Inflammation and Lipid Metabolism Relationships on The Example of NAFLD and Atherosclerosis Relationships

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Abstract

The relationships between the occurrence of diseases that share similarities are of particular interest to scientists and clinicians. Such an analysis can help understand underlying mechanisms and improve disease management. This review examines the relationship between Non-Alcoholic Fatty Liver Disease (NAFLD) and atherosclerosis. While lipid metabolism disorders are a key intersection in their pathogenesis, there are other significant connections. We also explore how one disease can act as a risk factor for the development of the other. A dedicated section is included on the treatment methods for these two pathologies.

Significance | This comprehensive review elucidates NAFLD's intricate link to atherosclerosis, highlighting shared pathogenic mechanisms and proposing innovative therapeutic strategies.

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Introduction

This comprehensive review aims to untangle the complex relationship between Non-Alcoholic Fatty Liver Disease (NAFLD) and atherosclerosis. It will delve into the shared pathogenic mechanisms of these conditions, emphasizing the disruptions in lipid metabolism, inflammation, and oxidative stress that drive their development and progression.

Additionally, the review will investigate the bidirectional relationship between NAFLD and atherosclerosis, exploring how they mutually act as risk factors for each other, potentially worsening the disease progression. It will offer insights into how one condition can serve as a predictor or precursor for the other.

The review will also thoroughly examine the implications for disease management, particularly focusing on the impact of NAFLD on cardiovascular risk factors. Proposed strategies for the prevention and management of both NAFLD and atherosclerosis, including lifestyle modifications, pharmacological interventions, and potential future therapeutic avenues, will be based on the latest research findings.

Furthermore, the review will illuminate emerging therapeutic approaches targeting cholesterol metabolism, liver-specific

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regulators, and innovative strategies. By providing insights into potential treatments and preventive measures for NAFLD and atherosclerosis, the review aims to provide a roadmap for the effective management of these interlinked chronic conditions.

Non-alcoholic fatty liver disease (NAFLD) is characterized by excessive fat accumulation in the liver without a clear cause such as alcohol consumption, genetic disorders, or the use of steatogenic drugs (Machado and Cortez-Pinto, 2014). NAFLD often progresses to chronic liver disease (CLD) and is considered a manifestation of hepatic metabolic syndrome (MS). Individuals with insulin resistance (IR), high oxidative stress levels, and risk factors such as metabolic syndrome (MS), diabetes mellitus (DM), adiposity, sedentary lifestyle, high-fat diet (HFD), and tobacco use are more prone to developing NAFLD. Cardiovascular disease (CVD) stands as the primary cause of mortality among individuals with NAFLD (Damba et al., 2020).

Association between CAD and NAFLD: trials

During coronary angiography, non-alcoholic fatty liver disease was identified in 58% of 612 individuals. Among individuals with non-alcoholic fatty liver disease, CAD was present in 84.6%, compared to 64.1% in those without the condition ($p < 0.001$). Regardless of metabolic and demographic factors, coronary artery disease was found to be 2.32 times more prevalent in individuals with non-alcoholic fatty liver disease than in those without the disorder (Langroudi et al., 2018). In a five-year study involving 2103 individuals with type 2 diabetes mellitus (T2DM), individuals with non-alcoholic fatty liver disease experienced an 84% higher frequency of cardiovascular disease events compared to those without the condition ($p < 0.001$), irrespective of cardiovascular risk factors.

In Japan, a prospective study followed 1637 healthy individuals for five years. At the end of the study, out of 1221 people evaluated, those with non-alcoholic fatty liver disease at baseline showed a higher occurrence of atherosclerotic cardiovascular disease (AS CVD), coronary artery disease, stroke, and brain hemorrhage (Hamaguchi et al., 2007). Non-alcoholic fatty liver disease was found to be an independent predictor of cardiovascular disease, with an odds ratio of 4.12 ($p = 0.004$). Metabolic syndrome and non-alcoholic fatty liver disease were identified as predictors of cardiovascular disease, with the former showing significant correlation with the disease.

Pisto and colleagues conducted a study on 988 patients from 1991 to 2009, revealing that cardiovascular (CV) events occurred in 29.2% of individuals with advanced steatosis, 24.2% with mild liver fat, and 13.5% with normal liver fat ($p < 0.001$). Severe steatosis was a predictor of cardiovascular disease, even after adjusting for gender, age, and group (HR: 1.92, $p < 0.01$). After accounting for factors such as tobacco use, alcohol intake, serum LDL-C levels, systolic blood pressure, and body mass index, the cardiovascular risk remained significant (HR: 1.74; $p < 0.01$) (Pisto et al., 2014).

The relationship between non-alcoholic fatty liver disease and coronary artery disease was studied in 273 individuals with type 2 diabetes mellitus (T2DM) experiencing chest pains and undergoing CCTA. After adjusting for gender, age, adiposity, high blood pressure, tobacco use, and LDL-C levels, non-alcoholic fatty liver disease was notably associated with coronary artery disease (OR: 2.128; $p = 0.04$) (Arslan and Yenerçağ, 2020).

In a prospective study, 80 individuals with metabolic syndrome (MS) were examined to investigate the relationship between non-alcoholic fatty liver disease detected by ultrasound imaging and the severity of coronary artery disease. The results indicated that patients with non-alcoholic fatty liver disease had a higher number of affected vessels (2.5 ± 0.9 versus 1.0 ± 1.0; $p < 0.001$), and the coronary artery disease was more advanced, as measured by the severity score ($p < 0.001$). Non-alcoholic fatty liver disease emerged as the sole independent predictor for coronary artery disease (Sepehrimanesh et al., 2020).

Another study involving 355 individuals undergoing coronary angiogram and abdominal ultrasound for non-alcoholic fatty liver disease found that non-alcoholic fatty liver disease was an independent factor associated with prevalent coronary artery disease (OR: 2.58; $p < 0.01$) and the severity of the disease determined by the severity score (OR: 2.02; $p < 0.05$) (Açikel et al., 2009).

Sun and colleagues conducted abdominal CT scans for non-alcoholic fatty liver disease in 542 individuals before performing coronary angiography for coronary artery disease. Logit regression analysis revealed that non-alcoholic fatty liver disease independently increased the risk of coronary artery disease detected on coronary angiography (OR: 7.585; $p < 0.001$). As the severity of coronary artery disease increased, the prevalence of non-alcoholic fatty liver disease also notably rose. The researchers concluded that patients with non-alcoholic fatty liver disease should be carefully monitored for both the presence of coronary artery disease and its severity (Sun and Lü, 2011).

Studies have shown that the development of coronary collaterals can improve the survival rate of individuals with diagnosed coronary artery disease. Attenuated collateral development has been linked to metabolic syndrome (MS) and insulin resistance (IR). In another study involving 151 individuals without diabetes mellitus (DM) who experienced persistent angina with significant stenosis in one or more primary coronary arteries (>95%), those with attenuated collateral development showed a higher prevalence of non-alcoholic fatty liver disease (82.9% in NAFLD individuals versus 49.4% in non-NAFLD individuals, $p < 0.001$), which was detected in 65% of the study participants (Bigler and Seiler, 2019).

Among those with non-alcoholic fatty liver disease, the average Rentrop collateral score was significantly lower compared to patients without the disorder ($p < 0.001$) (Arslan et al., 2012). Logit regression analysis indicated that non-alcoholic fatty liver disease was strongly correlated with impaired blood circulation in relation to factors associated with attenuated collateral development (OR: 6.2; 95% CI: 2.61–14.75).

Several trials have highlighted the association between non-alcoholic fatty liver disease and subclinical atherosclerosis (AS), with many confirming its independence from metabolic syndrome (MS) and cardiovascular risk factors. Coronary artery calcification (CAC) has been identified as an independent marker for the risk of coronary artery disease and serves as a surrogate endpoint for atherosclerosis (Koulaouzidis et al., 2021). Findings from a study involving 10,153 patients who underwent coronary calcium scanning and ultrasonography for fatty liver (FL) evaluation showed that FL was linked to a coronary artery calcification score above zero, independent of MS, coronary artery disease (CAD) risk factors, and pre-existing cardiovascular disease (OR: 1.21; $p = 0.04$) (Sung et al., 2012). The CARDIA trial, which included 2,424 individuals with an average age of 50 years, who underwent CT scans to assess liver fat, coronary artery calcification, and abdominal aortic calcification. Individuals with non-alcoholic fatty liver disease exhibited a higher occurrence of abdominal aortic calcification (65.1% versus 49.9%; $p < 0.001$) and coronary artery calcification (37.9% versus 26.0%; $p < 0.001$). This association remained significant even after adjusting for health and demographic factors (Leers et al., 2020).

