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NAFLD AS A PREDICTOR OF CARDIOVASCULAR EVENTS IN T2DM: A COMPREHENSIVE REVIEW

[1]Ritu Akanksha kujur, [2]Dr Sandhya Madan Mohan

[1]Research Schlor, [2]Assistant Professor(Principal)

[1]Department of Home Science

[1]Bhilai mahila Mahavidyalaya , Bhilai, Chhattisgarh, India, 490001

Abstract: **-** Non-alcoholic fatty liver disease (NAFLD) has emerged as a critical comorbidity in individuals with type 2 diabetes mellitus (T2DM), significantly increasing the risk of cardiovascular disease (CVD) and all-cause morbidity and mortality - even in cases of mild NAFLD. This review highlights the complex and strong association between NAFLD and CVD, particularly in patients with T2DM. The coexistence of these conditions appears to have a coactive effect on cardiovascular outcomes, likely due to overlapping pathophysiological mechanisms. (1) Many studies suggests that who have both NAFLD and T2DM are at particularly high cardiovascular risk. Some Non-invasive imaging techniques like coronary artery calcium scoring (CACS) and non -enhanced computed tomography (CT) for liver fat assessment offer hopeful tools for improved risk stratification in these individuals. Additionally, several traditional and anti-diabetic therapies have shown advantageous effects on both NAFLD and CVD. Long-term potential studies are defensible to validate whether treating NAFLD can individualistically reduce cardiovascular risk and improve patient outcomes.

Keywords: Non-alcoholic fatty liver disease, cardiovascular disease, diabetes, dyslipidemia, high blood pressure, metabolic syndrome, triglyceride, thrombosis.

INTRODUCTION:

Type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD) frequently co-exist as hallmark features and symbol of the metabolic syndrome and together they markedly increase the risk of cardiovascular disease (CVD). worldwide, NAFLD affects approximately 25–30 percent of adults, making it the most prevalent condition of chronic liver, and in people with T2DM the prevalence frequently

exceeds 50–70 percent—underlining a strong metabolic link between hepatic fat accumulation and dysglycemia. CVD remains the leading cause of death globally, responsible for around 17.9 million deaths each year, mainly due to myocardial infarction, fibrosis and stroke. Rather than being only a downstream outcome of diabetes, NAFLD individualistically contributes to cardiovascular risk via chronic inflammation, insulin resistance, endothelial dysfunction, dyslipidemia and rapid progression of atherosclerotic (2). T2DM helps determination of the development of NAFLD, and perverse metabolic feedback degenerates each condition when they co-occur, resulting in a greater chance of major macrovascular events than either condition alone. Most newly study, evidence directs that combining coronary artery calcium scoring with CT-derived liver fat measurement outperforms standard risk models such as the Framingham Risk Score for predicting CVD in people with T2DM. This review thus aims to lighten the overlapping pathophysiology of NAFLD, CVD and T2DM, evaluate their impact on long-term health outcomes, and assess the role of glucose-lowering treatments. and that possess metabolic and anti-inflammatory benefits in reducing both cardiovascular and liver-related complications—highlighting the resolve the incorporating NAFLD screening into cardiovascular risk assessment for those who with T2DM (4).

In a comprehensive meta-analysis by Zhou and colleagues, the association between nonalcoholic fatty liver disease (NAFLD) and early-stage atherosclerosis was thoroughly evaluated using four non-invasive biomarkers: arterial stiffness, coronary artery calcification (CAC), carotid intima-media thickness (CIMT)/plaques, and endothelial function (1). The analysis included 26 observational studies around 85,395 individuals, of whom 29,493 had NAFLD. The shared results demonstrated that people with NAFLD had a notably higher possibility of subclinical atherosclerosis compared to those without NAFLD, yielding an adjusted odds ratio of 1.60 (95% CI: 1.45–1.78). Subgroup outcomes further exposed significantly elevated risks: CIMT/plaques (OR ~1.74; 95% CI: 1.47–2.06), arterial stiffness (~1.56; 95% CI: 1.24–1.96), CAC (~1.40; 95% CI: 1.22–1.60), and endothelial dysfunction (~3.73; 95% CI: 0.99–14.09). These findings underscore a strong, independent link between NAFLD and markers of subclinical cardiovascular disease, highlighting the importance of early vascular assessment in this patient (15).

