Nonalcoholic fatty liver disease and its severity are associated with QTc lengthening in the general population

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1 BACKGROUND AND AIMS

- Nonalcoholic fatty liver disease (NAFLD) has become one of the most common causes of chronic liver disease in North America.[1,2]
- NAFLD, particularly its severe form nonalcoholic steatohepatitis (NASH), is associated with increased all-cause mortality especially related to cardiovascular disease. Prolonged heart rate corrected QT (QTc) interval is a known risk factor for cardiac death.
- However, there is paucity of data on the association between NAFLD and QTc interval prolongation.[3,4]
- In this study, we aim to (I) determine if underlying NAFLD is associated with increased QTc interval and (II) determine if the histological severity of NAFLD is associated with more severe QTc prolongation.

2 METHODS

Patient population and determination of NAFLD severity

Multi-Ethnic Study of Atherosclerosis (MESA) cohort

- A cohort of 6814 adult (age >18 years) men and women free of cardiovascular disease at enrolment in MESA
- Measurements of liver and spleen attenuation were obtained from abdominal CT scans
- Liver/spleen attenuation ratios (LSR) were calculated and individuals were classified into LSR ≥1 (Non-NAFLD) versus LSR <1 (NAFLD)
- Based on liver attenuation values (in Housfield units; HU), individuals were also classified into non-NAFLD (≥55 HU), mild NAFLD (40-54 HU), and moderate-severe NAFLD (<40 HU)

Virginia Commonwealth University (VCU) cohort

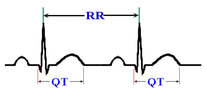
- A cohort of biopsy-proven non-cirrhotic adults with NAFLD (n=52) and age/gender matched non-NAFLD controls (n=67)
- Liver histology was scored using NASH Clinical Research Network (NASH CRN) criteria

Exclusion criteria

- Alcohol use >2 units/day, viral hepatitis, cardiac arrhythmias including atrial fibrillation, atrial flutter, supraventricular tachycardia, or patients taking antiarrhythmic medications

EKG measurements

- QTc was determined by Bazett formula using electrocardiogram (ECG) performed at initial enrolment in MESA or within 6 months of liver biopsy at VCU.



- QTc equals QT interval divided by square root of RR interval.
- Heart rate was obtained from ECG readings.

Other measurements/data

- Data on clinical and anthropometric measures, comorbidities, current medications and biochemical tests were obtained from the MESA database or VCU medical records.

Ethics

- The study was approved by the VCU Institutional Review Board and by the MESA Ancillary Studies Committee.

3 TABLE 1

Table 1: Baseline characteristic of 3892 individuals stratified by liver/spleen ratio (LSR)

