Electrocardiographic and echocardiographic changes in nonalcoholic fatty liver disease

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Context
Interactions between the heart and the liver have been described. The presence and severity of nonalcoholic fatty liver disease (NAFLD) was found to be associated with increased QTc interval and subclinical cardiac abnormalities.
Aim
The aim of this study was to evaluate the ECG and echocardiographic changes in patients with NAFLD and their correlation with disease severity.
Patients and methods
This study was conducted in Ain Shams University, Ain Shams Specialized, and Helwan University Hospitals in the period from May 2015 till May 2018. It was conducted on 50 patients with NAFLD and 50 controls. Clinical, laboratory, and ultrasonographic examinations were done for all included patients together with liver biopsies. ECG and echocardiography were also performed. Independent Student's *t*-test, χ^2-test, Fisher's exact test, and Pearson's correlation coefficient were used. Data were presented as mean±SD and number and percentage.
Results
Longer corrected QT was found in the NAFLD group in comparison with controls (406.6±26.8 and 380.0±24.5 ms, respectively). Significant correlation between QTc and liver size, grade of steatosis, and NAFLD activity score was found. Overall, 16 and 8% of patients with NAFLD had diastolic and valvular dysfunctions, respectively.
Conclusion
NAFLD is associated with significant QTc prolongation and structural heart changes, with significant correlation between QTc and disease severity.

Keywords:
ECG, echocardiography, nonalcoholic fatty liver disease, nonalcoholic fatty liver disease activity score

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Introduction

Patients with nonalcoholic fatty liver disease (NAFLD) have a higher mortality rate than the general population and are at increased risk of developing cardiovascular disease (CVD). The association between NAFLD and CVD appears to be independent of classical risk factors, glycemic control, medications, and presence of metabolic syndrome [1].

There is convincing evidence that worsening grades of NAFLD contribute to progressive cardiometabolic risk, such that nonalcoholic steatohepatitis (NASH) represents a marker as well as mediator of increased cardiovascular risk more than simple steatosis [2]. The presence and severity of NAFLD on ultrasound was found to be associated with increased QTc interval in patients with type 2 diabetes even after adjusting for multiple established risk factors and potential confounder [3]. Prolonged heart rate-corrected QT-interval more than 440 ms or above the median more than 416 ms was found to be a risk factor for ventricular arrhythmias and sudden cardiac death [3]. The possible molecular mediators linking NAFLD and CVD have been extensively reviewed including the release of proatherogenic mediators from the liver including C-reactive protein, interleukin-6, and plasminogen activator inhibitor-1 [4].

This study was designed to evaluate the ECG and echocardiographic changes in patients with NAFLD, and their correlation with disease severity.

Patients and methods

This case–control study was conducted at Ain Shams University Hospital from May 2015 till May 2018, after approval from the Research and Ethics Committee of the Faculty of Medicine, Ain Shams University. Informed consent was obtained from all individual participants included in the study.

This study included 100 participants. They were divided into two groups:

(1) Group 1: it included 50 patients with NAFLD diagnosed clinically, biochemically, radiologically, and pathologically.
(2) Group 2: it included 50 normal healthy controls with normal clinical, laboratory, radiological, and pathological examination and negative steatosis in liver biopsy.

Some patients and all controls were recruited from Ain Shams Center for Organ Transplant (ASCOT), Cairo, Egypt, from the normal living liver donors. Liver biopsy was routinely done for them. Patients with steatosis less than 5% and no other pathological abnormalities were enrolled in the control group.

Inclusion criteria

Adult patients 18 years and older with NAFLD diagnosed clinically, radiologically and pathologically were enrolled in NAFLD group. Patients with any degree of steatosis of at least 5% were included with or without inflammation or fibrosis. Liver biopsies were carried out for patients with clinical and radiological evidence of NAFLD with or without elevated liver enzymes in Ain Shams University, Ain Shams Specialized, and Helwan University Hospitals.

Exclusion criteria

Patients with positive history of alcohol use, defined as more than 21 drinks/week for men and more than 14 drinks/week for women, were excluded. Other exclusions included acute viral hepatitis, chronic viral hepatitis, liver cirrhosis, congenital heart disease, myocarditis, cardiac surgeries, ischemic heart disease, diabetes mellitus, hypertensive patients or those receiving antihypertensive medications, taking other medications (β-blockers, calcium channel blockers, digoxin, amiodarone, and adenosine), having thyroid disorders, smoker, cocaine users, and those with malignancy.