Patients with type 2 diabetes mellitus (T2DM) are more likely to develop non-alcoholic fatty liver disease (NAFLD), including its more advanced stages, regardless of other common risk factors like older age, high blood pressure, abnormal cholesterol levels, or a family history of liver cirrhosis linked to NAFLD (5). Given the well-established link between type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and non-alcoholic fatty liver disease (NAFLD), it is clinically important to determine whether NAFLD further increases CVD risk in individuals with T2DM. While many studies have explored the connection between NAFLD and CVD, most have included patients with and without diabetes, making it difficult to isolate the specific impact of NAFLD in the diabetic population. Some research has adjusted for diabetes and other cardiovascular risk factors, suggesting that NAFLD may be an independent contributor to CVD risk (7). However, studies focusing exclusively on individuals with T2DM are needed for a more accurate assessment. Current research, often cross-sectional in design and using imaging techniques like abdominal ultrasound, has shown mixed results (8). A few longitudinal studies have offered more insights. For example, a long-term follow-up study of 337 diabetic individuals found higher mortality in those with NAFLD, with cancer, liver disease, and heart disease being the leading causes of death. Similarly, a five-year prospective study involving over 2,000 T2DM patients revealed a significantly increased CVD risk in those with NAFLD, even after adjusting for several risk factors (14). A large retrospective study from Scotland supported these findings, showing that NAFLD in diabetics was associated with increased CVD events and mortality over a 4.5-year follow-up. Furthermore, a meta-analysis of 11 studies involving over

8,000 diabetic patients confirmed that those with NAFLD had twice the risk of CVD compared to those without. Despite this growing evidence, more research is required to determine if the severity of NAFLD further elevates CVD risk. Preliminary data using magnetic resonance elastography suggest that liver stiffness may be linked to indicators of cardiovascular risk, such as coronary artery calcium and epicardial fat, in T2DM patients (10).

NAFLD and type 2 diabetes mellitus (T2DM) are connected through several common biological mechanisms that contribute to a higher risk of cardiovascular disease. These include changes in lipid metabolism that promote atherosclerosis, increased levels of clotting factors that raise the risk of thrombosis, persistent insulin resistance, chronic low-grade inflammation, and disruptions in gut microbiota. Together, these interconnected pathways play a significant role in accelerating cardiovascular complications in individuals affected by both conditions (11).

Dyslipidemia is a major contributor to atherosclerosis, and people with NAFLD frequently show a diverse lipid pattern linked to insulin resistance, type 2 diabetes and metabolic syndrome. This includes lipoproteins which is high levels of triglyceride-rich, more small, dense LDL particles and low HDL (good cholesterol), which are considered harmful to heart health. Fat accumulation in the liver and insulin resistance rises the production of very low-density lipoproteins (VLDL), which increase the activity of an enzyme called CETP (13). This enzyme helps exchange triglycerides from VLDL with cholesterol from LDL and HDL, leading to the formation of smaller, denser LDL and HDL particles. Small dense LDL particles are more atherogenic, meaning they contribute to plaque buildup in arteries. Additionally, heart disease is closely linked with high triglyceride levels in the blood. Also, the liver plays a vital role in blood clotting by creating factors like PAI-1, which is slows down the breakdown of clots. In NAFLD, PAI-1 levels are increased, promoting a higher tendency for clot formation. Similarly, T2DM elevate clotting risk due to higher clotting agents, more active platelets, and decreased natural anticoagulants. Together, NAFLD and T2DM may significantly increase the risk of cardiovascular events and thrombosis.

