## Review Article

# Cardiac Steatosis — An Emerging Entity

**Aradhya Sekhar Bagchi[1], Ananda Bagchi[2]**

In this era of obesity pandemic and increased global prevalence of Type 2 DM (T2DM) and Metabolic Syndrome (Met S), cardiovascular diseases are also increasing globally and is a real concern for morbidity and mortality. In modern lifestyle with sedentary habits, excessive intake of calories and with unfavorable genotypes leads to lipid overflow resulting in failure of Subcutaneous Adipose Tissue (SAT) to expand and store the excess circulating Free Fatty Acids (FFA). This excess FFA is being deposited as Visceral Adipose Tissue (VAT) in the major organs like Liver, Heart, Pancreas, Skeletal muscles causing Hepatic Steatosis, Cardiac Steatosis etc. Nowadays Cardiac steatosis is considered as an important predisposing factor for Diastolic Dysfunction, AV block and Sudden Cardiac Death.

[*J Indian Med Assoc* 2024; **122(12):** 61-5]

***Key words*** **: Triglyceride, Subcutaneous Adipose Tissue (SAT), Free Fatty Acids (FFA), Visceral Adipose Tissue (VAT), Non-alcoholic Fatty Liver Disease (NAFLD).**

Cardiac Steatosis (the fatty heart), also known as lipomatosis cordis,where there is deposition of adipose tissue in the myocardium leading to fibrosis.This excessive adipose tissue deposition alters the normal physiology of the myocardium. Cardiac adiposity or steatosis has recently emerged as an important risk factor for the development of cardiovascular diseases, including diastolic dysfunction of heart and sudden cardiac death.The hypothesis is that accumulated fat impairs cardiac performance and induces structural remodeling as a result of lipotoxicity.

Now we are in the era of obesity pandemic and abdominal obesity in particular, which is associated with Insulin resistance and Type 2 DM (T2DM) causing serious metabolic derangements in our body leading to Metabolic Syndrome. Excess caloric intake and sedentary lifestyle combined with unfavorable genotype and several environmental factors result in lipid overflow, due to a failure of Subcutaneous Adipose Tissue (SAT) to expand and store the excess of circulating Free Fatty Acids (FFA)[1]. Consequently, the excessive fat is accumulated into different visceral organs like Liver, Heart, Pancreas and Skeletal muscles etc.

Ectopic fat deposits have been subdivided into those with local and those with systemic effect. Accordingly, perivascular, myocardial, and epi/pericardial fat have mainly local unfavorable effects, whereas visceral adipose tissue, or fat in the liver, heart or skeletal muscles have systemic effects due to the fundamental role of these organs in glucose, insulin, and lipid metabolism. Here both location and the amount of adipose tissue has got a bearing on the development of cardiovascular morbidity and mortality.

***Editor's Comment :***

- The association of Non-alcoholic Fatty Liver Disease (NAFLD) with the Cardiovascular system is quite complex and incompletely understood. NAFLD is suggested to be implicated in cardiac steatosis in many ways and seems to worsen the prognosis of both the diseases. Moreover, as there is no definitive treatment for NAFLD as yet, many CV drugs show promising results in NAFLD treatment both biochemically and histologically with fibrosis regression. So the coupling between NAFLD and Cardiac steatosis exists in true sense and despite the suggested results, further studies are needed for better understanding of the two-way liver-heart interplay and the roles of drugs in the pathophysiology and treatment of NAFLD and cardiac steatosis.