All included patients and controls were subjected to the following:

(1) Detailed medical history and complete physical examination, including age, sex, blood pressure measurement, weight, and BMI.
(2) Laboratory investigations, including aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, alkaline phosphatase, total bilirubin, direct bilirubin, total protein, serum albumin, α-fetoprotein, creatinine, blood urea nitrogen, fasting blood sugar, postprandial sugar, hemoglobin A1c, lipid profile, serum sodium, potassium, calcium, uric acid, and serum ferritin. The laboratory work was conducted at the Clinical Pathology Department.
(3) All biochemical tests were measured on Synchron CX9 autoanalyzer (Beckman Instruments Inc., Scientific Instruments Division, Fullerton, Brea, California, USA).
(4) CBC was done using Coulter counter (T660; Beckman Coulter Inc., Brea, California, USA).
(5) Full lipid profile, including total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein (LDL), was analyzed using Beckman Coulter AU480 System (Beckman Coulter Inc.).
(6) For exclusion of other liver diseases, viral markers, autoimmune markers, bilharzial antibodies, serum copper, urinary copper, ceruloplasmin, and serum ferritin levels were determined using standard tests.
(7) Abdominal ultrasound was conducted using a Toshiba Aplio XV scanner (Toshiba, Tokyo, Japan) equipped with a broadband 2.5–5-MHz curved array probe to assess the presence of liver steatosis, which was defined by the presence of diffuse hyperechoic echo texture (bright liver). Fibrosis, when present with noticeable steatosis, was identified by a coarse echocardiographic pattern. Measurement of liver and spleen size, portal vein diameter, portal vein velocity was done.
(8) Ultrasound-guided liver biopsy and histopathologic examination: ultrasonography-guided liver biopsies were conducted under conscious sedation using a 16-G Klatskin needle. The length of the histological specimens was no less than 2.5 cm. The histological examination of liver biopsy was conducted by the same pathologist. They were examined under a light microscope for histopathologic evaluation. Steatosis was graded on a scale from 0 to 3, where 0=no steatosis, S1=steatosis from 5 to 33%, S2=steatosis from 34 to 66%, and S3=steatosis>66%. Lobular inflammation was graded from 0 to 3, where inflammation grade 0=no inflammation, grade 1=<2 foci, grade 2=2

to 4 foci, and grade 3=>4 foci of inflammation per ×200 field. Ballooning is graded from 0 to 2, where grade 0=no ballooning, grade 1=few ballooning cells, and grade 2=many or prominent ballooning cells. Nonalcoholic fatty liver disease activity score (NAS) is the sum of the biopsy's individual scores for steatosis (0–3), lobular inflammation (0–3), and hepatocellular ballooning (0–2). Fibrosis is not included in the NAS. In the original study that derived the NAS, scores of 0–2 are considered not diagnostic of NASH; scores of 3–4 are considered borderline for NASH; and scores of 5–8 are considered diagnostic of NASH [5]. Fibrosis staging was graded on a scale from 0–4, where F0=no fibrosis, F1=zone 3 perisinusoidal and pericellular fibrosis, F2=zone 3 fibrosis with periportal fibrosis, F3=zone 3 fibrosis and portal fibrosis with bridging fibrosis, and 4=cirrhosis [6].

(9) 12-lead ECG [Bionet Cardiocare-2000 (EKG-2000), Bionet Co., Ltd., Guro-Gu, Seoul, REPUBLIC OF KOREA] were obtained for all patients and controls at amplitude of 20 mm/mV and a velocity of 50 mm/s. The patients and controls were subjected to computer-assisted ECG calculations and manual analysis. Comment on the heart rate, rhythm, axis deviation, P-wave amplitude and duration, PR interval duration, QRS duration and amplitude, premature atrial contractions, premature ventricular contractions, and ST wave changes was made. QT and QTc intervals were calculated using computer-assisted calculation. The QT-interval was defined as the interval from the onset of the QRS complex to the end of the T-wave, which was defined as its return to the T–P baseline. The measurements were carried out with a precision of 0.01 mm (0.4 ms). If the U wave was present, the QT-interval was measured to the nadir of the curve between the T and U waves. QT-intervals were corrected by the Bazett's Formula to compensate for its known dependence on heart rate: $QTc=QT/\sqrt{RR}$. Measurements on QT and RR intervals were carried out in three consecutive cardiac cycles in all leads, and average values were obtained [7].