Another study conducted a cross-sectional analysis of 3,796 participants in the MESA trial who underwent CT scans. The results indicated that non-alcoholic fatty liver disease was linked to elevated levels of inflammation, as indicated by high-sensitivity C-reactive protein (hs-CRP) ≥ 2 mg/L (OR: 1.47; 95% CI: 1.20–1.79), and coronary artery calcification > 0 (OR: 1.37; 95% CI: 1.11–1.68), independent of obesity, MS, and CAD risk factors (Al Rifai et al., 2015). An association was found between non-alcoholic fatty liver disease, obesity, metabolic syndrome, inflammation, and coronary artery calcification. Carotid intima-media thickness (CIMT) assessed by ultrasonography serves as a marker for subclinical AS. While CIMT can predict vascular events like stroke and myocardial infarction, it is more effective in predicting stroke risk than myocardial infarction risk. Studies have shown increased mean and maximal CIMT in individuals with non-alcoholic fatty liver disease compared to the control group. Non-alcoholic fatty liver disease independently predicted elevated mean CIMT (OR: 4.8; 95% CI: 1.8–12.8) and maximal CIMT (OR: 5.4; 95% CI: 2.0–14.4) after adjusting for obesity, lipid levels, metabolic syndrome, and insulin resistance (Bc et al., 2021). Another cross-sectional trial involving 8,632 patients demonstrated significantly elevated ba PWV and CIMT in individuals with non-alcoholic fatty liver disease compared to the control group ($p < 0.0001$ and $p < 0.0001$). Logit regression analysis indicated a 35% higher odds ratio (OR) for increased CIMT and a 30% higher OR for ba PWV in individuals with non-alcoholic fatty liver disease, independent of metabolic syndrome and CAD risk factors (Huang et al., 2012). Analyzing data from 10 studies involving 1,947 subjects revealed abnormal CIMT in 35.1% of individuals with non-alcoholic fatty liver disease compared to 21.8% of those without the condition ($p < 0.0001$) (Rampally et al., 2020). Additionally, analysis of four studies including 1,198 subjects showed that individuals with non-alcoholic fatty liver disease had a higher prevalence of coronary artery disease detected by coronary angiography, with 80.4% in the non-alcoholic fatty liver disease group and 60.7% in the non-non-alcoholic fatty liver disease group ($p < 0.001$) (Ampuero et al., 2015).

Brachial-ankle pulse wave velocity serves as an indicator of arterial stiffness. In a prospective trial involving 728 male and 497 female patients without diabetes mellitus (DM) and hypertension, brachial-ankle pulse wave velocity (ba PWV) was utilized to track the progression of arterial stiffness. Over a five-year period, multiple regression analysis revealed that non-alcoholic fatty liver disease emerged as a significant independent predictor for the development of brachial-ankle pulse wave velocity ($p < 0.001$) in both male and female subjects after adjusting for cardiovascular risk factors (Li et al., 2015).

The Cardio Ankle Vascular Index (CAVI) is an assessment of arterial wall stiffness extending from the aorta to the ankle, which also has predictive value for ischemic stroke. A study involving 443 participants who underwent carotid ultrasound tests, coronary angiograms, and CAVI assessments indicated that an elevated cardio ankle vascular index serves as an indicator for the development of coronary artery disease and atherosclerosis (AS) in the carotid artery (Izuhara et al., 2008, Anastasia et al. 2024a, Anastasia et al. 2024b, Zainab et al. 2024, Anastasia et al. 2024c, Anastasia et al. 2024d, Anastasia et al. 2024e, Anastasia et al. 2024f, Anastasia et al. 2024g, Anastasia et al. 2024h, Anastasia et al. 2023, Mathangi et al. 2021).

In a cross-sectional study of 2,954 patients, non-alcoholic fatty liver disease was associated with a 42% increased risk of arterial stiffening, with the risk escalating along with the severity of non-alcoholic fatty liver disease (Chung et al., 2015). The statistical significance of this association persisted even after adjustments for body mass index, waist circumference, tobacco use, diabetes mellitus, and hypertension. While the evidence linking non-alcoholic fatty liver disease to vascular disease and subclinical atherosclerosis (AS) is compelling, the underlying biochemical mechanisms driving this relationship remain incompletely understood. Further research is necessary to elucidate these

mechanisms and identify the markers responsible for the clinical observations mentioned, potentially leading to the development of essential therapeutic interventions.

Pathogenesis of NAFLD

In Figure 1, we present a schematic outline of the mechanisms involved in the development of Non-Alcoholic Fatty Liver Disease (NAFLD). The initial phases of fatty liver disease entail the accumulation of triglycerides (TG) in the liver from various sources of fatty acids (FAs). Primarily, elevated levels of free FAs are derived from increased fat tissue triglyceride hydrolysis, often due to unchecked hormone-sensitive lipase (HSL) activity in the context of insulin resistance. Additionally, excess synthesis of FAs from carbohydrates and uptake of FAs from dietary chylomicrons and very-low-density lipoproteins (VLDL) contribute to the process (Santos-Baez and Ginsberg, 2021).

The synthesis of TGs in the liver coincides with the production and release of VLDL, while the TGs accumulate in lipid droplets (LDs) within hepatocytes. The development of fatty liver disease occurs when there is an imbalance between liver fat accumulation and lipid clearance, resulting in excessive TG deposition in LDs. This imbalance can be induced by alterations in the proportions of FAs in the liver, rates of TG and apo-B synthesis, LD TG lipolysis, and FA beta-oxidation rates (Mulkern et al., 2008). The formation of small and large LDs (microvesicular and macrovesicular, respectively) is a bidirectional process that can be attenuated by interventions that reduce the absorption and synthesis of FAs, inhibit TG synthesis, enhance lipolysis and FA oxidation, or augment the synthesis and secretion of VLDL (Paar et al., 2012).

Predicting whether non-alcoholic fatty liver will progress to non-alcoholic steatohepatitis (NASH) and cirrhosis poses a significant challenge. Individuals with advancing disease display varying rates of progression, with some transitioning rapidly from NASH to fibrosis and cirrhosis, and occasionally, hepatocellular carcinoma (HCC). The degree of fibrosis observed in the initial liver biopsy serves as a robust indicator of the pace of progression. Some individuals with NAFLD exhibit a more gradual progression of the disease. While non-progression from non-alcoholic fatty liver to NASH is associated with better liver outcomes, it's important to recognize that having uncomplicated NAFLD still elevates the risk of cardiovascular disease development (Zeng et al., 2021; Kechagias et al., 2022).

NAFLD and Atherosclerotic CVD Risk

Non-alcoholic fatty liver disease is an important independent predictor of atherosclerotic cardiovascular disease even when corrected for other risk factors. In individuals with non-alcoholic fatty liver or to non-alcoholic steatohepatitis various CV risk factors are elevated. Non-alcoholic fatty liver disease is able to elevate risk factors for AS cardiovascular disease. We have graphically summarized the interplay between atherosclerosis and NAFLD in Figure 2. The gravity of this disorder is linked to increased frequency of occurrence of DM, hypertension and other atherosclerotic CVD risk factors (Motamed et al., 2020). Dyslipidaemia and glucose homeostasis dysregulation, which are primary risk factors for non-alcoholic fatty liver disease, also facilitate the elevation of atherosclerotic cardiovascular risk in non-alcoholic fatty liver disease. Although, the predisposition for ectopic lipid accumulation is believed to be linked to increased risk of atherosclerotic cardiovascular disease in addition to the risk related to traditional risk factors (Chew et al., 2022). Apart from the factors already mentioned, non-alcoholic fatty liver disease is linked to endothelial dysfunction, increased systemic inflammation, and the ectopic lipid accumulation in various organs such as epicardium, voluntary muscle, and pancreas. An elevation of the volume of epicardial adipose tissue is closely associated with increased endothelial dysfunction, intramyocardial inflammation, and rapid atherogenesis. Despite the previous meta-analysis indicating that non-alcoholic fatty liver disease was linked with all-cause mortality rather than cardiovascular disease mortality, and the recent studies revealing that fibrosis stages F3 and F4 were linked with elevated liver complications and overall mortality, cardiovascular disease remains the primary cause of death in individuals with non-alcoholic fatty liver disease (Lai et al., 2022).

The development of non-alcoholic fatty liver disease is a result of significant disruptions in lipid metabolism throughout the body. In the presence of IR, the metabolism of visceral fat is dysregulated. The HSL is not properly suppressed by insulin inside adipocytes, which enhances lipolysis of adipocyte TGs and free FA levels in the blood (Grefhorst et al., 2021). When the influx of FAs to the liver elevates, FAs may be utilized in different ways. First – they can be transferred to mitochondria and absorbed through beta-oxidation. Second – FAs can be re-assimilated into TGs, packaged into very-low-density-Lp and released into the bloodstream. Third – glycerol and odd-chain FAs derived from TGs may be directed to gluconeogenesis. Fourth – if these pathways are overloaded, excessive TGs may transform to cytosolic LDs, which can trigger progression of non-alcoholic fatty liver disease. The proneness for elevated lipid accumulation in the liver is aggravated by enhanced production of fats in the liver caused by IR (Ruiz-Sala and Peña-Quintana, 2021).

Management Considerations

Most guidelines recommend managing cardiovascular risk factors in individuals with non-alcoholic fatty liver disease to reduce the risk of cardiovascular morbidity and mortality (Tana et al., 2019), as shown in Figure 3.

