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Incidence of Fatty Liver and its Correlation with the Diabetes Mellitus in the General Population

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Abstract: *This article provides a concise summary of metabolic syndrome and diabetes mellitus in relevance to the enhanced likelihood of developing cardiovascular disease (CVD) in people with type 2 diabetes (DM2). It lists potential cardiovascular disease risk factors that explain why DM2 patients are prone to acquire CVD. T2DM and NAFLD diseases are caused by pathophysiological problems, such as being too fat and not responding well to insulin. NAFLD may be a sign of CVD and death in T2DM patients, who are at the edge of developing liver disease that leads to death. 10% of people who suffer from DM2 also have non-alcoholic steatohepatitis. Diet and exercise are helpful. Drugs like pioglitazone are used to improve insulin sensitivity, and antioxidants are used to reduce oxidative stress (such as vitamin E). But no one knows yet if these drugs are dangerous in the long run or if they can help reduce fibrosis.*

Key Words: Diabetes, Steatohepatitis, Pioglitazone, Hepatic Steatosis, Cardiovascular Disease

Introduction

A severe form of illness of the fatty liver is NASH which possibly happens to people who don't drink. Globally, non-alcoholic fatty liver disease is quickly overtaking alcoholism as the leading cause of long-term liver disease, most likely as a result of rising factors associated with type 2 diabetes and being overweight or obese (Paik, Golabi, Younossi, Mishra, & Younossi, 2020). The symptoms range from mere steatosis that can progress to NASH cirrhosis of the liver, and hepatocellular carcinoma (Krizanac, Mass Sanchez, Weiskirchen, & Asimakopoulos, 2021).

It has recently been identified as a significant disease burden for people suffering from type 2 diabetes mellitus (Francque et al., 2021). People who have type 2 diabetes not only do they have a higher prevalence of non-alcoholic fatty liver up to 70%, but they also appear to have a worse disease incidence (Hochreuter, Dall, Treebak, & Barrès, 2022). Non-alcoholic fatty liver appears to be

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linked with resistance developed against insulin and metabolic syndrome, and it may precede the onset of type-2 diabetes and cardiovascular problems. A range of liver problems that are not brought on by using alcohol is referred to as non-alcoholic liver conditions (Luukkonen et al., 2022).

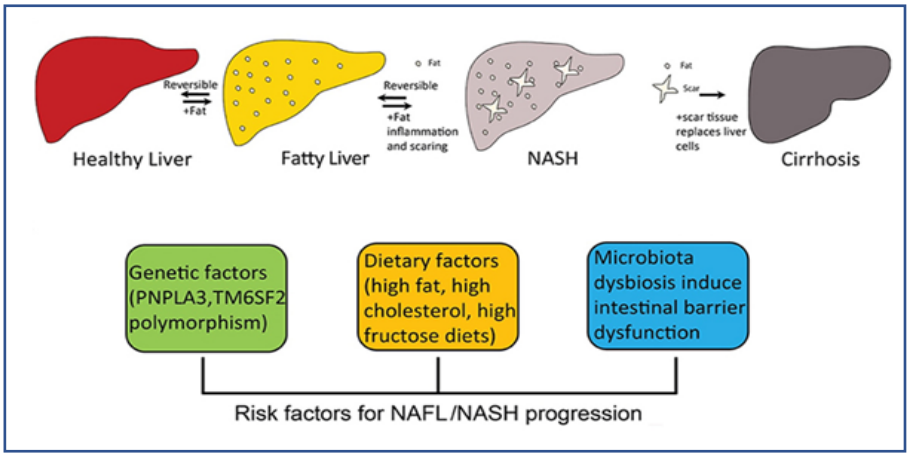

Figure 1: Fatty Liver Disease Progression and Factors Responsible for NAFL/NASH Progression.