(10) Transthoracic echocardiography examination (Vivid 3; GE Medical Systems, Milwaukee, Wisconsin, USA) using a 3-MHz transducer was conducted to both the study and control groups by the same cardiologist. Left ventricular (LV) ejection fraction, LV systolic and diastolic diameters, septal and posterior wall thickness and motion, right ventricular and atrial diameters were obtained by using the M-mode, 2-D, color, and pulse-continuous Doppler. Recording of any structural, functional, valvular, or cardiac wall abnormalities was done.

(11) Statistical examination: Data were analyzed on an IBM personal computer, using statistical package for special science software computer program, version 15 (IBM Corporation, Armonk, New York, USA). Data were described as mean±SD for quantitative variables and as frequency and percentage for qualitative variables. Independent Student's *t*-test was used for comparison of quantitative variables among two independent groups. χ^2-test was used for comparison of distribution of qualitative variables among different groups. Fisher's exact test was used when one expected cell or more are less than or equal to 5. Correlation between continuous variables was performed using Pearson's correlation coefficient. Results were evaluated at a 95% confidence interval and *P* value less than 0.05 was considered as significant.

Results

Both studied groups were age and sex matched. BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP), pulse rate, total cholesterol, triglycerides, serum creatinine, liver size, and portal vein diameter were significantly higher in the NAFLD group than the controls. Serum calcium and portal vein velocity were significantly lower in NAFLD group than controls (Table 1).

Thirty-eight (76%) patients with NAFLD had no fibrosis on liver biopsies, whereas eight (16%) had fibrosis stage F1, and four (8%) had fibrosis stage F2. Twelve (24%) patients with NAFLD had inflammation, whereas three (6%) had ballooning (Table 2).

QTc interval was significantly higher in NAFLD group than controls. Eight (16%) and four (8%) of patients with NAFLD had diastolic and valvular dysfunctions, respectively (Table 3).

There was a significant positive correlation between QTc interval and liver size, grade of steatosis, NAS score, and portal vein velocity (Table 4).

There was a positive correlation between QTc interval and platelets, and QT-interval and alkaline phosphatase, whereas there was a negative correlation between QTc interval and serum creatinine (Figs 1–3).

Table 1 Comparison between studied groups regarding clinical, biochemical, and radiological variables

Variables	Nonalcoholic fatty liver disease (*N*=50)	Control (*N*=50)	*P*
Age (years)			
Mean±SD	28.8±7.7	27.4±6.8	0.326[a]
Range	17.0–50.0	18.0–50.0	
Sex [*n* (%)]			
Male	37 (74.0)	42 (84.0)	0.220[b]
Female	13 (26.0)	8 (16.0)	
BMI (kg/m^2)			
Mean±SD	26.4±2.7	24.2±2.5	<0.001[a,*]
Range	19.4–31.0	19.3–30.0	
Systolic blood pressure (mmHg)			
Mean±SD	118.9±8.8	110.6±7.4	<0.00 [a,*]
Range	100.0–140.0	100.0–120.0	
Diastolic blood pressure (mmHg)			
Mean±SD	77.4±7.0	71.8±7.1	<0.001[a,*]
Range	60.0–90.0	60.0–80.0	
Pulse (beats/min)			
Mean±SD	75.2±12.6	68.1±11.7	0.005[a,*]
Range	54.0–105.0	51.0–100.0	
Total cholesterol (mg/dl)			
Mean±SD	179.5±37.8	161.9±29.1	0.010[a,*]
Range	118.0–277.0	103.0–241.0	
Triglycerides (mg/dl)			
Mean±SD	104.6±58.9	77.6±28.4	0.004[a,*]
Range	24.0–365.0	34.0–160.0	
Serum creatinine (mg/dl)			
Mean±SD	0.80±0.16	0.71±0.17	0.008[a,*]
Range	0.50–1.20	0.10–0.90	
Serum calcium (mmol/l)			
Mean±SD	9.3±0.7	9.6±0.6	0.027[a,*]
Range	7.0–10.6	7.3–10.3	
Liver size (cm)			
Mean±SD	14.8±1.0	14.4±0.5	0.009[a,*]
Range	13.2–17.6	14.0–15.0	
Portal vein diameter (mm)			
Mean±SD	11.5±1.2	11.0±1.2	0.044[a,*]
Range	8.0–13.0	8.0–13.0	
Portal blood velocity (cm/s)			
Mean±SD	21.4±4.5	23.8±4.1	0.006[a,*]
Range	14.0–36.0	15.0–35.0	

[a]Independent *t*-test. [b]χ^2-test. [*]Significant.