Diet and physical activity

It is recommended to implement lifestyle changes, dietary modifications, and exercise to achieve weight loss, which is an

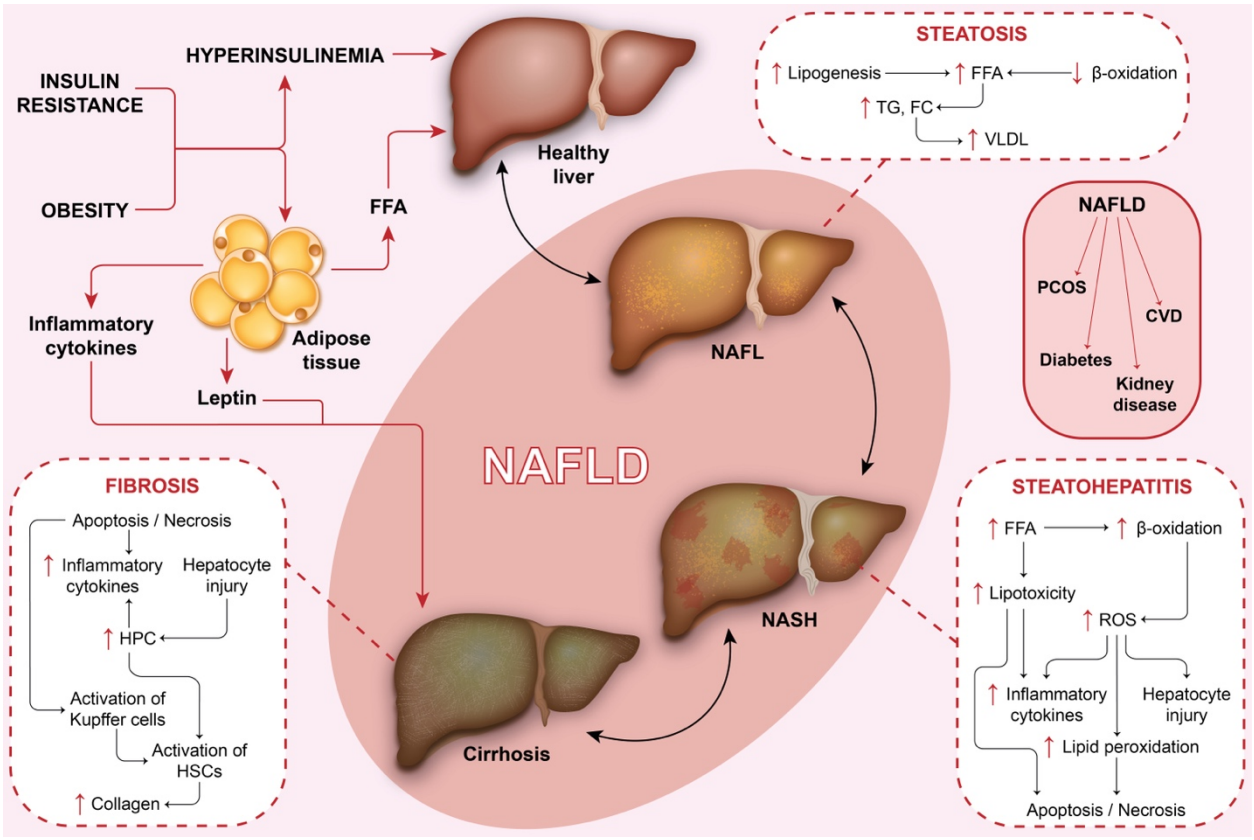

Figure 1. Mechanisms of NAFLD development.

Abbreviations: CRP - C-reactive protein; CVD - cardiovascular disease; FC - free cholesterol; FFA - free fatty acid; LDL - low-density lipoprotein; NAFL - nonalcoholic fatty liver; NASH - nonalcoholic steatohepatitis; PAI-1 - plasminogen activator inhibitor-1; TG - triglycerides; VLDL - very low-density lipoprotein.

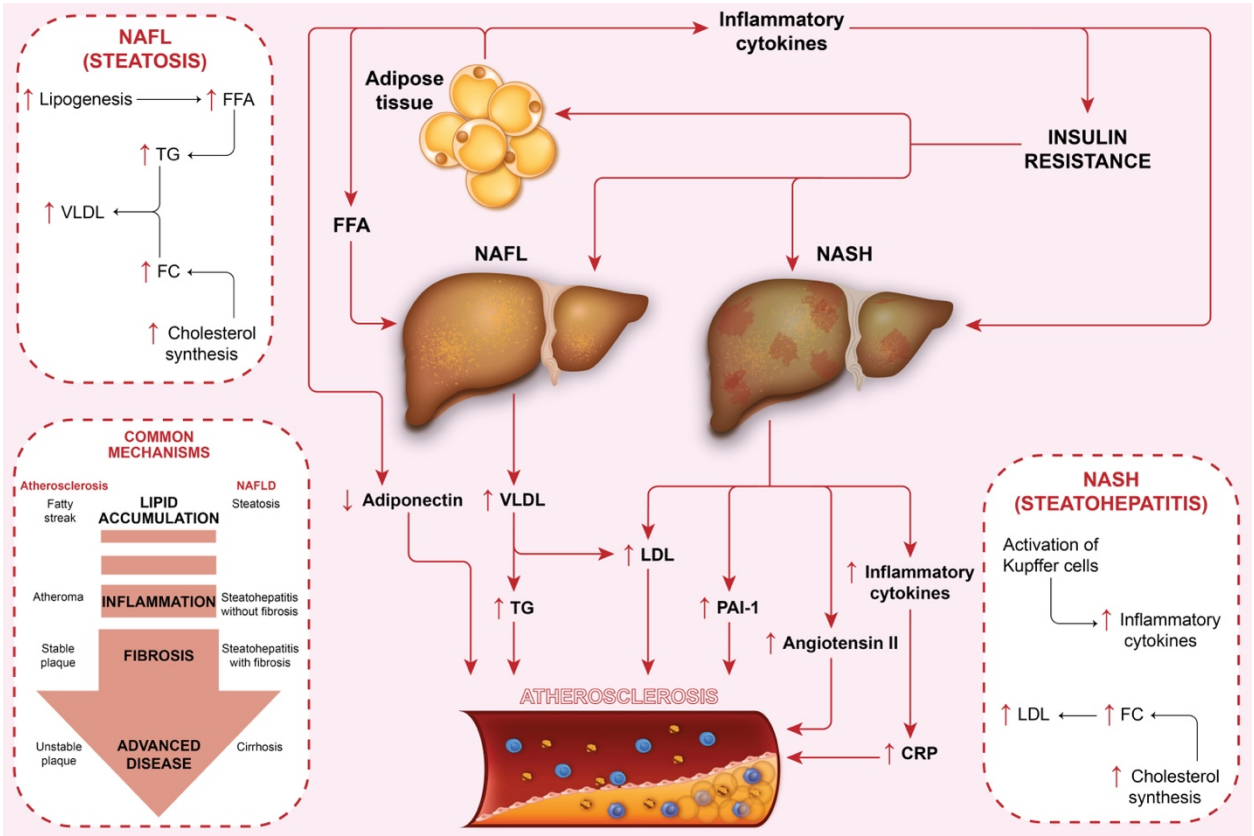

Figure 2. The interplay between NAFLD and atherosclerosis.

Abbreviations: CVD - cardiovascular disease; FC - free cholesterol; FFA - free fatty acid; HPC - hepatic progenitor cell ; HSCs - hepatic stellate cells; NAFL - nonalcoholic fatty liver; NAFLD - nonalcoholic fatty liver disease; NASH - nonalcoholic steatohepatitis; PCOS - polycystic ovary syndrome; ROS - reactive oxygen species; TG - triglycerides; VLDL - very low-density lipoprotein.