Even though it rarely causes harm, the illness can develop cirrhosis, fibrosis, and steatohepatitis until hepatic failure as shown in Figure 1. People who don't drink and don't have viral or autoimmune liver diseases are more likely to have NAFLD (Sivakrishnan & Pharm, 2019; Westfall, Jeske, & Bader, 2020). NAFLD is like liver disease caused by alcohol. In 1980, Ludwig and his colleagues wrote the first full report on this illness. Even though 20 slightly overweight people had never drunk alcohol, liver biopsies showed that they had hepatitis caused by alcohol (George et al., 2022). The recently discovered resistance to insulin and Type 2 diabetes includes a hazardous component called NAFLD. In accordance with various research, visceral obesity, dyslipidemia, and non-alcoholic fatty liver disease are all related (Ahadi et al., 2021; Polyzos, Kechagias, & Tsochatzis, 2021). The link shows that insulin intolerance is needed for NAFLD to happen (Watt, Miotto, De Nardo, & Montgomery, 2019). Several authors think that NAFLD is the metabolic syndrome's liver component (Fujii, Kawada, & Nafld, 2020). Patients with NAFLD who have any symptoms don t have higher levels of ALT, AST, and gamma-glutamyl transferases. ALT is a sign of NAFLD because it is the liver enzyme most linked to fat storage(Cho et al., 2023; Lonardo & Ndrepepa, 2022) .

NAFLD must be diagnosed using both invasive and non-invasive diagnostics. The most accurate method of detecting and indicating stages of liver problems is a biopsy of the liver (Lee et al., 2020). The lesion that is most therapeutically benign is the fatty liver (hepatic steatosis). Liver cells collect macro and microvesicles of fat, primarily triglycerides, without significantly inducing inflammation of the liver, hepatic necrosis, or scarring (Hartleb et al., 2022). The liver is a vital organ in the process of systemic metabolism, and it serves a crucial impact in the development of insulin intolerance and type II diabetic mellitus (T2DM) (Galicia-Garcia et al., 2020). The phenomenon behind these reactions is unknown, although they entail hepatic fat build-up, changes in the metabolism of energy-rich products, and signals indicating inflammation produced by many cell types, like immune cells. Lipotoxins, mitochondrial activity, cytokines, and adipocytokines have all been linked to NAFLD and T2DM (Meex, Blaak, & van Loon, 2019).

Diabetes mellitus, an endocrine disorder, causes high blood glucose levels (hyperglycemia). The immune system attacks healthy cells, stopping them from making insulin. This is what causes type 1 diabetes. Type 1 diabetes affects less than 10% of diabetics. Most children and teenagers have this kind. People with type 2 diabetes (DM2) have hyperglycemia as a result of beta cell loss and insulin resistance (Ahsan et al., 2020). Hyperglycaemia, insulin resistance, and insulin deficiency can all change how lipids are processed when you are fasting and after you eat. Because of this resistance or insufficiency, insulin can't work on its target tissues. This causes lipid metabolic problems (dyslipidemia) (Papakonstantinou, Oikonomou, Nychas, & Dimitriadis, 2022). Dyslipidaemia, a disorder characterized by high triglyceride levels, low HDL cholesterol levels, and microscopic, aggregated LDL particles that are more likely to cause heart disease than larger, less dense LDL particles, is linked to DM2. Similar to DM2, obesity causes a drop in High-Density Lipoprotein cholesterol and an elevation in triglycerides in the blood (Clifton, 2019).

The Link between Diabetes and Metabolic Disorder

In 1988, Reaven wrote about insulin intolerance syndrome (also known as Syndrome X). The phrase "metabolic syndrome" has become prevalent to refer to insulin intolerance syndrome. It was previously believed that it was brought on by elevated insulin, insulin resistance, varying glucose tolerance, high triglyceride levels, and low HDL cholesterol levels in the blood (Lemieux & Després, 2020) as shown in Table 1. The old definition didn't include being overweight or having a big waist. Metabolic syndrome was defined as having central obesity, high triglyceride levels, hypertension, low HDL cholesterol levels, and dysglycemia (low glucose during fasting) (Engin, 2017). In the last few decades, diabetes has become more common. In 1985, around the world, 30 million individuals had diabetes. According to the WHO, 366 million more people will have diabetes by 2030, up from the estimated 171 million people who would have it in the year 2000. The main reasons for this rise are that people are living longer and getting fatter (Ogurtsova et al., 2017).

Table 1. Bostock-Cox (2020) Study showed the Risk Factors of Metabolic Illness and how they Affect Both Males and Females.