Table 2 Liver pathology among the studied groups

Variables	Nonalcoholic fatty liver disease (*N*=50)	Control (*N*=50)	*P*[a]
Steatosis			
Mean±SD	20.5±18.0	–	–
Range	10.0–70.0	–	
NAS score			
Mean±SD	2.5±1.4	–	–
Range	1.0–6.0	–	
Fibrosis [*n* (%)]			
F0	38 (76.0)	50 (100.0)	<0.001[a,*]
F1	8 (16.0)	0 (0)	
F2	4 (8)	0 (0)	
F3	0 (0)	0 (0)	
Inflammation [*n* (%)]	12 (24.0)	0 (0.0)	<0.001[a,*]
Ballooning [*n* (%)]	3 (6.0)	0 (0.0)	0.242[a]

NAS, nonalcoholic fatty liver disease activity score. [a]Fisher's exact test. *Significant.

Table 3 ECG and echocardiographic findings among the studied groups

Variables	Nonalcoholic fatty liver disease (*N*=50)	Control (*N*=50)	*P*[a]
QT (ms)			
Mean±SD	364.9±25.2	367.3±26.7	0.646[a]
Range	316.0–418.0	306.0–430.0	
QTc (ms)			
Mean±SD	406.6±26.8	380.0±24.5	<0.001[a,*]
Range	336.0–474.0	332.0–420.0	
PR (ms)			
Mean±SD	148.8±16.6	142.8±21.4	0.124[a]
Range	93.0–194.0	110.0–204.0	
QRS (ms)			
Mean±SD	94.1±16.9	93.1±10.7	0.715[a]
Range	78.0–192.0	78.0–118.0	
Ejection fraction%			
Mean±SD	63.6±4.7	64.0±4.7	0.657[a]
Range	55.0–74.0	55.0–73.0	
P-wave abnormality	1 (2.0)	3 (6.0)	0.617[b]
T-wave abnormality	0 (0.0)	0 (0.0)	–
Axis abnormality	0 (0.0)	0 (0.0)	–
Rhythm abnormality	0 (0.0)	0 (0.0)	–
Diastolic dysfunction	8 (16.0)	0 (0.0)	0.006[b,*]
Valve dysfunction	4 (8.0)	0 (0.0)	0.117[b]

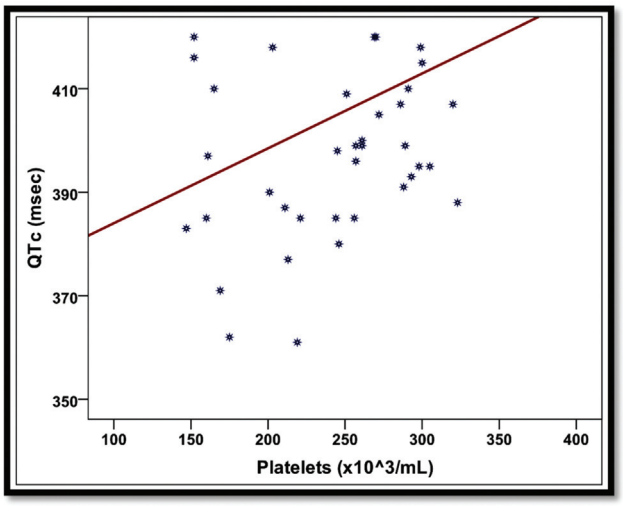
[a]Independent *t*-test. [b]Fisher's exact test. *Significant.

Table 4 Correlation between ECG and ejection fraction on one hand and ultrasound and pathology on the other hand in nonalcoholic fatty liver disease group

	QT	QTc	PR	QRS	EF
Liver size					
r	0.121	0.349	0.051	–0.007	–0.099
P	0.408	0.013*	0.725	0.959	0.493
Spleen size					
r	0.208	0.079	0.168	0.161	0.070
P	0.152	0.586	0.245	0.263	0.627
PVD					
r	0.058	0.119	0.163	0.018	0.037
P	0.692	0.412	0.259	0.899	0.799
PV velocity					
r	0.064	0.289	–0.146	0.050	0.216
P	0.662	0.042*	0.311	0.731	0.133
Steatosis					
r	–0.012	0.441	–0.046	–0.049	–0.094
P	0.936	0.001*	0.750	0.738	0.517
NAS score					
r	0.072	0.518	0.062	–0.128	–0.132
P	0.621	<0.001*	0.669	0.375	0.359

EF, ejection fraction; NAS, nonalcoholic fatty liver disease activity score; PVD, portal vein diameter; PV, portal vein. * Significant.