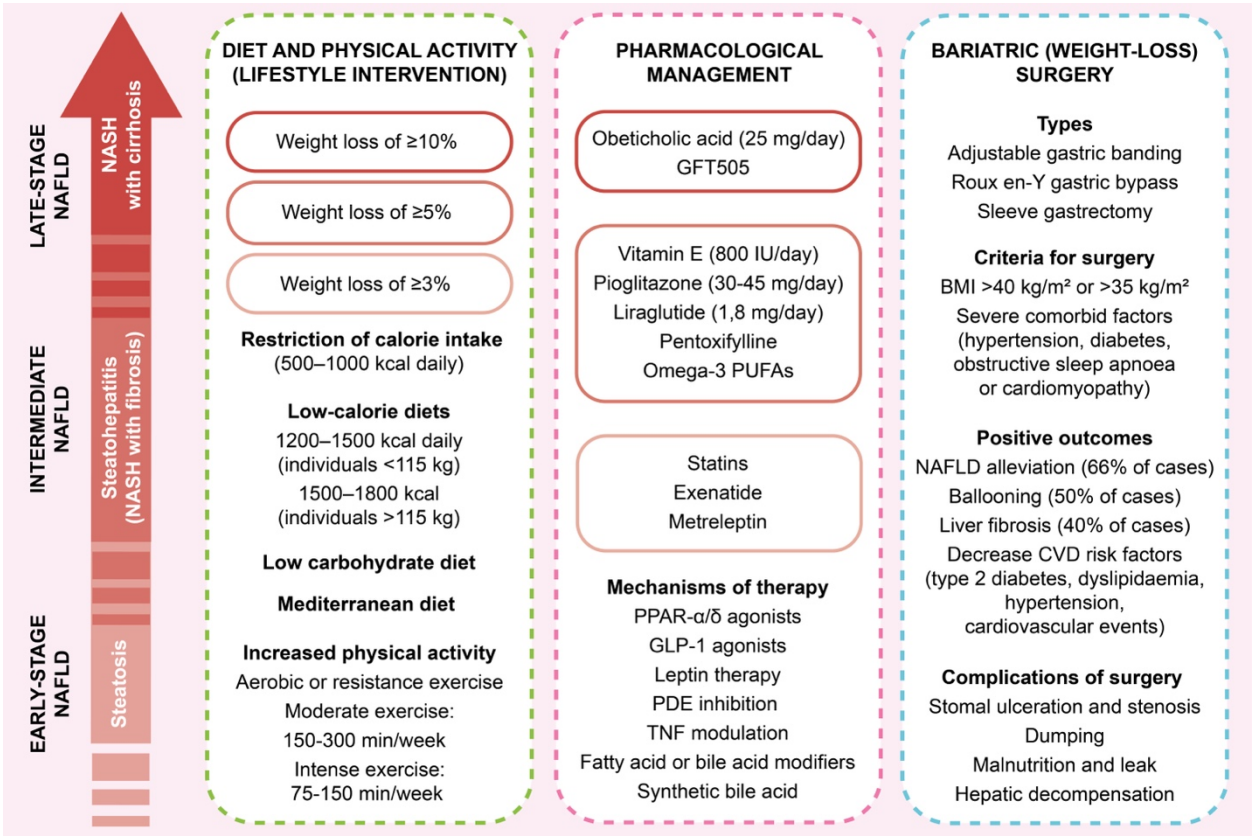

Figure 3. Recommendations for the management of NAFLD.

Abbreviations: BMI - body mass index; CVD - cardiovascular disease; GLP-1 - glucagon-like peptide-1; PDE - phosphodiesterase; PUFAs - polyunsaturated fatty acids; TNF - tumor necrosis factor.

effective strategy for preventing non-alcoholic fatty liver disease and cardiovascular disease. Weight loss of ≥3% is suggested to alleviate fatty liver disease, ≥5% can reduce liver inflammation, and ≥10% can address liver fibrosis. Organized programs that emphasize balanced nutrition and regular exercise for gradual and consistent weight loss are advised (Fernández et al., 2022).

The dietary recommendations include low-calorie diets with a deficit of 500-1000 kcal from the individual's original intake, or a daily intake of 1200-1800 kcal. Although APWP guidelines do not specify a particular diet for patients with non-alcoholic fatty liver disease, two analyses found no benefits of low-fat or low-carbohydrate diets on liver lipid content and function (Hydes et al., 2020). While calorie reduction appears to be the main driver of the diet's positive effects on non-alcoholic fatty liver disease, a separate meta-analysis indicated that the Mediterranean diet may also improve cardiovascular risk factors associated with the condition, suggesting potential advantages for individuals with NAFLD in terms of cardiovascular health (Asbaghi et al., 2020).

Exercise is strongly recommended for individuals with non-alcoholic fatty liver disease, as it plays a proven role in cardiovascular health. Research shows that aerobic exercise does not necessarily offer more benefits than resistance exercise in reducing fatty liver disease. However, aerobic exercise has been shown to improve more cardiovascular risk factors (such as triglycerides, low-density lipoprotein cholesterol, total cholesterol, high-density lipoprotein cholesterol, and body mass index) compared to resistance exercise in individuals with NAFLD (van der Windt et al., 2018). Resistance exercise, on the other hand, is less taxing on energy while delivering similar results as aerobic exercise, making it a suitable option for individuals with NAFLD who struggle with aerobic exercise or have lower cardiorespiratory fitness. Therefore, many guidelines recommend incorporating both resistance and aerobic training in various combinations.

Guidelines from organizations such as EASL-EASD-EASO, ALEH, APWP, AGA, and ACC/AHA recommend different durations and intensities of exercise for individuals with non-alcoholic fatty liver disease, ranging from 150-200 minutes of moderate exercise per week to 75-150 minutes of intense aerobic workouts. ACC/AHA also advises healthcare providers to prescribe personalized exercise programs to improve patient adherence to the training regimen (Bae, 2020; Arnett et al., 2019).

Pharmacological management

Although lifestyle changes targeting weight loss are effective in preventing and managing non-alcoholic fatty liver disease, they can be difficult to achieve and sustain in the long term. Therefore, the demand for pharmacological interventions for non-alcoholic fatty liver disease is significant; however, there are currently no approved medications for this condition (Kwak and Kim; 2018).

Pioglitazone and vitamin E

Guidelines recommend the off-label use of vitamin E (800 IU per day) and pioglitazone (30-45 mg per day) in selected individuals with non-alcoholic steatohepatitis without cirrhosis. It is advisable to consider pioglitazone for individuals with steatohepatitis and type 2 diabetes, and vitamin E for those without diabetes. Pioglitazone has also shown beneficial effects in non-alcoholic steatohepatitis patients without type 2 diabetes. It is believed to increase adiponectin levels, which are directly associated with non-alcoholic fatty liver disease severity (Bril et al., 2019).

Unlike rosiglitazone, pioglitazone has not been linked to adverse effects on serum lipid concentrations and is not associated with a higher risk of myocardial infarction. However, pioglitazone should be avoided in individuals with heart failure (HF) due to potential weight gain (2-3.5 kg) and edema. Prescribing medications that promote weight gain to individuals advised to lose weight may seem contradictory. Prolonged pioglitazone therapy may elevate the risk of bladder cancer, although the significant positive impact on non-alcoholic steatohepatitis is believed to outweigh this risk (Biswas et al., 2012). Pioglitazone therapy should not be administered to individuals with existing bladder cancer.

The precise mechanism by which vitamin E treats non-alcoholic steatohepatitis is not fully understood, but its antioxidant properties likely play a role. However, long-term use of high doses of vitamin E (≥400 IU per day) needed for non-alcoholic steatohepatitis treatment is associated with an increased risk of overall mortality that escalates with dosage. Additionally, vitamin E should not be used in men with a history of prostate cancer, as it may raise the risk of this condition (Sanyal et al., 2010).

The PIVENS study, a major research effort in non-alcoholic steatohepatitis therapy using pioglitazone and vitamin E lasting two years, supports the use of vitamin E treatment for a maximum duration of two years (Chalasani et al., 2009).

Statins

Another important aspect to consider is the use of statins in individuals with non-alcoholic fatty liver disease. Dyslipidemia is a common issue among patients with non-alcoholic fatty liver disease, affecting approximately 69% of cases. Statin therapy is recommended to address dyslipidemia in non-alcoholic fatty liver disease, which can help reduce the cardiovascular risk associated with this condition (Tzanaki et al., 2022). Despite previous concerns regarding their potential negative effects on individuals with elevated liver function tests (a common occurrence in non-alcoholic fatty liver disease), studies have shown that statins can actually improve liver function tests and reduce cardiovascular mortality more effectively in individuals with mildly abnormal liver

function. Additionally, a meta-analysis of studies with histological endpoints indicated a reduction in fatty liver disease, although no significant impact on liver fibrosis was observed. Therefore, statins should be considered for use in individuals with non-alcoholic fatty liver disease. Nevertheless, their effects on liver histology are not fully elucidated and warrant further meticulous long-term investigation (Blais et al., 2016).

GLP-1 RA and SGLT-2i

Non-alcoholic fatty liver disease and cardiovascular disease are commonly found in patients with type 2 diabetes. GLP-1 RA and SGLT-2i are two classes of antidiabetic medications that have shown effectiveness against these conditions. Their positive impact is partly attributed to their ability to reduce body weight, although their mechanisms of action differ (Makri et al., 2022). Currently, there is more evidence from randomized controlled trials with liver biopsies supporting the use of GLP-1RAs over SGLT-2i. A meta-analysis revealed that GLP-1RAs can reduce fatty liver disease and hepatocyte ballooning, a key marker of liver cell damage. However, these drugs did not show a significant impact on liver fibrosis (Lv et al., 2020).

In a 4-year study, liraglutide (1.8 mg per day) was used in non-alcoholic steatohepatitis patients, leading to better alleviation of fatty liver disease compared to placebo (83% versus 45%) and resulting in the resolution of non-alcoholic steatohepatitis (39% versus 9%). While there was a lower incidence of liver fibrosis worsening in individuals receiving liraglutide compared to placebo (9% versus 36%), liraglutide did not show superior efficacy in alleviating liver fibrosis (Armstrong et al., 2016). Recent research showed that the application of semaglutide in individuals with non-alcoholic steatohepatitis for 72 weeks in a phase IIb study led to the resolution of the condition without additional adverse effects on fibrosis compared to placebo (0% - 0.1 mg, 36% - 0.2 mg, 59% - 0.4 mg, 17% - placebo). However, semaglutide did not show better efficacy in alleviating liver fibrosis compared to placebo (Liava and Sinakos, 2021).