Risk Factors	Levels Associated
Obesity/over-weight	BMI can be equal to or more than 30 kg/m2 OR A waist measurement of more than 94 cm in males & more than 80 cm in females (variations can occur in different races)
An elevated level of glucose in the blood	Fasting glucose in blood equal to or more than 5.6 mmol/l
High blood pressure	130 mm/Hg systolic BP OR 85 mm/Hg diastolic BP
Triglycerides	0.1.7 mmol/l or more than that
Low HDL cholesterol	Less than 1.03 mmol/l in males Less than 1.3 mmol/l in females

Heart disease is more prevalent among people who are have type 2 diabetes by 2-4 times. Most people who suffer from type 2 diabetes die from heart disease or stroke (Einarson, Acs, Ludwig, & Panton, 2018). In the Reykjavik Study, which looked at about 18000 older people, high glucose, triglycerides, and systolic blood pressure had a bigger effect on death causing and non-deadly

coronary heart disease in females than in males. Women had less non-HDL cholesterol than men before menopause, but after menopause, they had more. Postmenopausal women had higher total cholesterol and smaller LDL particles than premenopausal women (Fonseca et al., 2019). They also had more triglycerides before and after eating. A higher relative rare disease risk and a lack of research on postmenopausal women led to the idea for this thesis.

Alcohol-unrelated Fatty Liver Disease

As almost all NAFLD patients are asymptomatic, the disease is frequently diagnosed incidentally during gastrointestinal ultrasonography or by increased aminotransferases (ALT) levels in addition to other physiological and biochemical characteristics. No one knows what makes the fat build up in the liver. Early insulin resistance causes the liver to release more FFA (Caputo, Gilardi, & Desvergne, 2017). When gets get into the liver, triglycerides go up. The number of fatty acids within the liver that are categorized as free rises as a result of lipid synthesis. De novo lipogenesis might not add much to the amount of fat in the liver. Lipogenic transcription factor activation is made worse by high insulin levels, high FFA flow, and high blood sugar. Hepatic FFA storage goes down when the liver exports lipids and but FFAs more slowly. Acetyl-CoA carboxylase is turned into malonyl-CoA when fatty acids, glucose, or insulin are present. Malonyl-CoA is made more. Malonyl-CoA stops CPT1 from moving FFA into the mitochondria. CPT-1 suppression decreases the oxidation of FFA and increases the collection and restoration of long-chain fatty-acyl CoA, which makes it easier to make triglycerides as shown in Figure 2. Heart disease is more likely to happen if you have NAFLD, but no one knows why understood (Geidl-Flueck & Gerber, 2017).

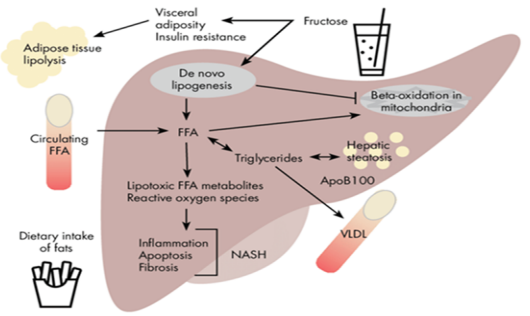

Figure 2: Contribution of Dietary Fructose and Trans Fats to the Onset of Fatty Liver Disease which is not caused by Alcohol.

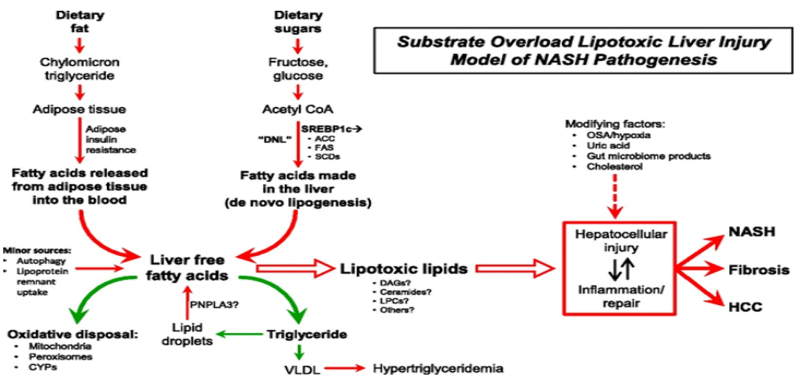

Figure 3. The Causative agents of Fatty Liver Disease which is not caused by Alcohol.