Figure 1



Correlation between QTc and platelets in nonalcoholic fatty liver disease group.

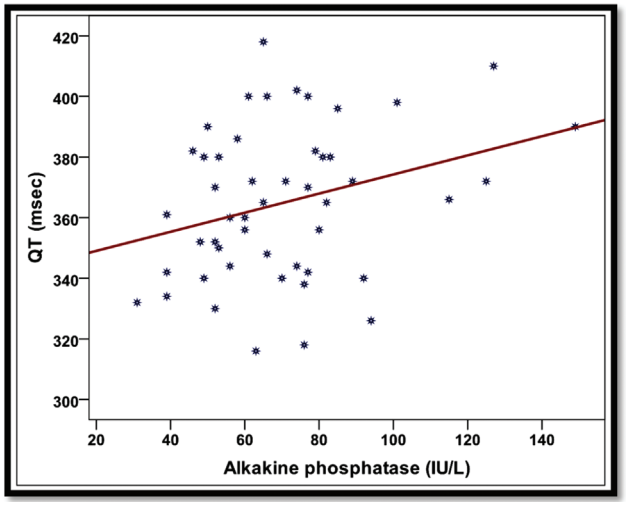
Discussion

Interactions between the heart and the liver have been described, with heart diseases affecting the liver, liver diseases affecting the heart, and conditions affecting both.

Convincing evidence substantiates the existence of a link between NAFLD and functional and structural myocardial alterations in both adults and children [8].

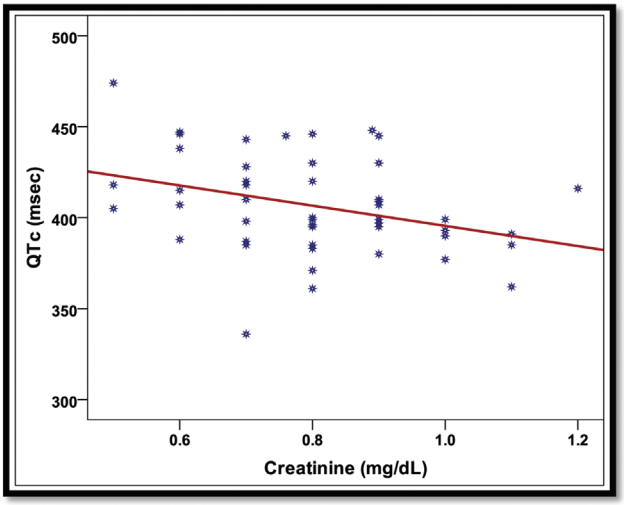
This study showed a significant prolongation of QTc in patients with NAFLD in comparison with controls. Moreover, there were significant positive correlations between QTc interval on one hand and liver size, hepatic steatosis, and NAS score on the other hand. This agrees with Targher *et al.* [3], who found that the presence and severity of ultrasonographic NAFLD was associated with a 2.2-fold increased rate of prolonged QTc interval and sudden cardiac death, independently of age, sex, hypertension, diabetes-related variables, and other comorbid conditions.

Figure 2



Correlation between QT and alkaline phosphatase in nonalcoholic fatty liver disease group.

Figure 3



Correlation between QTc and creatinine in nonalcoholic fatty liver disease group.

In this study, significant positive correlations were found between QTc interval and platelets count. A significant correlation between QT dispersion and platelet count was evident in a previous study performed on centenarians [9].

In this study in the NAFLD group, significant positive correlations were found between QT-interval and alkaline phosphatase. In a study on severely obese patients with BMI more than 40 with or without metabolic syndrome, patients with prolonged QTc more than 440 ms had lower calcium levels and elevated alkaline phosphatase concentrations. Impaired calcium/phosphate metabolism and subsequent elevated alkaline phosphatase was suggested in obese population [10].

In this study, there was a significant negative correlation between QTc and serum creatinine. Although a nonsignificant correlation between QTc and serum creatinine was found in a previous study, significant correlation between QTc interval and serum lactate in shift-workers was observed [11]. In a previous study on patients with chronic renal disease, there were significant negative correlations between QT and QTc intervals and blood pH level before correction [12]. There is a strong association between chronic kidney disease (CKD) and cardiovascular events. Increased arrhythmia risk in kidney disease is one of the main predominant factors in increased mortality and sudden cardiac death [12].