Two studies on SGLT-2i use in non-alcoholic fatty liver disease indicated improvements in liver function tests and lipid profiles. However, data on SGLT-2i and histological endpoints remain limited. A comprehensive analysis of randomized controlled trials in diabetic patients demonstrated that GLP-1 RA and SGLT-2i can reduce total mortality, cardiovascular mortality, nonfatal myocardial infarction, and end-stage kidney disease (Mirarchi et al., 2022). It is essential to note that non-alcoholic fatty liver disease is associated with chronic kidney disease, with the risk increasing with the development of liver fibrosis and non-alcoholic steatohepatitis. SGLT-2i was more effective in reducing mortality and heart failure compared to GLP-1 RA, while the latter showed greater efficacy in reducing nonfatal ischemic stroke compared to SGLT-2i, which had no such effect (Zhou et al., 2022; Patorno et al., 2021).

OCA

Obeticholic acid (OCA), a FXR agonist, has been licensed for primary biliary cirrhosis (cholangitis). A number of researches have demonstrated promising results of obeticholic acid treatment of non-alcoholic steatohepatitis and liver fibrosis. Obeticholic acid administered at a dose of 25 mg during 72 weeks alleviated inflammation, fatty liver disease, and liver fibrosis significantly better that placebo (phase IIb randomized controlled trial) (Obeticholic Acid, 2019). An eighteen-month analysis of phase III, ongoing randomized controlled trial in individuals with non-alcoholic steatohepatitis without cirrhosis, showed that obeticholic acid at a dose of 25 or 10 mg reduced liver fibrosis better than placebo (23% versus 18%) while not exacerbating steatohepatitis. Obeticholic acid was the only compound that proved to ameliorate liver histology (Younossi et al., 2019). Although, it elevated low-density-Lp cholesterol and reduced high-density-Lp cholesterol, which is why the therapy had to be terminated in some individuals. The negative impact of obeticholic acid on low-density-Lp cholesterol, but not in high-density-Lp cholesterol, was mitigated by atorvastatin administered at a dose of 10 mg followed by titration as needed. The positive impact of obeticholic acid on non-alcoholic steatohepatitis and fibrosis may be limited by its negative impact on lipid profile, particularly with regards to cardiovascular disease. It is anticipated that future research will determine if obeticholic acid can be combined with statins or substituted with another FXR agonist, without any negative impact on lipid profile (Handhle et al., 2021). In addition to cardiovascular concerns, the drug is associated with a high incidence of pruritus (ranging from 23% to 50%), which may result in termination of the treatment in some cases. The guidelines mentioned above acknowledge the significance of managing arterial hypertension in individuals with non-alcoholic fatty liver disease as a crucial risk factor, but do not recommend any drug categories. Although there is a lack of head-to-head trials for the arterial hypertension treatment in non-alcoholic fatty liver disease, ARBs can be selected as first-line options due to their positive histological results and the fact that they are the first-line option in type 2 diabetes. Although, more information is required to establish effective ways of treatment of arterial hypertension in individuals with non-alcoholic fatty liver disease (Francque et al., 2021).

Bariatric surgery

Bariatric surgery may be considered for individuals with non-alcoholic fatty liver disease and severe obesity if lifestyle changes and pharmaceutical treatments are ineffective. A network meta-analysis has shown that bariatric procedures are more successful in

promoting weight loss compared to other treatments. Currently, two of the most common bariatric procedures are Adjustable

Gastric Banding (AGB) and Roux-en-Y Gastric Bypass (RYGB) (Sarno et al., 2022). RYGB is more effective in achieving weight loss but is associated with more adverse effects, including a higher risk of complications. Cohort trials meta-analysis in individuals with non-alcoholic fatty liver disease and severe obesity have demonstrated that bariatric interventions resulted in improvement in fatty liver disease, liver ballooning, and fibrosis in 66%, 50%, and 40% of cases, respectively. While bariatric procedures are considered highly effective, they also carry certain risks (Schwenger et al., 2018).

Multiple meta-analyses have indicated that bariatric interventions can lower cardiovascular risk factors such as type 2 diabetes, dyslipidemia, hypertension, and cardiovascular events. Based on these findings, bariatric interventions could be a viable option for managing non-alcoholic fatty liver disease and cardiovascular issues in selected patients with severe obesity. However, there is a lack of research on the impact of weight loss specifically on non-alcoholic fatty liver disease and cardiovascular health. A study utilizing the US NIS database with a sample size of over 45,000 patients with both non-alcoholic fatty liver disease and severe obesity found that prior bariatric surgery was independently associated with a reduced risk of myocardial infarction and ischemic stroke. Nonetheless, further prospective studies are required to evaluate the long-term effects of various bariatric procedures (Srinivasan et al., 2022).

Conclusion and Future directions

In recent decades, research has highlighted that disruptions in liver cholesterol and lipoprotein (Lp) metabolism play a central role in linking non-alcoholic fatty liver disease to atherosclerotic cardiovascular disease (AS CVD). The homeostasis of liver cholesterol can be disturbed through various mechanisms, including increased cholesterol biosynthesis, elevated cholesterol esterification, and imbalanced cholesterol outflow/inflow. These disturbances lead to elevated concentrations of free cholesterol within hepatocytes, fostering the development of non-alcoholic fatty liver disease and AS.

Lipoprotein metabolism is a complex process involving the transport of cholesterol and triglyceride molecules from the liver to peripheral muscle and fat tissues, as well as the elimination of excess cholesterol from hepatocytes. Non-alcoholic fatty liver disease disrupts this process, resulting in AS-associated dyslipidemia characterized by higher levels of cholesterol in the bloodstream, particularly in small low-density lipoprotein (LDL) particles, and reduced concentrations of high-density lipoprotein (HDL).

While the traditional concept of reverse cholesterol transport regulates cholesterol and lipoprotein metabolism between the liver and peripheral tissues to prevent hyperlipidemia and AS, the intricate regulatory network within the liver extends beyond this pathway. For example, the deletion of hepatocyte ABCA1, a crucial transporter involved in high-density lipoprotein synthesis, does not influence the traditional reverse cholesterol transport mechanism. Incorporating the traditional reverse cholesterol transport mechanism, liver cholesterol transport involves multiple crucial stages, forming a liver-focused operational model that offers a more comprehensive representation of liver Lp and cholesterol metabolism. This model enhances our understanding of liver Lp and cholesterol metabolism and introduces innovative possibilities for developing effective therapeutic strategies to manage non-alcoholic fatty liver disease with AS complications.

While cholesterol-targeted medications are commonly used in cases of atherosclerotic cardiovascular disease (AS CVD), there is currently no approved medication specifically for non-alcoholic fatty liver disease. Elevated free cholesterol in hepatocytes' mitochondria and endoplasmic reticulum can lead to mitochondrial dysfunction and endoplasmic reticulum stress, triggering apoptotic and necrotic processes in cells. Cholesterol crystals can activate hepatic stellate cells (HSCs) and macrophages, initiating inflammation and liver fibrosis. Notably, studies have shown that these crystals can activate the NLRP3 inflammasome in macrophages within early AS plaques, causing chronic inflammation characteristic of AS. Research indicates that NLRP3 activation in stellate macrophages and hepatocytes may promote inflammation in non-alcoholic fatty liver disease, although the exact triggers for this activation remain unclear. The crystallization of cholesterol in stellate macrophages and hepatocytes, similar to macrophages in the subintimal space in AS, may induce this process. Therefore, hepatic cholesterol deposition, rather than triglycerides, is associated with hepatocyte death, leading to liver damage and contributing to the progression from fatty liver to non-alcoholic steatohepatitis (NASH).

Pharmacological management of cholesterol metabolism could offer new therapeutic possibilities for treating non-alcoholic fatty liver disease, not only to alleviate liver conditions but also to reduce the risk of AS. Current cholesterol-targeted therapies involve inhibiting HMG-CoA reductase with statins and Niemann-Pick C1-Like 1 with ezetimibe. Evidence suggests that statin therapy is safe for individuals with non-alcoholic fatty liver disease and may help lower serum aminotransferase levels. A cohort study of 1201 individuals with non-alcoholic fatty liver disease revealed that statin therapy can protect against NASH, fatty liver, and liver fibrosis in a dose-dependent manner. Statins not only inhibit cholesterol synthesis but also demonstrate protective effects against inflammation and fibrosis. Statins can improve liver histology and

reduce AS cardiovascular morbidity and mortality in individuals with non-alcoholic fatty liver disease. However, statins are currently underutilized due to concerns about elevated liver enzymes.