The accumulation of fat in the liver, known as intrahepatic steatosis, is linked with the buildup of certain harmful fats like diacylglycerols and ceramides. These substances interfere with insulin signaling, leading to insulin resistance in the liver (16). As a result, NAFLD can negatively impact blood sugar control in people with type 2 diabetes (T2DM). Individuals who have both T2DM and NAFLD frequently need stronger diabetes medications to manage their blood glucose levels compared to those with T2DM alone. Uncontrol blood glucose may partly explain the higher risk of heart disease seen in persons with both conditions. Although many clinical trials that aimed to reduce blood glucose levels showed mixed results in avoiding heart disease, novel studies with longer follow-up periods and better strategy have shown positive cardiovascular effects of certain anti-diabetic drugs. Additionally, some research using genetic and traditional methods has shown that people hereditarily prone to high blood glucose are easily to develop coronary artery disease, and research support the idea that high glucose levels play a direct and vital role. High blood glucose may damage blood vessels by encouraging inflammation, causing smooth muscle cells to grow, and impairing the inner lining of arteries, all of which contribute to heart disease.

NAFLD and type 2 diabetes (T2DM) are both interlinked to a determined, low-level inflammation in the body, which is contribute to the develop atherosclerosis. This inflammatory state is marked by the release of various inflammatory substances like tumor necrosis factor-alpha (TNF-α), interleukins (IL-1, IL-6), and proteins such as

fibrinogen, Fetuin-A, and C-reactive protein. The accumulation of fat in the liver causes triggering inflammatory pathways like NF-kB and MAPK and also stress in the endoplasmic reticulum. It also leads to complications in the mitochondria, resulting in oxidative stress. recent clinical trials have shown that blocking IL-1β with a monoclonal antibody can decrease the risk of repetitive cardiovascular events, even without depressing cholesterol levels, While the exact role of this inflammation in heart disease is still being studied.

Over the past decade, changes in the gut microbiome—known as gut dysbiosis—have been commonly linked to metabolic situations like type 2 diabetes (T2DM) and non-alcoholic fatty liver disease (NAFLD). These changes have been detected throughout all stages of NAFLD and can help to identify progressive liver damage such as cirrhosis or fibrosis. Common patterns include a higher level of bacteria like Roseburia and E. coli and lower number of Lactobacillus, which are seen in both NAFLD and T2DM (10). Gut dysbiosis is directly connected to heart disease (CVD). When the intestinal barrier is weak, injurious substances like lipopolysaccharides (LPS) can enter the bloodstream. This can also increase levels of certain gut-derived compounds such as short-chain fatty acids (SCFAs) and trigger inflammation and trimethylamine N-oxide (TMAO). TMAO, in particular, may contribute to cellular stress and inflammation, even though the exact mechanisms are still being studied. Overall, these gut-related changes may play a vital role in the link between NAFLD, CVD, and T2DM.

Because cardiovascular disease (CVD) is closely linked to type 2 diabetes (T2DM), it is important that anti-diabetic medications do not rise the risk of heart problems. In the past decade, many blood glucose-lowering drugs have been assessed for their safety and impact on heart health in people with T2DM. As a result, treatment strategies for T2DM have changed suggestively. Since non-alcoholic fatty liver disease (NAFLD) and T2DM both involve to insulin resistance.

Given the high occurrence of NAFLD in T2DM, and CVD individuals, routine checkup screening for liver disease may be useful. Early screening can help manage both cardiac and liver health more beneficial. Lifestyle modification and intervention, treatment strategies focusing both traditional and non-traditional method such as weight management, dietary changes and increase physical activities are very useful for managing T2DM, NAFLD and CVD (1).

CONCLUSION:

The findings from this review clearly show a close and strong link between non-alcoholic fatty liver disease (NAFLD) and an increased risk of cardiovascular disease (CVD), especially in who have type 2 diabetes (T2DM). Since T2DM and NAFLD frequently occur together and share communal risk factors, it can be difficult to separate their individual effects on cardiac health. However, studies suggest that having both conditions increases the risk of CVD more than having just one. This may be due to shared disease mechanisms like inflammation and insulin resistance. As a result, individual who have both NAFLD and T2DM should be considered at high cardiovascular risk and may use strategies for benefit and prevention from more aggressive heart disease. Additionally, newer imaging tools like non-contrast CT scans and many other techniques have shown ability in helping to evaluate the risk of heart problems in T2DM patients with NAFLD.

RECOMMENDATIONS

Further research is needed to clarify the underlying mechanisms and optimize treatment approaches for these patients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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