## Cardiac Steatosis :

Though it is well recognised that, adipose tissue accumulation occurs in all three cardiac sites like pericardium, myocardium and epicardium, they differ in their capacity of fat accumulation. Pericardial site has got the highest capacity and cardiomyoctes have got the least. One study by Kristopher Nyman, *et al*, has shown that increased pericardial fat is more important than epiicardial fat in causing LV Diastolic dysfunction. though the exact cause of it is not known[2]. Pericardial fat has also been reported to be associated with Insulin Resistance (IR) and also 10

[1]MD (Medicine), Senior Resident, Department of Neurology, National Institute of Mental Health and Neuro Sciences, Bangalore, Karnataka 560029

[2]MD (Medicine), Senior Consultant, Department of Medicine, Dum Dum Municipal Specialised Hospital and Cancer Research Center, Kolkata, West Bengal 700028 and Corresponding Author

***Received on : 31/08/2024***
***Accepted on : 18/09/2024***

years CAD risk more strongly than Epicardial fat. In Type 2 DM patients, increased myocardial Triglyceride (TG) concentration, which is an important marker for cardiac steatosis, is being related to the development of LV Diastolic Dysfunction though subclinical LV Dysfunction may also be associated with obesity and metabolic syndrome[7]. Increased myocardial fat has also adverse metabolic consequences like impaired lipid oxidation, oxidative stress and mitochondrial defects and this cardiac lipotoxicity is one of the important causes of LV Dysfunction and promotes cardiac fibrosis and apoptosis.

A recent study by Marit Graner, *et al,* has focused on different components of cardiac steatosis and its relationship with intra abdominal ectopic fat deposits and their association with different cardio-metabolic risk factors in non-diabetic individuals with or without metabolic syndrome.

In another large cohort study of 579 men with HIV with 353 men without HIV in the age group of 40 to 70 years, epicardial adipose tissue volume was more with HIV patients which is irrespective of BMI but was associated with increasing duration of combination ART.

### Assessment of Cardiac Fat :

Assessment of cardiac fat can be done by using Cardiac proton Magnetic Resonance Spectroscopy (MRS) which is a reproducible and non-invasive technique for measurement of myocardial triglyceride content by measuring their unique resonance frequency when passed through a magnetic field. Both MRS & CMR techniques, allow determination of cardiac function, its lipid accumulation status and fibrosis.

### Cardiac Steatosis, Non-alcoholic Fatty Liver Disease (NAFLD) & T2DM — Are they Interrelated ?

There is a vicious spiral of worsening disease when NAFLD coexists with T2DM. Current evidence suggests that, with NAFLD, both cardiac steatosis and liver fibrosis are associated with an increased risk of incident Cardiovascular Disease (CVD), although it is unclear whether any specific NAFLD histological type contributes to a differentially greater risk of CVD. Presence of either NAFLD or T2DM increases the risk and development/progression of the other: liver fat raises the risk of incident T2DM; and further progression of liver disease to liver fibrosis further increases risk of T2DM. Coexistent T2DM and NAFLD often makes it difficult to achieve good glycaemic control due to marked hepatic and peripheral insulin resistance. T2DM also increases progression of liver disease with an increased risk of NASH, advanced fibrosis, cirrhosis and/or hepatocellular carcinoma. Both NAFLD and T2DM independently increase risk of Cardiac steatosis and other cardiac diseases. Fig 1 is a schematic illustration of the vicious spiral of worsening disease that manifests when NAFLD is accompanied by T2DM, thereby increasing the risk of Cardiac steatosis and other cardiac diseases (Fig 1A), and a summary of some of the potential CVD and cardiac risk factors in NAFLD (Fig 1B)[7].