Ezetimibe is a common lipid-lowering medication that inhibits the NPC1L1 protein and has been successfully used to manage and prevent non-alcoholic fatty liver disease. Its positive effects may be attributed to its reduction in cholesterol influx, leading to decreased apoptosis, liver inflammation, and insulin resistance. Research on the use of ezetimibe in non-alcoholic fatty liver disease is still limited. New strategies targeting key membrane transporters/receptors (SR-BI, LDLR, ABCA1, ABCG5, ABCG8), enzymes (ACAT2, HMGCR, CYP7A1), nuclear regulators (FXR, SREBP-2, HNF4α, PPAR), or aspects of cholesterol metabolism aim to reduce hepatic free cholesterol deposition, thereby preventing the development of AS and non-alcoholic fatty liver disease.

Many questions remain unanswered regarding cholesterol transport and metabolism within the liver. The liver's ABCA1 protein plays a critical role in producing new high-density lipoprotein (HDL) particles, while macrophage ABCA1 has a less significant role in this process. However, an excess of liver-specific ABCA1 expression can impair HDL function despite increased cholesterol levels in the bloodstream. The role of liver ABCA1 in non-alcoholic fatty liver disease and AS remains complex. Cholesterol outflow mediated by liver ABCA1 can reduce hepatic free cholesterol deposition but may increase the risk of AS and hyperlipidemia.

The role of the hepatic low-density lipoprotein (LDL) receptor in non-alcoholic fatty liver disease and AS is equally intricate. Further research is needed to fully grasp the functions of hepatic ABCA1 and the LDL receptor in these conditions. Investigating how hepatic ABCA1 enhances HDL function and the liver's response to different signals in cholesterol metabolism could be beneficial. Additional studies are essential to determine the best approach for targeting major regulators of hepatic cholesterol transport through transcriptional, post-transcriptional, or post-translational modifications. Future investigations into hepatic cholesterol metabolism should prioritize the development of animal models that accurately mimic both non-alcoholic fatty liver disease and AS. The current understanding of cholesterol metabolism in non-alcoholic fatty liver disease and AS is primarily derived from studies on genetically modified mice and rats subjected to dietary interventions. However, murine and rat models may not fully capture the complexity of the pathological changes that occur in the development of these conditions in humans. Larger animal models offer significant advantages due to their closer biochemical, genetic, metabolic, and physiological resemblance to humans, making them superior models for bridging basic research with clinical applications.

Author contributions

A.V.P. prepared the original draft. V.N.S., D.F.B., N.A.O., M.A.P., V.A.K., and A.N.O. reviewed and edited the writing. All authors have read and agreed to the published version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

References

Açikel, M., Sunay, S., Koplay, M., Gündoğdu, F., & Karakelleoğlu, S. (2009). Evaluation of ultrasonographic fatty liver and severity of coronary atherosclerosis, and obesity in patients undergoing coronary angiography. Anadolu kardiyoloji dergisi : AKD = the Anatolian journal of cardiology, 9(4), 273–279.

Al Rifai, M., Silverman, M. G., Nasir, K., Budoff, M. J., Blankstein, R., Szklo, M., Katz, R., Blumenthal, R. S., & Blaha, M. J. (2015). The association of nonalcoholic fatty liver disease, obesity, and metabolic syndrome, with systemic inflammation and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis, 239(2), 629–633. https://doi.org/10.1016/j.atherosclerosis.2015.02.011

Ampuero, J., Gallego-Durán, R., & Romero-Gómez, M. (2015). Association of NAFLD with subclinical atherosclerosis and coronary-artery disease: meta-analysis. Revista espanola de enfermedades digestivas, 107(1), 10–16.

Anastasia V. Poznyak, Ludmila V Nedosugova, Vasily N. Sukhorukov. (2023i). Hepatitis C and atherosclerosis: inflammatory interplay, Journal of Angiotherpay, 7(1), 1-10, 9361

Anastasia V. Poznyak, Varvara A. Orekhova, Vasily N. Sukhorukov. (2024a). Platelet Implication in Atherosclerosis Pathogenesis, Journal of Angiotherapy, 8(1), 1-8, 9385

Anastasia V. Poznyak, Vasily N. Sukhorukov, Igor A. Sobenin et al. (2024g). Exploring the Link between Chronic Inflammation and Atherosclerosis-Endometriosis Association, Journa of Angiotherapy, 8(3), 1-8, 9556

Anastasia V. Poznyak, Victoria A. Khotina, Alexandra A. Melnichenko et al., (2024b). Vitamin D Deficiency As A Contributor To Atherosclerosis Development – A Review, Journal of Angiotherapy, 8(2), 1-11, 9389

Anastasia V. Poznyak, Victoria A. Khotina, Roghayyeh Vakili-Ghartavol. (2024c). Interplay And Causative Relationship Between Frailty And Atherosclerosis, Journal of Angiotherapy, 8(2), 1-11, 9449

Anastasia V. Poznyak, Victoria A. Khotina, Roghayyeh Vakili-Ghartavo. (2024d). Neoatherosclerosis And Paleoatherosclerosis: Complications After Stenting, Journal of Angiotherapy, 8(2), 1-9, 9450

Anastasia V. Poznyak, Victoria A. Khotina, Roghayyeh Vakili-Ghartavo. (2024e). Neoatherosclerosis And Paleoatherosclerosis: Complications After Stenting, Journal of Angiotherapy, 8(2), 1-9, 9450

Anastasia V. Poznyak, Victoria A. Khotina, Roghayyeh Vakili-Ghartavol et al. (2024f). The Role of Natural Compounds for Atherosclerosis Treatment: Lessons Learned from The Use of Curcumin, Journal of Angiotherapy, 8(3), 1-8, 9555

Anastasia V. Poznyak, Victoria A. Khotina, Victor Y Glanz et al. (2024h). Advances in Cellular Models of Atherosclerosis, Journal of Angiotherapy, 8(3), 1-8, 9503

Armstrong, M. J., Gaunt, P., Aithal, G. P., Barton, D., Hull, D., Parker, R., Hazlehurst, J. M., Guo, K., LEAN trial team, Abouda, G., Aldersley, M. A., Stocken, D., Gough, S. C., Tomlinson, J. W., Brown, R. M., Hübscher, S. G., & Newsome, P. N. (2016). Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet (London, England), 387(10019), 679–690. https://doi.org/10.1016/S0140-6736(15)00803-X

Arnett, D. K., Blumenthal, R. S., Albert, M. A., Buroker, A. B., Goldberger, Z. D., Hahn, E. J., Himmelfarb, C. D., Khera, A., Lloyd-Jones, D., McEvoy, J. W., Michos, E. D., Miedema, M. D., Muñoz, D., Smith, S. C., Jr, Virani, S. S., Williams, K. A., Sr, Yeboah, J., & Ziaeian, B. (2019). 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation, 140(11), e596–e646. https://doi.org/10.1161/CIR.0000000000000678

Arslan, U., & Yenerçağ, M. (2020). Relationship between non-alcoholic fatty liver disease and coronary heart disease. World journal of clinical cases, 8(20), 4688–4699. https://doi.org/10.12998/wjcc.v8.i20.4688

Arslan, U., Kocaoğlu, I., Balcı, M., Duyuler, S., & Korkmaz, A. (2012). The association between impaired collateral circulation and non-alcoholic fatty liver in patients with severe coronary artery disease. Journal of cardiology, 60(3), 210–214. https://doi.org/10.1016/j.jjcc.2012.05.003

Asbaghi, O., Choghakhori, R., Ashtary-Larky, D., & Abbasnezhad, A. (2020). Effects of the Mediterranean diet on cardiovascular risk factors in non-alcoholic fatty liver disease patients: A systematic review and meta-analysis. Clinical nutrition ESPEN, 37, 148–156. https://doi.org/10.1016/j.clnesp.2020.03.003

Bae J. Y. (2020). Resistance Exercise Regulates Hepatic Lipolytic Factors as Effective as Aerobic Exercise in Obese Mice. International journal of environmental research and public health, 17(22), 8307. https://doi.org/10.3390/ijerph17228307

Bc, B., Jaiswal, R. K., Gupta, P. K., Paudel, R., & Subedi, R. K. (2021). Carotid Intima-media Thickness in Patients with Non-alcoholic Fatty Liver Disease Attending a Tertiary Care Center: A Descriptive Cross-sectional Study. JNMA; journal of the Nepal Medical Association, 59(237), 454–459. https://doi.org/10.31729/jnma.5719

Bigler, M. R., & Seiler, C. (2019). The Human Coronary Collateral Circulation, Its Extracardiac Anastomoses and Their Therapeutic Promotion. International journal of molecular sciences, 20(15), 3726. https://doi.org/10.3390/ijms20153726

Biswas, A., Rabbani, S. I., & Devi, K. (2012). Influence of pioglitazone on experimental heart failure and hyperlipidemia in rats. Indian journal of pharmacology, 44(3), 333–339. https://doi.org/10.4103/0253-7613.96305

Blais, P., Lin, M., Kramer, J. R., El-Serag, H. B., & Kanwal, F. (2016). Statins Are Underutilized in Patients with Nonalcoholic Fatty Liver Disease and Dyslipidemia. Digestive diseases and sciences, 61(6), 1714–1720. https://doi.org/10.1007/s10620-015-4000-6