The monosaccharides which include glucose and fructose are converted into fatty acids in the liver, and fatty acids themselves, which are next supplied here to hepatocytes from tissue with high-fat content, are the principal metabolic substrates (Tsameret, Chapnik, & Froy, 2023). NASH is an excess of dietary carbohydrates and fatty acids as shown in Figure 3. Carbohydrates are taken through food intake, while lipid metabolite/fatty acids are generated mostly from tissue, with high-fat content, especially in the presence of insulin intolerance. Carbohydrates are broken down into fatty acids if there are not enough lipids and more carbohydrates are in storage. Fatty acids residing in the liver can either be oxidized by mitochondrial reactions or transformed back into triglycerides in order to transport into the bloodstream as VLDL. NASH with accompanying fibrosis has a worse prognosis due to its higher susceptibility to progress to cirrhosis with consequences of hepatic failure and hepatocellular cancer. Currently, a liver biopsy is required to diagnose NASH; however, serum-based indicators of hepatocyte death, such as cytokeratin-18 fragments, show potential as non-invasive diagnostic tools (Vilar-Gomez & Chalasani, 2018).

Table 2. Differentiation between NAFLD and Non-NAFLD diabetic patients (Bhatt et al., 2017).

Parameters	NAFLD	Non NAFLD	p
Age (Yr.)	56.93 12.97	53.54 13.8	0.2
BMI	28.27 3.77	26.19 4.02	0.009
Waist hip ratio	0.93 0.06	0.87 0.07	0.001
FBS (mg/dl)	122.1 42.8	110 24.02	0.07
HBAIC (%)	8.15 1.39	7.85 1.18	0.24
HOMA-IR	5.86 6.79	3.8 1.99	0.03
QUIKI	0.3 0.03	0.31 0.02	0.04
Insulin	17.61 11.13	13.77 5.65	0.02
HDL (mg/dl)	40.03 7.02	14.42 6.66	0.07
LDL (mg/dl)	120.06 37.3	112.13 33.64	0.2
Cholesterol (mg/dl)	195.08 36.9	186.9 39.04	0.2
Triglyceride (mg/dl)	200.9 63.4	168.5 42.62	0.003
AST (IU/L)	18.64 15.60	13.69 9.64	0.06
ALT (IU/L)	19.8 15.86	14.97 10.08	0.05

New Determinants of Cardio-Metabolic Risk

People suffering from diabetes mellitus are more likely to get cardiovascular disease as well and there are several other well-known risk factors. Some of the factors which are responsible for these conditions are elevated LDL and reduced HDL, as well as hypertension, tobacco inhalation, high blood sugar, and a rise in triglyceride levels (Mahmoud & Sulaiman, 2019) as shown in Figure 4. But these factors only elaborate a small part of why people with DM2 are more likely to get heart disease. So, researchers have investigated other risk factors or variables that might explain why people with diabetes are more likely to get heart disease (CVD2) (Pedron et al., 2022). There are many different cases, such as acute postprandial dysmetabolism, endothelial dysfunction, low-grade inflammation, fatty liver disease not related to alcoholic intake, stress caused by oxidation reaction, and advanced glycation end-products. In the next few paragraphs, we'll talk about these other possible contributing factors. A risk factor is a characteristic that is connected to an outcome, perhaps directly or indirectly, no matter what is thought to be the cause of the outcome. The

relationship between a potential cause and the result is assumed to be causal in the context of a risk factor. In the occurrence of a threat predictor, the factor predicts the occurrence without the need to establish that it caused it. The existence of a contributing factor maybe not only means that there is a risk marker, but it also means that the organism is in some way vulnerable to the bad effects of the risk factor. There is a statistical link between the presence of a risk marker and the disease, but this link does not always mean that one thing causes the other. It is also a possible sign of how bad the disease is. Current recommendations emphasize primary obesity prevention measures as well as screening for clustering of various CMR variables to prioritize treatments (Knuuti & Revenco, 2020).