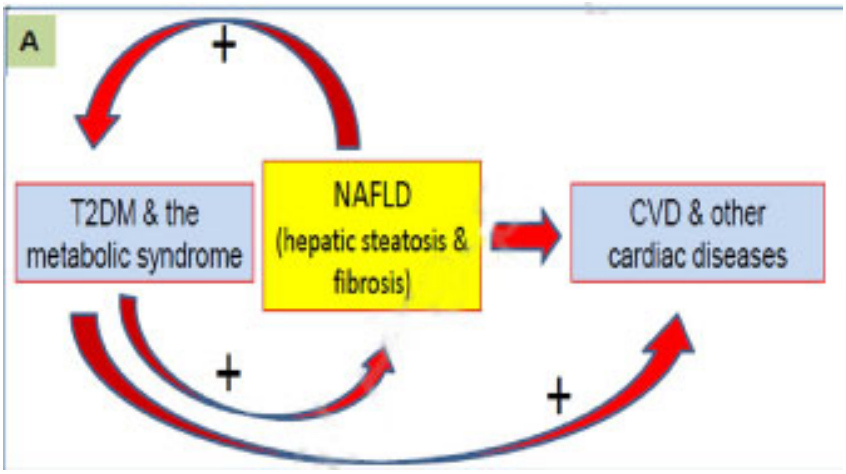


Fig 1(A) — Pathophysiological link between NAFLD, T2DM and Cardiac steatosis

| B | Established and potential risk factors for CVD/cardiac diseases in NAFLD |
|---|---|
| | Atherogenic dyslipidaemia |
| | T2DM |
| | Other metabolic syndrome features such as hypertension, abdominal obesity |
| | Proinflammatory cytokines such as C-reactive protein, interleukin-6, fetuin-A |
| | Reactive oxygen species |
| | Steatotic hepatocyte-derived extracellular vesicles |
| | Plasminogen activator inhibitor-1 |
| | Gut-derived factors (such as modified bile acids, trimethylamine oxide, lipopolysaccharide, aromatic acid metabolites, p-cresyl sulphate, indoxyl sulphate, short-chain fatty acids, incretins) |
| | NAFLD-related genotypes such as *GCKR* variants |

Fig 1(B) — Risk factors for cardiovascular diseases in NAFLD

### Factors that Correlate with an Increased Incidence of Cardiac Steatosis :

It includes Aging, Female Sex, Obesity, Insulin Resistance, Diabetes Mellitus, CAD, Human Immunodeficiency Virus–Related Therapies. In many Endocrine and metabolic derangements Cardiac steatosis can be a part of redistribution of visceral fat. It is possible that the patient's truncal obesity, moon facies and abdominal striae were secondary to an under recognized Cushing syndrome. Cushing syndrome, either iatrogenic due to concomitant use of mirtazapine and budesonide or a cortical adenoma, could have deepened the intra-myocardial accumulation of fat.

**NAFLD & Cardiac steatosis :** Non-alcoholic Fatty Liver Disease (NAFLD) is associated with an increased risk of cardiovascular disease. In NAFLD where hepatic steatosis and fibrosis are cardinal features are also associated with subclinical myocardial dysfunction. This association is linked to altered myocardial glucose uptake and subsequent deposition.

Emerging data on the interplay between NAFLD and Cardiac steatosis show a complex two-way relationship between the two conditions. On one hand, as previously stated, NAFLD was suggested to be a major risk factor for Cardiac steatosis[3]. On the other hand, reverse relationship is also true regarding the effect of cardiac pathology, mainly acute and chronic heart failure, on hepatic disease.

### Prevention Strategies :

Due to the strong association between NAFLD and Cardiac steatosis, and the increased risk of mortality from CV events in patients with NAFLD[6], a number of primary and secondary prevention strategies were recommended by the American College of Cardiology, the American Heart Association, the European Association for the Study of the Liver and the Italian Association for the Study of the Liver. Both NAFLD and CVD share and target the common traditional risk factors like healthy dietary pattern,moderate exercise and optimal body weight management for their Primary prevention strategies[4]. For instance, in one prospective study on 293 patients with NASH, lifestyle modifications that are beneficial for CVD (decrease in calorie intake and increase in exercise) achieved regression of fibrosis and resolution of steatohepatitis in 19% and 25% of patients, respectively reducing the incidence of cardiac steatosis also.