Bril, F., Biernacki, D. M., Kalavalapalli, S., Lomonaco, R., Subbarayan, S. K., Lai, J., Tio, F., Suman, A., Orsak, B. K., Hecht, J., & Cusi, K. (2019). Role of Vitamin E for Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes: A Randomized Controlled Trial. Diabetes care, 42(8), 1481–1488. https://doi.org/10.2337/dc19-0167

Chalasani, N. P., Sanyal, A. J., Kowdley, K. V., Robuck, P. R., Hoofnagle, J., Kleiner, D. E., Unalp, A., Tonascia, J., & NASH CRN Research Group (2009). Pioglitazone versus vitamin E versus placebo for the treatment of non-diabetic patients with non-alcoholic steatohepatitis: PIVENS trial design. Contemporary clinical trials, 30(1), 88–96. https://doi.org/10.1016/j.cct.2008.09.003

Chew, N. W. S., Chong, B., Ng, C. H., Kong, G., Chin, Y. H., Xiao, W., Lee, M., Dan, Y. Y., Muthiah, M. D., & Foo, R. (2022). The genetic interactions between non-alcoholic fatty liver disease and cardiovascular diseases. Frontiers in genetics, 13, 971484. https://doi.org/10.3389/fgene.2022.971484

Chung, G. E., Choi, S. Y., Kim, D., Kwak, M. S., Park, H. E., Kim, M. K., & Yim, J. Y. (2015). Nonalcoholic fatty liver disease as a risk factor of arterial stiffness measured by the cardioankle vascular index. Medicine, 94(12), e654. https://doi.org/10.1097/MD.0000000000000654

Damba, T., Bourgonje, A. R., Abdulle, A. E., Pasch, A., Sydor, S., van den Berg, E. H., Gansevoort, R. T., Bakker, S. J. L., Blokzijl, H., Dullaart, R. P. F., van Goor, H., & Moshage, H. (2020). Oxidative stress is associated with suspected non-alcoholic fatty liver disease and all-cause mortality in the general population. Liver international : official journal of the International Association for the Study of the Liver, 40(9), 2148–2159. https://doi.org/10.1111/liv.14562

Fernández, T., Viñuela, M., Vidal, C., & Barrera, F. (2022). Lifestyle changes in patients with non-alcoholic fatty liver disease: A systematic review and meta-analysis. PloS one, 17(2), e0263931. https://doi.org/10.1371/journal.pone.0263931

Francque, S. M., Marchesini, G., Kautz, A., Walmsley, M., Dorner, R., Lazarus, J. V., Zelber-Sagi, S., Hallsworth, K., Busetto, L., Frühbeck, G., Dicker, D., Woodward, E., Korenjak, M., Willemse, J., Koek, G. H., Vinker, S., Ungan, M., Mendive, J. M., & Lionis, C. (2021). Non-alcoholic fatty liver disease: A patient guideline. JHEP reports : innovation in hepatology, 3(5), 100322. https://doi.org/10.1016/j.jhepr.2021.100322

Grefhorst, A., van de Peppel, I. P., Larsen, L. E., Jonker, J. W., & Holleboom, A. G. (2021). The Role of Lipophagy in the Development and Treatment of Non-Alcoholic Fatty Liver Disease. Frontiers in endocrinology, 11, 601627. https://doi.org/10.3389/fendo.2020.601627

Hamaguchi, M., Kojima, T., Takeda, N., Nagata, C., Takeda, J., Sarui, H., Kawahito, Y., Yoshida, N., Suetsugu, A., Kato, T., Okuda, J., Ida, K., & Yoshikawa, T. (2007). Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. World journal of gastroenterology, 13(10), 1579–1584. https://doi.org/10.3748/wjg.v13.i10.1579

Handhle, A., Viljoen, A., & Wierzbicki, A. S. (2021). Elevated Lipoprotein(a): Background, Current Insights and Future Potential Therapies. Vascular health and risk management, 17, 527–542. https://doi.org/10.2147/VHRM.S266244

Huang, Y., Bi, Y., Xu, M., Ma, Z., Xu, Y., Wang, T., Li, M., Liu, Y., Lu, J., Chen, Y., Huang, F., Xu, B., Zhang, J., Wang, W., Li, X., & Ning, G. (2012). Nonalcoholic fatty liver

disease is associated with atherosclerosis in middle-aged and elderly Chinese. Arteriosclerosis, thrombosis, and vascular biology, 32(9), 2321–2326. https://doi.org/10.1161/ATVBAHA.112.252957

Hydes, T. J., Ravi, S., Loomba, R., & E Gray, M. (2020). Evidence-based clinical advice for nutrition and dietary weight loss strategies for the management of NAFLD and NASH. Clinical and molecular hepatology, 26(4), 383–400. https://doi.org/10.3350/cmh.2020.0067

Izuhara, M., Shioji, K., Kadota, S., Baba, O., Takeuchi, Y., Uegaito, T., Mutsuo, S., & Matsuda, M. (2008). Relationship of cardio-ankle vascular index (CAVI) to carotid and coronary arteriosclerosis. Circulation journal : official journal of the Japanese Circulation Society, 72(11), 1762–1767. https://doi.org/10.1253/circj.cj-08-0152

Kechagias, S., Ekstedt, M., Simonsson, C., & Nasr, P. (2022). Non-invasive diagnosis and staging of non-alcoholic fatty liver disease. Hormones (Athens, Greece), 21(3), 349–368. https://doi.org/10.1007/s42000-022-00377-8

Koulaouzidis, G., Charisopoulou, D., Kukla, M., Marlicz, W., Rydzewska, G., Koulaouzidis, A., & Skonieczna-Żydecka, K. (2021). Association of non-alcoholic fatty liver disease with coronary artery calcification progression: a systematic review and meta-analysis. Przeglad gastroenterologiczny, 16(3), 196–206. https://doi.org/10.5114/pg.2021.109063

Kwak, M. S., & Kim, D. (2018). Non-alcoholic fatty liver disease and lifestyle modifications, focusing on physical activity. The Korean journal of internal medicine, 33(1), 64–74. https://doi.org/10.3904/kjim.2017.343

Lai, Y. H., Su, C. H., Hung, T. C., Yun, C. H., Tsai, C. T., Yeh, H. I., & Hung, C. L. (2022). Association of Non-Alcoholic Fatty Liver Disease and Hepatic Fibrosis with Epicardial Adipose Tissue Volume and Atrial Deformation Mechanics in a Large Asian Population Free from Clinical Heart Failure. Diagnostics (Basel, Switzerland), 12(4), 916. https://doi.org/10.3390/diagnostics12040916

Langroudi, T. F., Haybar, H., Parsa, S. A., Mahjoorian, M., Khaheshi, I., & Naderian, M. (2018). The severity of coronary artery disease was not associated with non-alcoholic fatty liver disease in a series of 264 non-diabetic patients who underwent coronary angiography. Romanian journal of internal medicine = Revue roumaine de medecine interne, 56(3), 167–172. https://doi.org/10.2478/rjim-2018-0009

Leers, J. M., Knepper, L., van der Veen, A., Schröder, W., Fuchs, H., Schiller, P., Hellmich, M., Zettelmeyer, U., Brosens, L. A. A., Quaas, A., Ruurda, J. P., van Hillegersberg, R., & Bruns, C. J. (2020). The CARDIA-trial protocol: a multinational, prospective, randomized, clinical trial comparing transthoracic esophagectomy with transhiatal extended gastrectomy in adenocarcinoma of the gastroesophageal junction (GEJ) type II. BMC cancer, 20(1), 781. https://doi.org/10.1186/s12885-020-07152-1

Li, N., Zhang, G. W., Zhang, J. R., Jin, D., Li, Y., Liu, T., & Wang, R. T. (2015). Non-alcoholic fatty liver disease is associated with progression of arterial stiffness. Nutrition, metabolism, and cardiovascular diseases : NMCD, 25(2), 218–223. https://doi.org/10.1016/j.numecd.2014.10.002

Liava, C., & Sinakos, E. (2021). Semaglutide for nonalcoholic steatohepatitis: closer to a solution?. Hepatobiliary surgery and nutrition, 10(4), 541–544. https://doi.org/10.21037/hbsn-21-231

Lv, X., Dong, Y., Hu, L., Lu, F., Zhou, C., & Qin, S. (2020). Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for the management of nonalcoholic fatty liver disease (NAFLD): A systematic review. Endocrinology, diabetes & metabolism, 3(3), e00163. https://doi.org/10.1002/edm2.163

Machado, M. V., & Cortez-Pinto, H. (2014). Non-alcoholic fatty liver disease: what the clinician needs to know. World journal of gastroenterology, 20(36), 12956–12980. https://doi.org/10.3748/wjg.v20.i36.12956

Makri, E. S., Makri, E., & Polyzos, S. A. (2022). Combination Therapies for Nonalcoholic Fatty Liver Disease. Journal of personalized medicine, 12(7), 1166. https://doi.org/10.3390/jpm12071166

