association of NAFLD with conduction defects and

Table III. Results of multiple regression analysis to assess the independent relationships of NAFLD with QTc and prolonged QTc interval (>450 ms).

	Multiple linear regression analysis			Multiple logistic regression analysis		
	QTc (ms)			Prolonged QTc (≥450 ms)		
Total	β	95% CI	p	Odds ratio	95% CI	p
Unadjusted	10.8	7.3-14.4	<0.001	2.80	1.92-4.08	<0.001
Model 1	8.5	4.4-12.5	<0.001	2.58	1.67-3.99	<0.001
Model 2	7.2	2.8-11.5	0.001	2.39	1.47-3.87	<0.001
Model 3	6.4	1.2-11.8	0.017	2.05	1.13-3.71	0.016
Premenopausal women	β	95% CI	p	Odds ratio	95% CI	p
Unadjusted	10.9	4.5-17.3	<0.001	2.20	1.23-4.01	0.008
Model 1	7.5	0.4-14.7	0.039	1.85	0.95-3.60	0.071
Model 2	8.3	0.8-15.8	0.291	1.85	0.86-3.98	0.118
Model 4	5.8	-2.1-13.8	0.149	1.47	0.62-3.50	0.381
Postmenopausal women	β	95% CI	p	Odds ratio	95% CI	p
Unadjusted	10.2	3.9-16.4	0.001	2.96	1.54-5.69	0.001
Model 1	9.1	2.1-16.1	0.011	3.46	1.62-7.41	0.001
Model 2	8.6	1.3-15.8	0.021	3.47	1.53-7.88	0.003
Model 4	7.7	0.9-15.4	0.038	2.87	1.15-7.12	0.023

Model 1: adjusted for age and body mass index. Model 2: adjusted for age, body mass index, smoking status, and regular exercise. Model 3: adjusting for age, body mass index, smoking status, regular exercise, mean arterial pressure, fasting plasma glucose, triglycerides, HDL-cholesterol, aspartate aminotransferase, alanine aminotransferase, calcium potassium levels and menopausal status. Model 4: adjusting for age, body mass index, smoking status, regular exercise, mean arterial pressure, fasting plasma glucose, triglycerides, HDL-cholesterol, aspartate aminotransferase, alanine aminotransferase, calcium and potassium levels.

identified NAFLD as a risk factor of conduction defects in multivariate logistic regression with a backward elimination method (adjusted OR: 2.38, 95% CI: 1.51–3.73). Furthermore, Targher et al. [11] reported that patients with NAFLD had a significantly higher prevalence of premature ventricular conduction and no sustained ventricular tachycardia as compared with those without NAFLD among patients with type 2 diabetes. They also reported a positive association between NAFLD and QTc prolongation (adjusted OR: 2.26, 95% CI: 1.4–3.7) in 400 Italian outpatients with type 2 diabetes [11].

However, the previous study populations included patients with type 2 diabetes with a high prevalence of NAFLD of around 72%. Also, the previous studies reported prolonged QTc intervals in subjects with NAFLD in Western populations, and little is known about East Asian populations in this regard. Recently, Hung et al. [12] found that the adjusted ORs (95% CIs) of the prolongation of QTc were 1.31 (1.16–2.24) in women and 1.87 (1.16–2.24) in apparently healthy Taiwan individuals. Our study confirmed that the positive associations between NAFLD and prolonged QTc interval can be applied to apparently healthy Korean women.

Several mechanisms could explain the significant relationship between the NAFLD components and prolonged QTc intervals. Nonalcoholic fatty liver disease is now regarded as a hepatic manifestation of obesity and the metabolic syndrome [15]. Obese individuals are prone to cardiac autonomic dysfunction such as sympathetic hyperactivity and augmenting myocardial refractoriness, which leads to arrhythmogenic potential [16, 17]. Also, insulin resistance, the core feature of metabolic syndrome, may lead to decreased potassium, affecting the prolongation of ventricular repolarization [18, 19]. Moreover, NAFLD is induced by a low-grade inflammation, which increased the visceral adipose tissue to promote proinflammatory mediators [15]. Subclinical inflammation mediated by inflammatory cytokines may affect myocardium by modulating specific ion channels. These processes result in the prolongation of action potential duration, which in turn increases QTc duration [20].

Our study had several limitations. First, it was of a cross-sectional design, suggesting that caution should be used in causal and temporal interpretations; thus, it cannot be concluded whether NAFLD is a risk factor actively involved in the development of QTc prolongation. Further large prospective studies are warranted to explain these possible associations between NAFLD and QTc prolongation. Second, because the study participants were volunteers undergoing health promotion screenings in a single hospital and appeared to be slightly healthier individuals than most community-based cohorts, the study population may not be representative of the general population. Third, we did not consider the effects of medicines such as anti-arrhythmics or anti-depressants in relation to cardiac rhythm. Because, this study used the secondary dataset from a health promotion center, these variables were not fully adjusted in the statistical models.

CONCLUSION

We confirmed the arrhythmogenic potential of NAFLD in apparently healthy Korean women, particularly in postmenopausal women. Our findings suggest that careful monitoring of ECGs is necessary to evaluate possible arrhythmic risk in individuals with NAFLD.

Conflicts of interest: None to declare.

Authors' contribution: T.-H. C. data collection and writting the manuscript. J.-Y.S. contribution to the discussion and revision. Y.-J.L. data analysis, editing and reviewing the manuscript.

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