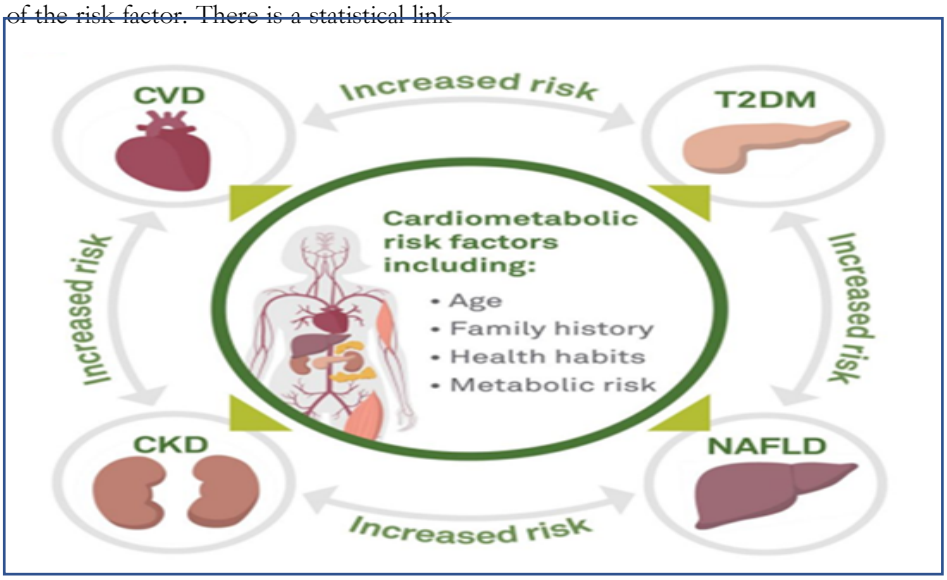

Figure 4: CVD Linkage to type 2 Diabetes (T2DM), Non-alcoholic Fatty Liver Failure (NAFLD), and Chronic Renal Failure (CKD).

Table 3. Several Biochemical and Clinical Factors were Assessed by Fatty Liver Status in type 2 Diabetes Patients Visiting DCSH.

Characteristics		Fatty Liver Status			
		All samples (N = 101)	FLI ⩾ 60 (n = 59)	FLI < 60 (n = 42)	*P* value
BMI (Mean SD)		25.82 3.64	28.04 2.43	22.70 2.62	<0.001
WC		(98, 16)	(103, 7)	(82, 16)	<0.001
Blood pressure	Systolic	(125, 21)	(130, 21)	(120, 17)	<0.001
	Diastolic	(80, 14)	(85, 13)	(74.5, 10)	<0.001
FBS (mg/dl)		(170, 92)	(170, 84)	(166.5, 100)	0.59
Triglyceride/TG (mg/dl)		(156, 61)	(175, 137)	(143.5, 41)	<0.001
GGT (IU/mL)		(17, 12)	(21, 16)	(13, 11)	<0.001
HbA1c (%)		(8, 2.9)	(8.4, 3.1)	(6.85, 1.8)	0.002
Fatty liver index		(60.53, 43.05)	(63.66, 11.04)	(15.81, 15.31)	<0.001

BMI: body mass index; DCSH: Dessie Comprehensive Specialized Hospital; DM: diabetes mellitus; FBS: fasting blood sugar; GGT: gamma-glutamyltransferase; FLI: fatty liver index; HbA1c: hemoglobin A1C; HTN: hypertension, OHD: oral hypoglycemic drug; WC: waist circumference.

How do Various Cardio Metabolic Hazardous Determinants Relate to each other?

It is hard to find a connection between risk factors for cardiometabolic disease and heart disease. There isn't enough information to figure out what caused these new risk indicators. NAFLD can be caused by postprandial metabolic malfunctioning and metabolic syndrome (Rahman et al., 2022). Both options are available. Nevertheless, fatty livers may exacerbate postprandial dysmetabolism, particularly in diabetics2. Due to these risk factors, people with type 2 diabetes and metabolic syndrome are more prone to getting heart disease. Before trying to lessen the risk of cardiovascular disease (CVD) in high-risk groups, it is important to know how these risk factors interact with each other and how much each one adds to the risk. On the other hand, physical exercise is linked to a decreased likelihood of heart mortality rate and can ameliorate a range of metabolic risk factors linked to the condition. Physical exercise is a frequently advised treatment option for patients to improve metabolic factors that increase the risk such as high-density lipoprotein (HDL) cholesterol, excess adiposity, hypertension, and glucose metabolism and regulation (Nyawo et al., 2021).

