REVIEW ARTICLE
NOCTURNAL BLOOD PRESSURE ASSESSMENT, AN ENTITY OF HIGH PROGNOSTIC VALUE, NOT UTILIZED TO ITS POTENTIAL IN CLINICAL PRACTICE

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Abstract: Non-alcoholic fatty liver disease (NAFLD) is a prevalent condition that affects a significant portion of the global population and imposes a heavy clinical and economic burden. Recent studies have provided substantial evidence linking NAFLD to cardiac electrical abnormalities, including atrial and ventricular arrhythmias, heart blocks, conduction delays, and ECG changes. These cardiac electrical disturbances play a significant role in cardiac diseases that are the leading cause of death in NAFLD patients. This paper aims to provide an update on the proposed mechanisms underlying arrhythmogenesis in NAFLD and summarize the latest research findings in this field. Managing NAFLD requires a comprehensive approach that includes treating the underlying liver condition and regular ECG monitoring to detect and address any potential cardiac complications. Meta-analyses are recommended for future research further to elucidate the association between NAFLD and cardiac arrhythmias. Understanding and effectively managing the cardiac implications of NAFLD will contribute to improved patient care and outcomes.

Keywords: NAFLD, cardiovascular disease, conduction defects, atrial fibrillation, ventricular arrhythmias, ECG changes

Citation: Mukhtar MU, Zahoor S, Abid M, Rehman ZU, Aslam MA, Jehangir HMS, Firdous S. Association of Non-Alcoholic Fatty Liver Disease with Cardiac Arrhythmias and Cardiac Conduction Defects: A Review of the Literature. Pak Heart J. 2023:56(02):133-139. DOI: https://doi.org/10.47144/phj.v56i2.2236

INTRODUCTION

Fatty liver disease (FLD) encompasses both alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD). It poses a significant clinical burden due to its cirrhosis and hepatocellular carcinoma progression.¹ While chronic alcohol consumption is often blamed as the primary cause of liver damage, NAFLD, arising from non-alcoholic factors, is actually the leading cause of FLD. In fact, NAFLD accounts for approximately 75% of the overall burden of chronic liver disease (CLD), with a global prevalence of around 25%.² Consequently, NAFLD has been strongly linked to cardiovascular disease (CVD), making it an independent risk factor for CVD.³ The association between NAFLD and CVD extends to structural, functional, and conduction defects of the heart, including coronary artery disease (CAD), cardiomyopathy, subclinical atherosclerosis, left ventricular hypertrophy, valvular diseases, epicardial fat deposition, and systolic and diastolic dysfunction leading to heart failure. CVD is the primary cause of mortality in NAFLD patients, significantly impacting their outcomes. Moreover, NAFLD is associated with an elevated risk of all-cause mortality.⁴⁻⁵

This review focuses on summarizing the clinical evidence and shedding light on the role of NAFLD in causing cardiac electrical abnormalities, particularly conduction defects such as arrhythmias, bundle branch blocks, QT prolongation, and ECG changes.⁶ To achieve this, the review will discuss the basic definitions of NAFLD, explore the underlying mechanisms, and review important studies conducted in this area.

Non-alcoholic fatty liver disease:

NAFLD encompasses a range of fatty liver disorders caused by factors other than alcohol consumption, genetic diseases, and steatogenic drugs. It manifests as a spectrum of conditions in individuals with minimal or no alcohol intake (less than 20 grams of ethanol/week). This spectrum includes non-alcoholic fatty liver (NAFL) characterized by hepatic steatosis (≥5% fat accumulation in the liver), non-alcoholic steatohepatitis (NASH) characterized by hepatic steatosis with hepatocyte injury, and liver cirrhosis.⁷
Pathophysiology of arrhythmogenesis:

The precise mechanisms underlying how NAFLD contributes to cardiac arrhythmias remain unclear. However, chronic inflammation, inflammatory mediators, insulin resistance, and intestinal dysbiosis have been implicated in inducing structural and electrical changes in the heart, leading to arrhythmias. NAFLD is associated with a chronic inflammatory state, common to metabolic disorders. Adipose tissue deposition in various locations, including the heart, acts as a source of pro-inflammatory cytokines such as IL-1, IL-6, and TNFα while reducing the production of the anti-inflammatory adiponectin. Inflammatory markers like CRP, Factor VIII, and PAI-1 are elevated in the blood of NAFLD patients. Some of these cytokines have been shown to play a role in arrhythmogenesis, with IL-1β, for example, demonstrated to prolong action potential duration (APD) and alter Ca2+ and K+ currents in mice. Furthermore, the IL-17 family has been associated with an increased risk of atrial fibrillation (AF). Collectively, these pro-inflammatory cytokines may alter the expression of K+ channels at the gene level, affecting cardiac currents and leading to prolonged APD and QTc intervals, ultimately resulting in arrhythmias.