### Modifying NAFLD-related CVD Risk : Pharmacotherapy :

At present, there are no approved pharmacological treatments for NAFLD, and the cornerstone of NAFLD management remains lifestyle modifications which includes dietary restrictions and exercise. No FDA approved treatments are available for NAFLD but guidelines recommend : Vit E (if no Type 2 DM), Pioglitazone (if DM/pre DM), Metformin and Aspirin. For Diabetes, treatment of body weight as a coprimary outcome in obese patients with GLP1RA have emerging evidence of NASH resolution and also CV risk reduction and SGLT2 Inhibitors, which have emerging evidence for reducing liver fat and enzymes as well as CV risk reduction. Therefore, this section specifically focuses on the current pharmacological treatments for modifying NAFLD-related CVD risk[5].

**Dietary Restrictions :** Carbohydrate restriction has rapid benefits in hepatic steatosis. Diet with <30 gm carbohydrates will cause weight loss of 1.8% and mean reduction of liver fat of 43.8% which will return to baseline within 1 to 3 months. So it is advisable to stick to low calorie, low carbohydrate, low fat and low dietary sugar content.

### Metformin Therapy :

In the management of NAFLD drugs including metformin, Thiazolidinediones (TZD) and aspirin have shown promising results.Though metformin has been very useful in improving liver functions, it failed to improve the histological features as shown in one meta-analysis of Randomized Controlled Trials (RCTs) involving a total of 417 participants Moreover, metformin was shown to improve weight loss, improved insulin sensitivity and lipid profiles (decreased LDL and increased HDL levels) in NAFLD patients, which might in turn decrease the CV risk related to NAFLD.

### Thiazolidinediones (TZD) Therapy :

In another meta-analysis including 8 RCTs and a total of 516 patients evaluating TZD effect on histology of biopsy-proven NASH, TZD treatment (5 RCTs evaluating pioglitazone; 3 evaluating rosiglitazone) was associated with improved fibrosis and NASH resolution – a trend seen in patients with or without T2DM. Side effects of TZD therapy was weight gain and limb edema and because of the short duration of the trials with small sample sizes, reports of congestive heart failure or increased CV mortality could not be documented.

### Aspirin Therapy :

In a recent prospective cohort study with 361 adults with biopsy-confirmed NAFLD with nine-year follow-up, daily aspirin use was associated with significantly lower odds for NASH and fibrosis with greatest benefit with at least four years of aspirin use – an association not seen with other non-aspirin NSAIDs. Furthermore, a cross-sectional study including 11,416 patients showed an inverse correlation between regular aspirin use (defined as 15 times in the prior month) and prevalent NAFLD, although this was limited to older men (>60 years). Aspirin, and not ibuprofen use, reduces liver fibrosis in adults with NAFLD.

### GLP-1 Receptor Agonists :

GLP-1 Receptor Agonists (GLP-1R) were investigated as potential agents for the management of NAFLD. Early studies demonstrated decreasing and normalizing AST levels in T2DM patients receiving exenatide with elevated AST levels at baseline, compared to those who did not receive it. Recent meta-analyses showed association of GLP-1Ras, mainly exenatide and liraglutide and also semaglutide, with reduced Body Mass Index (BMI) and Waist Circumference (WC) and liver fat fraction.

In a recent clinical trial, the Liraglutide Efficacy and Action in NASH (LEAN) by Armstrong, *et al*, 52 overweight patients with NASH were randomized to receive liraglutide or placebo (26 in each group)[8]. The results of this small pilot study showed that patients in the experimental treatment arm had 4.3 times higher chance of histologically-proven NASH resolution along with documented CV mortality benefit (Fig 2).

### SGLT2 Inhibitors+ GLP-1 RAs :

SGLT2 inhibitors are another class of anti-diabetic drugs with proven CV mortality benefit even in nondiabetics as well with recent beneficial evidences in NAFLD treatment. Recent phase III randomized controlled trial by Frías, *et al*, 695 patients with T2DM were randomized into 3 groups - First group received exenatide plus placebo, Second group received dapagliflozin plus placebo Third group received a combination of the two drugs and followed up for 28 weeks. The results of this study showed that all groups had a decrease in the traditional CV risk factors, such as Blood Pressure, HbA1c and glucose levels, that were more pronounced and superior in the group receiving both drugs. this was a very useful trial.