Mathangi R, Selvaraj J, Reji M, Jaideep M, Ponnulakshmi R, Nalini D, Samyuktha. P, Pugazharasan. (2021). Relationship Between Ob Gene Product and Lipid Profile in The Pathogenesis of Atherosclerosis, Journal of Angiotherapy, 5(2), 2151

Mirarchi, L., Amodeo, S., Citarrella, R., Licata, A., Soresi, M., & Giannitrapani, L. (2022). SGLT2 Inhibitors as the Most Promising Influencers on the Outcome of Non-Alcoholic Fatty Liver Disease. International journal of molecular sciences, 23(7), 3668. https://doi.org/10.3390/ijms23073668

Motamed, N., Ajdarkosh, H., Ahmadi, M., Perumal, D., Ashrafi, G. H., Nikkhah, M., Faraji, A. H., Maadi, M., Khoonsari, M., Rezaie, N., Farahani, B., Safarnezhad Tameshkel, F., Ameli, M., Panahi, M., Karbalaie Niya, M. H., & Zamani, F. (2020). Non-alcoholic fatty liver disease is not independent risk factor for cardiovascular disease event: A cohort study. World journal of hepatology, 12(6), 323–331. https://doi.org/10.4254/wjh.v12.i6.323

Mulkern, R. V., Salsberg, S. L., Krauel, M. R., Ludwig, D. S., & Voss, S. (2008). A paradoxical signal intensity increase in fatty livers using opposed-phase gradient echo imaging with fat-suppression pulses. Pediatric radiology, 38(10), 1099–1104. https://doi.org/10.1007/s00247-008-0946-2

Obeticholic Acid. (2019). In LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. National Institute of Diabetes and Digestive and Kidney Diseases.

Paar, M., Jüngst, C., Steiner, N. A., Magnes, C., Sinner, F., Kolb, D., Lass, A., Zimmermann, R., Zumbusch, A., Kohlwein, S. D., & Wolinski, H. (2012). Remodeling of lipid droplets during lipolysis and growth in adipocytes. The Journal of biological chemistry, 287(14), 11164–11173. https://doi.org/10.1074/jbc.M111.316794

Patorno, E., Pawar, A., Bessette, L. G., Kim, D. H., Dave, C., Glynn, R. J., Munshi, M. N., Schneeweiss, S., Wexler, D. J., & Kim, S. C. (2021). Comparative Effectiveness and Safety of Sodium-Glucose Cotransporter 2 Inhibitors Versus Glucagon-Like Peptide 1 Receptor Agonists in Older Adults. Diabetes care, 44(3), 826–835. https://doi.org/10.2337/dc20-1464

Pisto, P., Santaniemi, M., Bloigu, R., Ukkola, O., & Kesäniemi, Y. A. (2014). Fatty liver predicts the risk for cardiovascular events in middle-aged population: a population-based cohort study. BMJ open, 4(3), e004973. https://doi.org/10.1136/bmjopen-2014-004973

Rampally, V., Biri, S. K., Nair, I. K., & Vadlakonda, A. (2020). Determination of association between nonalcoholic fatty liver disease and carotid artery atherosclerosis among nondiabetic individuals. Journal of family medicine and primary care, 9(2), 1182–1186. https://doi.org/10.4103/jfmpc.jfmpc_957_19

Ruiz-Sala, P., & Peña-Quintana, L. (2021). Biochemical Markers for the Diagnosis of Mitochondrial Fatty Acid Oxidation Diseases. Journal of clinical medicine, 10(21), 4855. https://doi.org/10.3390/jcm10214855

Santos-Baez, L. S., & Ginsberg, H. N. (2021). Nonalcohol fatty liver disease: balancing supply and utilization of triglycerides. Current opinion in lipidology, 32(3), 200–206. https://doi.org/10.1097/MOL.0000000000000756

Sanyal, A. J., Chalasani, N., Kowdley, K. V., McCullough, A., Diehl, A. M., Bass, N. M., Neuschwander-Tetri, B. A., Lavine, J. E., Tonascia, J., Unalp, A., Van Natta, M., Clark, J., Brunt, E. M., Kleiner, D. E., Hoofnagle, J. H., Robuck, P. R., & NASH CRN (2010). Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. The New England journal of medicine, 362(18), 1675–1685. https://doi.org/10.1056/NEJMoa0907929

Sarno, G., Schiavo, L., Calabrese, P., Álvarez Córdova, L., Frias-Toral, E., Cucalón, G., Garcia-Velasquez, E., Fuchs-Tarlovsky, V., & Pilone, V. (2022). The Impact of Bariatric-Surgery-Induced Weight Loss on Patients Undergoing Liver Transplant: A Focus on Metabolism, Pathophysiological Changes, and Outcome in Obese Patients Suffering NAFLD-Related Cirrhosis. Journal of clinical medicine, 11(18), 5293. https://doi.org/10.3390/jcm11185293

Schwenger, K. J. P., Fischer, S. E., Jackson, T., Okrainec, A., & Allard, J. P. (2018). In nonalcoholic fatty liver disease, Roux-en-Y gastric bypass improves liver histology while persistent disease is associated with lower improvements in waist circumference and glycemic control. Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery, 14(9), 1233–1239. https://doi.org/10.1016/j.soard.2018.06.007

Sepehrimanesh, M., Niknam, R., Ejtehadi, F., Fattahi, M. R., & Safarpour, A. (2020). Association Between Non-Alcoholic Fatty Liver Disease and Metabolic Syndrome with Gallstone Disease, South Iran: A Population-Based Study. Diabetes, metabolic syndrome and obesity : targets and therapy, 13, 1449–1458. https://doi.org/10.2147/DMSO.S246949

Srinivasan, M., Thangaraj, S. R., Arzoun, H., Thomas, S. S., & Mohammed, L. (2022). The Impact of Bariatric Surgery on Cardiovascular Risk Factors and Outcomes: A Systematic Review. Cureus, 14(3), e23340. https://doi.org/10.7759/cureus.23340

Sun, L., & Lü, S. Z. (2011). Association between non-alcoholic fatty liver disease and coronary artery disease severity. Chinese medical journal, 124(6), 867–872.

Sung, K. C., Wild, S. H., Kwag, H. J., & Byrne, C. D. (2012). Fatty liver, insulin resistance, and features of metabolic syndrome: relationships with coronary artery calcium in 10,153 people. Diabetes care, 35(11), 2359–2364. https://doi.org/10.2337/dc12-0515

Tana, C., Ballestri, S., Ricci, F., Di Vincenzo, A., Ticinesi, A., Gallina, S., Giamberardino, M. A., Cipollone, F., Sutton, R., Vettor, R., Fedorowski, A., & Meschi, T. (2019). Cardiovascular Risk in Non-Alcoholic Fatty Liver Disease: Mechanisms and Therapeutic Implications. International journal of environmental research and public health, 16(17), 3104. https://doi.org/10.3390/ijerph16173104

Tzanaki, I., Agouridis, A. P., & Kostapanos, M. S. (2022). Is there a role of lipid-lowering therapies in the management of fatty liver disease?. World journal of hepatology, 14(1), 119–139. https://doi.org/10.4254/wjh.v14.i1.119

van der Windt, D. J., Sud, V., Zhang, H., Tsung, A., & Huang, H. (2018). The Effects of Physical Exercise on Fatty Liver Disease. Gene expression, 18(2), 89–101. https://doi.org/10.3727/105221617X15124844266408

Younossi, Z. M., Ratziu, V., Loomba, R., Rinella, M., Anstee, Q. M., Goodman, Z., Bedossa, P., Geier, A., Beckebaum, S., Newsome, P. N., Sheridan, D., Sheikh, M. Y., Trotter, J., Knapple, W., Lawitz, E., Abdelmalek, M. F., Kowdley, K. V., Montano-Loza, A. J., Boursier, J., Mathurin, P., … REGENERATE Study Investigators (2019). Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet (London, England), 394(10215), 2184–2196. https://doi.org/10.1016/S0140-6736(19)33041-7

Zainab Abdlkadhim Aboshnin, Safa Azhar Razzaq, Zahraa Ibraheim Jawad Shubber, (2024). Impact of Dapagliflozin on Atherosclerosis through Inflammation and Oxidative Pathways, Journal of Angiotherapy, 8(2), 1-7, 9478

Zeng, F., Zhang, Y., Han, X., Zeng, M., Gao, Y., & Weng, J. (2021). Predicting Non-Alcoholic Fatty Liver Disease Progression and Immune Deregulations by Specific Gene Expression Patterns. Frontiers in immunology, 11, 609900. https://doi.org/10.3389/fimmu.2020.609900

Zhou, X. D., Cai, J., Targher, G., Byrne, C. D., Shapiro, M. D., Sung, K. C., Somers, V. K., Chahal, C. A. A., George, J., Chen, L. L., Zhou, Y., Zheng, M. H., & CHESS-MAFLD consortium (2022). Metabolic dysfunction-associated fatty liver disease and implications for cardiovascular risk and disease prevention. Cardiovascular diabetology, 21(1), 270. https://doi.org/10.1186/s12933-022-01697-0