Elevated levels of free fatty acids (FFAs) in NAFLD also contribute to arrhythmogenesis. Excess FFAs are deposited as triglycerides in the heart, leading to intracellular stress and subsequent apoptosis of myocardial cells—a phenomenon known as myocardial lipotoxicity. This process can damage the heart's conduction system. Notably, the severity of triglyceride deposition in the myocardium and the presence of pericardial fat have been associated with a higher prevalence of AF. Additionally, the excess FFA in NAFLD undergoes β-oxidation, a metabolic process occurring in mitochondria that generates reactive oxygen species (ROS) as a byproduct. ROS can damage mitochondria, reducing ATP production and causing cardiac dysfunction when occurring in cardiomyocytes.

Historically, the association between NAFLD and various cardiac complications was attributed to shared risk factors with CVD, such as metabolic syndrome, type 2 diabetes mellitus (T2DM), and obesity. However, emerging evidence suggests that NAFLD directly contributes to the pathogenesis of associated cardiac complications rather than being a mere bystander. This review primarily focuses on studies that either excluded patients with co-morbidities or reported an independent association between NAFLD and cardiac diseases, excluding confounding factors like metabolic syndrome and T2DM.

Figure 1: Pathogenesis of arrhythmias in NAFLD
NAFLD and atrial fibrillation:

Several studies conducted in the past decade have consistently demonstrated a strong association between non-alcoholic fatty liver disease (NAFLD) and atrial fibrillation (AF). Targher et al. conducted a study that revealed a significant association between NAFLD and type 2 diabetes mellitus (T2DM). In another study by Sinner et al., participants with moderate to severe alcohol consumption were excluded, and it was found that elevated liver transaminases (ALT and AST) were associated with AF. Cai et al. conducted a meta-analysis involving 614,637 individuals, which revealed that NAFLD was associated with an increased risk of AF, even after adjusting for concurrent cardiometabolic factors. The meta-analysis estimated a 1.3-fold increase in the risk of AF per 1000 person-years in NAFLD patients (95% CI 0.5-2.1). The study concluded that the presence of concurrent cardiometabolic factors in NAFLD partially contributes to the heightened risk of AF. Similarly, in another meta-analysis by Minhas et al., it was observed that NAFLD conferred a 1.5 times higher likelihood of mortality from AF.

In addition to non-alcoholic steatohepatitis (NASH), an advanced form of NAFLD, was found to be associated with a twofold higher prevalence of AF in NAFLD patients. Whitsett et al. demonstrated a higher prevalence of heart failure and cerebrovascular disease in NAFLD patients with concurrent AF, underscoring the significance of AF as a prominent risk factor for cardiovascular disease. Taken together, multiple studies conducted in the past five years have established the association between NAFLD and AF.

Recent studies have further supported this association. Roh et al. investigated 334,280 individuals, diagnosing NAFLD based on the fatty liver index (FLI). Their findings indicated an elevated risk of AF in patients with NAFLD, with a higher FLI correlating to an increased risk of AF. Importantly, these patients had no other significant co-morbidities. Similarly, a recent study conducted in Germany assessed the impact of NAFLD on cardiovascular risk in a primary care population, and it found that individuals with NAFLD had a hazard ratio of 1.15 (p = 0.005) for AF, indicating a 1.15 times higher likelihood of mortality from AF.

Additionally, non-alcoholic steatohepatitis (NASH), an advanced form of NAFLD, was found to be associated with a twofold higher prevalence of AF in NAFLD patients. Whitsett et al. demonstrated a higher prevalence of heart failure and cerebrovascular disease in NAFLD patients with concurrent AF, underscoring the significance of AF as a prominent risk factor for cardiovascular disease. Taken together, multiple studies conducted in the past five years have robustly established the association between NAFLD and AF. These findings are concisely summarized in Table 1.