The trial showed that combination treatment had stronger effects than each drug alone in ameliorating markers of hepatic and cardiac steatosis and fibrosis in patients with T2DM. Another study showed that NAFLD patients with T2DM who received dapagliflozin alone had a significant decrease in Controlled Attenuation Parameter (CAP), liver stiffness and AST and GGT levels compared with controls[8]. Other

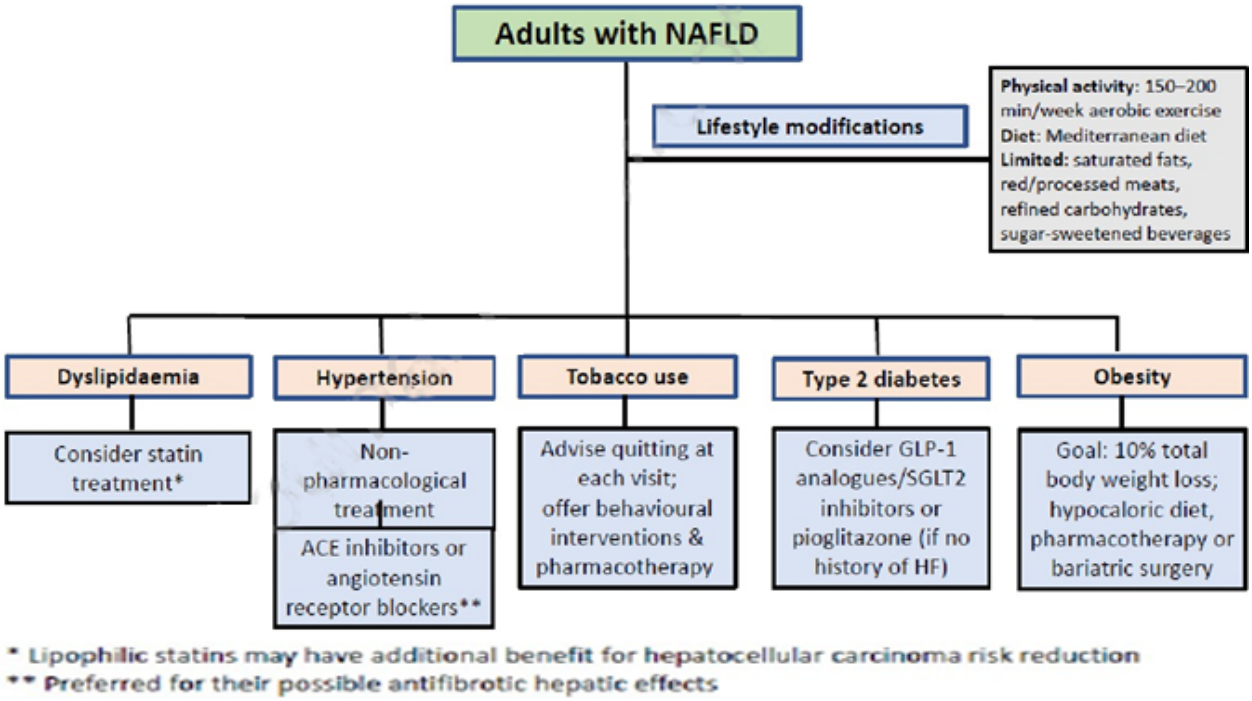


Fig 2 — Suggested treatment options for NAFLD with Cardiac Steatosis

studies also demonstrated the potential of dapagliflozin monotherapy to reduce liver fat assessed by MRI, liver injury biomarkers such as enzyme levels, and achieve histological improvement with fibrosis regression in NAFLD patients with T2DM and improvement in cardiac status.

### RAAS Inhibitors :

RAAS activation was shown to be upregulated in NAFLD and to play a role in development of inflammation and insulin resistance, both of which are possible risk factors for NAFLD and Cardiac Steatosis..In an observational cohort study by Peluci, *et al* which included 118 diabetic pts with a median follow up period of 36 months have shown that ACEI or ARB reduces the histological fibrosis progression in NAFLD patients.There are some other studies with ARB which has also shown reduction of ASTlevels as well histological improvement.