	LSR ≥1; Non-NAFLD (N=3226)	LSR<1; NAFLD (N=666)	p-value
Age, years	63.31 ± 10.52	61.09 ± 9.65	4.40E-07
Male gender, n (%)	1434 (44.5%)	301 (45.2%)	7.43E-01
QTc, ms	417.69 ± 21.24	424.16 ± 22.67	1.81E-12
Liver attenuation, Hounsfeld Units	62.30 ± 7.86	42.30 ± 11.81	9.25E-203
Race:			2.59E-06
a. Caucasian, n (%)	1214 (37.6%)	218 (32.7%)	
b. Chinese American, n (%)	294 (9.1%)	73 (11.0%)	
c. African American, n (%)	1055 (32.7%)	132 (19.8%)	
d. Hispanic, n (%)	663 (20.6%)	243 (36.5%)	
Anthropometric measures			
BMI, kg/m2	28.03 ± 5.18	31.23 ± 5.43	7.42E-46
Systolic blood pressure, mmHg	127 ± 22	130 ± 21	8.14E-05
Diastolic blood pressure, mmHg	71 ± 10	73 ± 10	3.34E-06
Heart rate, beats/min	62.54 ± 9.57	65.61 ± 9.89	7.52E-14
Waist circumference, cm	97.30 ± 13.68	105.94 ± 13.33	5.34E-49
Comorbidities			
Metabolic syndrome, n (%)	1065 (33.1%)	434 (65.3%)	2.65E-56
High cholesterol by self report, n (%)	1203 (37.3%)	278 (41.9%)	3.02E-03
Diabetes mellitus by 2003 ADA criteria:			3.90E-22
a. Impaired fasting glucose, n (%)	373 (11.6%)	154 (23.2%)	
b. Untreated diabetes, n (%)	71 (2.2%)	48 (7.2%)	
c. Treated diabetes, n (%)	300 (9.3%)	102 (15.3%)	
Hypertension stage:			1.08E-03
a. Stage 1 hypertension, n (%)	612 (19.0%)	129 (19.4%)	
b. Stage 2 hypertension, n (%)	169 (5.2%)	48 (7.2%)	
c. Stage 3 hypertension, n (%)	61 (1.9%)	15 (2.3%)	
Cigarette smoking status:			1.50E-01
a. Previous, n (%)	1173 (36.5%)	222 (33.5%)	
b. Current, n (%)	369 (11.5%)	72 (10.9%)	
Alcohol use:			5.28E-02
a. Never used alcohol, n (%)	684 (21.4%)	171 (25.9%)	
b. Former alcohol use, n (%)	806 (25.2%)	150 (22.8%)	
c. Current alcohol use, n (%)	1712 (53.5%)	338 (51.3%)	
Medications			
Statin use, n (%)	478 (14.8%)	100 (15.0%)	9.34E-01
Beta blocker, n (%)	271 (8.4%)	80 (12.0%)	3.33E-03
Angiotension 2 antagonist, n (%)	117 (3.6%)	37 (5.6%)	1.90E-02
Biochemistry			
Sodium, mEq/L	146.75 ± 3.53	146.74 ± 3.63	9.64E-01
Potassium, mEq/L	4.30 ± 0.37	4.30 ± 0.39	9.63E-01
Chloride, mEq/L	110.45 ± 3.45	110.24 ± 3.53	1.74E-01
Bicarbonate, mEq/L	23.22 ± 1.87	22.79 ± 1.79	1.83E-07
Calcium, mEq/L	9.65 ± 0.39	9.67 ± 0.40	2.12E-01
Phosphorus, mEq/L	3.67 ± 0.52	3.70 ± 0.52	3.02E-01
Total cholesterol, mg/dl	194.01 ± 34.95	195.27 ± 39.14	3.95E-01
HDL cholesterol, mg/dl	51.689 ± 14.84	44.75 ± 11.96	1.38E-29
Triglycerides, mg/dl	122.03 ± 70.78	181.40 ± 158.82	1.54E-50
Total VLDL particles, nmol/L	72.38 ± 40.46	84.55 ± 44.23	3.31E-12
C-reactive protein, mg/L	3.68 ± 5.94	5.13 ± 5.93	6.85E-09
Interleukin-6, pg/ml	1.55 ± 1.19	1.90 ± 1.32	1.27E-11

4 FIGURE 1

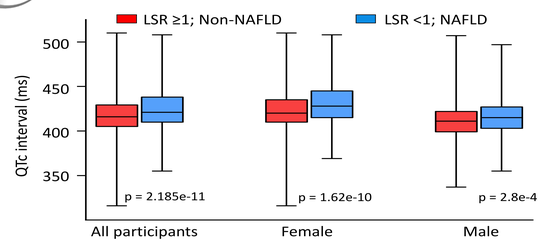


Figure 1: Mean QTc interval in non-NAFLD versus NAFLD individuals, defined by LSR ≥1 (non-NAFLD) versus <1 (NAFLD). Mean QTc was significantly higher in NAFLD individuals compared to non-NAFLD individuals. The difference persisted when the data was stratified by gender.