### Table 1: NAFLD and Atrial Fibrillation

<table>
<thead>
<tr>
<th>Study (author, year, study design)</th>
<th>Sample size</th>
<th>Diagnosis of NAFLD</th>
<th>Study Measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang, 2020, retrospective, cross-sectional study</td>
<td>NAFLD: 6293</td>
<td>Ultrasonography</td>
<td>Association between AF in patients of advanced NAFLD cirrhosis</td>
<td>Advanced liver fibrosis in NAFLD is associated with an increased risk of AF</td>
</tr>
<tr>
<td>Roh et al., 2020, prospective cohort study</td>
<td>Total: 334,280</td>
<td>Fatty liver index</td>
<td>Incidence of AF in NAFLD</td>
<td>NAFLD patients have an increased risk of AF. Higher the FLI, higher the risk of AF</td>
</tr>
<tr>
<td>Labenz et al., 2020, retrospective cohort study</td>
<td>Total: 44,096 NAFLD: 22,048</td>
<td>According to the International Classification of Diseases, 10th revision</td>
<td>Incidence of AF along with MI, CAD, and stroke</td>
<td>NAFLD is an independent risk factor for AF, CAD, and MI. Hazard ratio for AF in patients of NAFLD is 1.15</td>
</tr>
<tr>
<td>Whitsett et al., 2019, retrospective cohort study</td>
<td>NASH: 9108</td>
<td>According to the International Classification of Diseases, 9th Revision</td>
<td>Incidence of AF in NASH</td>
<td>Patients with NASH have a two-fold higher incidence of AF</td>
</tr>
<tr>
<td>Karajamaki et al., 2015, prospective cohort study</td>
<td>Total: 958 NAFLD: 249</td>
<td>Ultrasonography</td>
<td>Risk of AF in NAFLD</td>
<td>NAFLD is independently associated with the risk of AF</td>
</tr>
</tbody>
</table>

Meta-analyses have further contributed to our understanding of the association between NAFLD and AF. Cai et al. conducted a meta-analysis involving 614,637 individuals, which revealed that NAFLD was associated with an increased risk of AF, even after adjusting for concurrent cardiometabolic factors. The meta-analysis estimated a 1.3-fold increase in the risk of AF per 1000 person-years in NAFLD patients (95% CI 0.5-2.1). The study concluded that the presence of concurrent cardiometabolic factors in NAFLD partially contributes to the heightened risk of AF. Similarly, in another meta-analysis by Minhas et al., it was observed that NAFLD conferred a 2.5-fold higher likelihood of developing new-onset atrial fibrillation (OR = 2.47, CI = 1.30-4.66, p = 0.005).
conducted a study involving 400 diabetic patients with NAFLD diagnosed using ultrasonography. They found that 77 patients exhibited abnormally prolonged QTc intervals (>440 ms), which is associated with a 2.3-fold increased risk of sudden cardiac death (SCD). The severity of NAFLD was positively correlated with both the quantitative increase in QTc duration and the proportion of patients with prolonged QTc. Importantly, the association between NAFLD and prolonged QTc persisted even after adjusting for known risk factors and confounders.27 Hung et al. also conducted a cross-sectional study involving 31,116 individuals from the general population, confirming the association between NAFLD and prolonged QTc.28,29

The association of NAFLD with ventricular arrhythmias was investigated by Mantovani et al., who observed a threefold increased risk of ventricular arrhythmias in diabetic patients with NAFLD. Specifically, they noted an increased incidence of greater than 30 premature ventricular contractions (PVC) per hour, non-sustained ventricular tachycardia (VT), or both in their patients.30 Numerous recent studies have provided further evidence linking NAFLD to ventricular arrhythmias and changes in electrocardiogram (ECG) readings. These findings are summarized in Table 2.