### Bariatric Surgery :

An effective treatment strategy for severe obesity – has been shown to cause a significant decrease in liver transaminases and histology improvement in NAFLD patients. Many studies have shown that morbidly obese pts with NASH improve remarkably when they underwent B ariatric surgery, NASH disappeared in 85% of them and levels of liver transaminases significantly decreased. Moreover, bariatric surgery was shown to improve the traditional CV risk factors reducing cardiac steatosis as well.

### Vitamin E :

Vitamin E was also studied as a potential treatment for NAFLD due to its anti-oxidative properties. In patients with NASH, Vitamin E supplementation in one meta-analysis of three trials analyzing 242 patients with NASH, resulted in improved ALT levels, steatosis, lobular inflammation and ballooning but not fibrosis of the liver. However, Vitamin E supplementation was shown in other studies to have doubtful apparent effects on CV outcomes.

### Obeticholic Acid, Saroglitazar and Elafibranor :

Other drugs, including obeticholic acid, saroglitazar, and elafibranor are currently being investigated for NAFLD in large clinical trials. Obeticholic acid is a bile acid derivative that can bind to and activate farnesoid X receptors, which in turn can increase insulin sensitivity, decrease hepatic gluconeogenesis, and protect against cholestasis liver injury. Elafibranor is a dual PPAR-$\alpha/\delta$ agonist - both receptors being implicated in the activation of inflammatory changes within the liver. Saroglitazar is a dual PPAR$\alpha/\gamma$ agonist indicated mainly for the treatment of Diabetic Dyslipidemia and hypertriglyceridemia not controlled by statins. This drug is currently being investigated as a potential treatment for NAFLD in an ongoing phase 2 trial with a very promising result. Further studies are needed before more stringent recommendations can be done on the use of obeticholic acid, saroglitazar and elafibranor.

## References


1 Bugianesi E, Gastaldelli A — Hepatic and cardiac steatosis: are they coupled? *Heart Fail Clin* 2012; **8(4):** 663-70.
2 Targher G, Corey KE, Byrne CD — NAFLD, and cardiovascular and cardiac diseases: Factors influencing risk, prediction and treatment. *Diabetes Metab* 2021; **47(2):** 101215.
3 Tuzzolo A, Febres-Aldana CA, Poppiti R — Severe Myocardial Steatosis: Incidental Finding or a Significant Anatomic Substrate for Sudden Cardiac Arrest? *Am J Forensic Med Pathol* 2020; **41(1):** 42-47.
4 Nyman K, Granér M, Pentikäinen MO, Lundbom J, Hakkarainen A, Sirén R, *et al* — Cardiac steatosis and left ventricular function in men with metabolic syndrome. *J Cardiovasc Magn Reson* 2013; **15(1):** 103.
5 Lee YH, Kim KJ, Yoo ME, Kim G, Yoon HJ, Jo K, *et al* — Association of non-alcoholic steatohepatitis with subclinical myocardial dysfunction in non-cirrhotic patients. *J Hepatol* 2018; **68(4):** 764-72.
6 Ramadan MS, Russo V, Nigro G, Durante-Mangoni E, Zampino R — Interplay between Heart Disease and Metabolic Steatosis: A Contemporary Perspective. *J Clin Med* 2021; **10(8):** 1569.
7 Rijzewijk LJ, van der Meer RW, Smit JW, Diamant M, Bax JJ, Hammer S, *et al* — Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. *J Am Coll Cardiol* 2008; **52(22):** 1793-9.
8 McGavock JM, Lingvay I, Zib I, Tillery T, Salas N, Unger R, *et al* — Cardiac steatosis in diabetes mellitus: a 1H-magnetic resonance spectroscopy study. *Circulation* 2007; **116(10):** 1170-5.