5 FIGURE 2

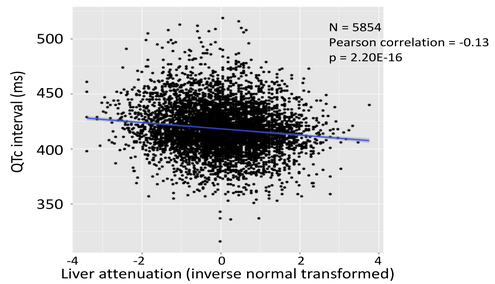


Figure 2: Inverse correlation between liver attenuation and QTc interval among 5854 men and women enrolled in MESA .

6 FIGURE 3

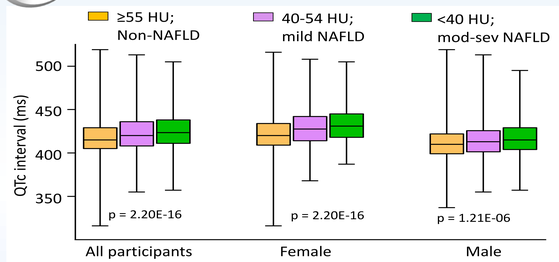


Figure 3: Mean QTc interval in non-NAFLD versus NAFLD individuals, defined by liver attenuation values ≥ 55 HU (non-NAFLD) versus 40-54 HU (mild NAFLD) versus <40 HU (moderate-severe NAFLD). There was a step-wise increase in mean QTc in association with disease severity in all participants as well as in sub-group analyses of females and males, with significant p-value for trend as indicated for each group.

7 FIGURE 4

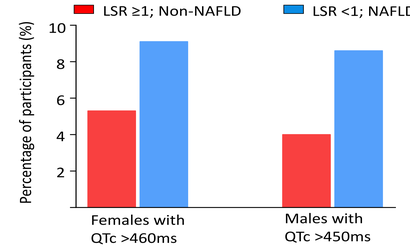


Figure 4: Association of NAFLD with clinically significant QTc prolongation. Compared to non-NAFLD individuals, those with NAFLD showed increased proportion of clinically significant QTc prolongation >460 ms in women (5.3 % versus 9.1 %; OR 1.8; 95% CI 1.2 to 2.7), and >450ms in men (4.0% versus 8.6%; OR 2.2; 95% CI 1.4 to 3.6).

8 FIGURE 5

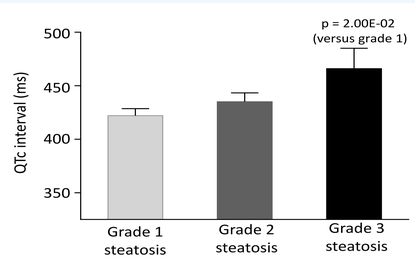


Figure 5: Increasing severity of hepatic steatosis as measured on liver histology was significantly associated with a step-wise increase in QTc interval. Other histologic features i.e., lobular inflammation, hepatocellular ballooning and NAFLD activity score did not demonstrate any significant relationship with QTc interval (data not shown).

9 CONCLUSIONS

- Among 3892 participants with data on LSR who met eligibility criteria for the analysis, 666 individuals (17%) had NAFLD determined by LSR <1, while the remainder did not have NAFLD. Among 5854 individuals with available data on liver attenuation who met eligibility criteria, 1042 individuals (18%) had mild NAFLD, 360 individuals (6.1%) had moderate to severe NAFLD, while the rest had no evidence of NAFLD.
- The presence of NAFLD was associated with an increase in incidence and severity of metabolic risk factors, including diabetes mellitus, hypertension, and metabolic syndrome.
- Individuals with NAFLD had significantly higher QTc interval compared to those without NAFLD. There was a step-wise increase in the mean QTc interval in association with NAFLD severity.
- NAFLD was associated with higher likelihood of clinically significant QTc prolongation of >450 ms in men and >460 ms in women
- Among various histologic features examined on liver biopsy, only severity of hepatic steatosis was significantly associated with QTc interval. Other features, including lobular inflammation, hepatocellular ballooning and NAFLD activity score did not significantly associate with QTc.
- We conclude that the presence and severity of NAFLD, particularly hepatic steatosis, is associated with lengthening of the QTc interval.

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