### Table 2: NAFLD, ventricular arrhythmias, and ECG changes

<table>
<thead>
<tr>
<th>Study (author, year, study design)</th>
<th>Sample size</th>
<th>Diagnosis of NAFLD</th>
<th>Study Measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung et al., retrospective cross-sectional study, 2020.31</td>
<td>Total: 764 NAFLD: 180 Non-NAFLD: 584</td>
<td>Ultrasonography</td>
<td>Association between NAFLD and QTc interval prolongation in Korean women</td>
<td>On average, QTc was raised by 6.4 ms in NAFLD patients. OR of QTc prolongation in NAFLD was 2.05</td>
</tr>
<tr>
<td>Alsawaby et al., 2020, prospective case-control study,32</td>
<td>NAFLD: 50 Non-NAFLD: 50</td>
<td>Ultrasonography, biopsy</td>
<td>Association of NAFLD with QTc interval</td>
<td>Patients with NAFLD had longer QTc intervals than patients in the control group. An increase in QTc is associated with the severity of liver size, steatosis, and NAFLD activity score.</td>
</tr>
<tr>
<td>Yu et al., 2019 prospective observational study,29</td>
<td>NAFLD: 1155</td>
<td>Ultrasonography</td>
<td>Association between NAFLD and QTc prolongation in Korean women</td>
<td>NAFLD is associated with QTc prolongation. The quantitative increase in QTc corresponds to the severity of NAFLD</td>
</tr>
<tr>
<td>Xiao et al., 2020, retrospective cross-sectional study,33</td>
<td>Total: 32,922 NAFLD: 9454</td>
<td>Ultrasonography</td>
<td>Non-specific ST-T segment changes in patients of NAFLD</td>
<td>NAFLD is an independent risk factor for non-specific ST-T segment changes</td>
</tr>
<tr>
<td>Tak et al., 2019, prospective cross-sectional study,34</td>
<td>Total: 174 NAFLD: 97</td>
<td>Ultrasonography</td>
<td>Changes in ventricular repolarization in NAFLD</td>
<td>NAFLD patients had longer QT, QTc.</td>
</tr>
</tbody>
</table>

### NAFLD and cardiac conduction defects:

Cardiac conduction defects encompass abnormalities that affect the conduction system of the heart, including the atrioventricular (AV) node, the His-Purkinje system, and other components. While conduction delays are common in young individuals due to high vagal tone, the presence of persistent conduction defects is not a normal physiological occurrence and can be associated with various pathological conditions, including NAFLD. It is well-established that NAFLD can lead to cardiac fibrosis and damage to the conduction system of the heart. As a result, individuals with NAFLD may experience various conduction defects, such as atrial conduction delay, heart blocks, bundle branch blocks, and increased PR interval. These abnormalities have been identified through electrocardiogram (ECG) studies conducted on patients with NAFLD. Several studies conducted in the past decade have further explored the relationship between NAFLD and specific conduction defects in the heart, providing valuable insights into this association. These findings are summarized in Table 3.

### Table 3: NAFLD and cardiac conduction defects

<table>
<thead>
<tr>
<th>Study (author, year, study design)</th>
<th>Sample size</th>
<th>Diagnosis of NAFLD</th>
<th>Study Measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Nimer et al., 2020, prospective, cross-sectional observational study,37</td>
<td>NAFLD: 74 Non-NAFLD: 23</td>
<td>Ultrasonography</td>
<td>Association between NAFLD and cardiac conduction and ventricular repolarization</td>
<td>Patients with NAFLD had significantly longer PR intervals, significantly shorter QTcB and JTc intervals, and a higher Tp-e/QTcB ratio</td>
</tr>
</tbody>
</table>
CONCLUSION

In conclusion, while the number of studies exploring the role of NAFLD in causing electrical abnormalities of the heart is limited, our review of the available research supports the notion that NAFLD is an independent risk factor for cardiac arrhythmias and electrical dysfunction. The exact mechanisms underlying arrhythmogenesis in NAFLD are not yet fully understood. Nevertheless, lifestyle modifications, including regular exercise, weight loss, and adopting healthy dietary habits, have shown the potential to slow the progression of NAFLD.

Maintaining a good lipid profile is also important. Medical interventions such as anti-hyperlipidemic medications and insulin-sensitizing agents, as well as surgical weight reduction procedures, may be considered as part of the treatment plan.

Given the strong arrhythmogenic potential of NAFLD, regular ECG monitoring of patients is advised, alongside the treatment of NAFLD itself. Cardiovascular disease (CVD) remains the leading cause of death in NAFLD, highlighting the importance of diagnosing and treating cardiac complications associated with the condition. However, it is worth noting that further studies are needed to effectively...
establish and confirm the association between NAFLD and cardiac electrical abnormalities. Continued research in this field will contribute to a better understanding of the pathophysiological mechanisms involved and guide the development of targeted interventions for patients with NAFLD and cardiac arrhythmias. In summary, the management of NAFLD must include the proper diagnosis and treatment of its cardiac complications, as addressing these aspects is crucial for effectively managing the disease and reducing associated risks.

AUTHORS’ CONTRIBUTION

SZ: conceptualization, MA, ZUR, and HMSJ: reviewed the literature. MUMr: drafted the manuscript, MAA: revised and reviewed the manuscript, and SF: gave expert opinion and supervised the study. All authors gave final approval, and agree to be accountable for all aspects of the work.

Conflict of interest: Authors declared no conflict of interest.

Disclosures: All the figures/pictures in this manuscript are author’s own work.

REFERENCES


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