Diastolic and valvular cardiac dysfunctions were detected in 16 and 8% of patients with NAFLD respectively in this study. Case–control studies have reported strong associations of NAFLD with early changes in LV morphology and/or diastolic dysfunction [13]. Adult individuals with NAFLD in the absence of severe obesity, hypertension, and diabetes were reported to have mildly increased LV mass and early features of LV diastolic dysfunction [14]. NAFLD on ultrasound was found to be associated with LV diastolic dysfunction in a community-based cohort of Korean adults, independently of established cardiovascular (CVD) risk factors and metabolic syndrome features [15]. A systematic review and meta-analysis of nine cross-sectional studies have confirmed that NAFLD (diagnosed on ultrasonography or histology) is associated with subclinical cardiac abnormalities [16].

Studies have suggested that NAFLD is independently associated with the presence of cardiac calcification in both the aortic and mitral valves in both nondiabetic and type 2 diabetic individuals [17]. NAFLD was associated with a 3.5-fold increased rate of AVS, mitral annular calcification, or both after adjustment for potential confounding variables [17]. It was shown that NAFLD diagnosed on ultrasound was associated with an increased prevalence of aortic valve sclerosis independent of multiple cardiometabolic risk factors [18].

Significant higher BMI, SBP, DBP, heart rate, total cholesterol, and triglycerides were found in the NAFLD group in comparison with the controls in this study. A previous study on a Brazilian cohort of 5362 healthy middle-aged men and women presented for yearly physical examination and testing found higher BMI in those diagnosed with NAFLD. They

also found higher incidence of NAFLD in patients with prehypertension and hypertension [19]. Another study found close association between SBP, DBP, triglyceride, high-density lipoprotein cholesterol, and LDL cholesterol and the risk for NAFLD [20]. NAFLD is associated with insulin resistance and metabolic syndrome [21]. There may be a genetic predisposition to NAFLD related to the risk factors of acquiring metabolic syndrome [22]. Quantity of liver fat has been reported to be predictive of metabolic syndrome and CVD risk [23].

Several mechanisms have been postulated for development of cardiovascular pathologies in patients with NAFLD, including genetic predisposition, insulin resistance, atherogenic dyslipidemia, oxidative stress, chronic inflammation, reduced levels of the adiponectin, and altered production of procoagulant and anticoagulant factors like fibrinogen, plasminogen activator inhibitor-1, and tumor growth factor. These mechanisms may work synergistically [24,25]. Visceral fat is metabolically active and secretes several hormones that help regulate inflammation [26]. NAFLD is considered to have chronic subclinical inflammation and associated with many inflammatory markers. Increased cardiovascular risk has been linked to increased levels of inflammatory cytokines and markers such as interleukin-6, tumor necrosis factor, C-reactive protein, and fibrinogen. Oxidative stress is thought to trigger changes in endothelial function leading to formation and deposition of oxidized LDL in the subintimal space [27].

Significant higher serum creatinine and lower serum calcium were found in the NAFLD group in comparison with the control group in this study. A recent meta-analysis of 33 studies for a total of over 2000 participants found that NAFLD was associated with an increased prevalence as well as incidence of CKD [28].There are similarities in the risk factors for CKD and NAFLD including hypertension, obesity, dyslipidemia, and insulin resistance, which may be the cause for the association between NAFLD and renal and cardiac diseases [3]. The renin–angiotensin system (RAS) is also believed to play a key role in the pathogenesis of NAFLD and CKD. Adipocytes express all components of RAS and contribute up to 30% of circulating renin, angiotensin-converting enzyme, and angiotensin II [29]. In the kidney, RAS activation plays a key role in determining renal ectopic lipid deposition which is known to cause oxidative stress and inflammation through hemodynamic effects of glomerular efferent arteriole vasoconstriction leading to glomerulosclerosis [30].

Regarding the lower serum calcium levels in patients with NAFLD, there are some similarity with a previous study but on severely obese patients, in whom lower serum calcium was found probably owing to impaired calcium/phosphate metabolism. Improvement of calcium levels was detected with successful weight reduction in those patients [10]. NAFLD and vitamin D deficiency are often found together, and although this is not unexpected, given their similar associations with obesity and sedentary lifestyle, a growing body of evidence points to a closely linked and potentially causative relationship between vitamin D deficiency and NAFLD [31].

Conclusion

NAFLD is associated with significant prolongation of the QTc interval, with significant direct correlation between the QTc interval and grade of steatosis and disease severity assessed by NAFLD activity score. Significant ventricular dysfunction was observed with nonsignificant higher percentage of valvular dysfunction in patients with NAFLD.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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