The Connection between NAFLD and Increased Cvd Risk

Recent cross-sectional studies have shown that people with fatty liver disease unrelated to alcohol had thicker intima-media of the carotid artery. (cIMT). These trials found NAFLD even though the "gold standard," a liver biopsy, was not done. NAFLD was found through liver enzymes or ultrasounds (

-Tehran et al., 2021

). Targher and his coworkers found that patients whose biopsy has proved that their NAFLD had much higher cIMT than healthy people of the same age, gender, and BMI. They also found that the histology of NAFLD might be able to predict cIMT in people who don't have insulin intolerance or metabolic syndrome. When type 2 diabetes is under control, a slight rise in ALT, which is a stand-in for NAFLD, is linked to a modification in the sensitivity of insulin and a drop in brachial artery blood flow-mediated vasodilation. Even if they have insulin intolerance and metabolic syndrome, people with NAFLD have worse flow-mediated vasodilation in their brachial arteries than healthy people. This result is proved by the fact that people with Diabetes Type 2 (DM2) had worse flow-mediated vasodilation in their brachial arteries than healthy controls. Ioanou and his colleagues used the Framingham risk score to compare ALT levels with the over the following ten years, there is a risk of cardiovascular disease as predicted (FRS) (Ioannou, Weiss, Boyko, Mozaffarian, & Lee, 2006). People with NAFLD are more likely to get CVD because people with high levels of ALT had a much higher FRS. Few long-term studies have been done on ALT, CVD, and death. We looked at the relationship between ALT at the start of the study and the Hoorn Study tells that, a demographic group of Caucasian men and women, examined all-cause death rates, heart disease, and coronary artery disease between the ages of 50 and 75. (CVD and CHD, respectively).

Researchers looked at Caucasians. After considering metabolic syndrome and other heart diseases, we found a strong link between ALT and the risk of CHD. ALT levels did not predict CVD or any other cause of death on their own. The second find was just like the first one Arndt and his team made. The death rate of 8,043 male construction workers was not affected by ALT (Judi & Khatib, 2008). Nakamura and his colleagues found a link between ALT and death results from all other factors/reasons in both males and females in Japan. This link was only seen in people whose BMIs were below the population average of 22.7 kg/m² (Hai Nam et al., 2022).

Mechanisms Liking NAFLD to Higher Cardiovascular Events

There is new evidence that NAFLD may make you more likely to get cardiovascular disease (CVD). NAFLD may raise the risk of CVD because it is strongly linked to metabolic syndrome and DM2. But this possible connection isn't certain. NAFLD makes you more likely to get type 2 diabetes and metabolic syndrome for several reasons, most of which may be linked (Gracen et al., 2022). The physiological process behind NAFLD and CVD may involve a complicated interplay of insulin resistance, vascular endothelium malfunction, hyperlipidemia, oxidative stress, altered adipocytokine profiles, and induction of the proinflammatory cascade. Patients with NAFLD can benefit from lifestyle changes and medication. NAFLD is likely to be linked with an elevated risk of CVD, making the hypothesis more appropriate that NAFLD can act both as an indicator and an early CVD regulator. Hepatic insulin resistance and subclinical inflammation are frequent mechanisms associated with the pathophysiology of fatty liver and CAD. Increased FFA, which promotes lipotoxicity and hinders endothelium-dependent vasodilation, increases oxidative stress, and has a cardiac toxic impact, is a hallmark of the hepatic insulin resistance condition of fatty liver infiltration (Sletten, Peterson, & Schaffer, 2018).

Postprandial Dysmetabolism

Triglycerides and FFAs were higher in non-diabetic adults with NASH who ate a high-fat diet than in healthy adults who didn't have NASH. Triglycerides after a meal were much lower in healthy people than in people with NASH. A 75-g oral glucose tolerance test showed that patients with NAFLD who had abnormal ALT and/or AST levels had higher glucose levels than those whose levels were normal (Won et al., 2021). These people had higher levels of glucose than people whose ALT/AST levels were normal. After the test, their levels of glucose were much higher. When obese type 2 diabetics were scanned with a CT machine, increased hepatic steatosis correlated positively with blood triglycerides and negatively with HDL-cholesterol. Both links were there. Toledo and his group of helpers found it. Hepatic steatosis did not change LDL cholesterol or apolipoprotein B100. But significant hepatic steatosis was linked to LDL particles that were smaller. These results suggest that hepatic steatosis may make these patients more likely to get heart disease. VLDL particles become more triglyceride-enriched, HDL cholesterol decreases, and extremely tiny, dense LDL particles rise (Hinds Jr et al., 2020).

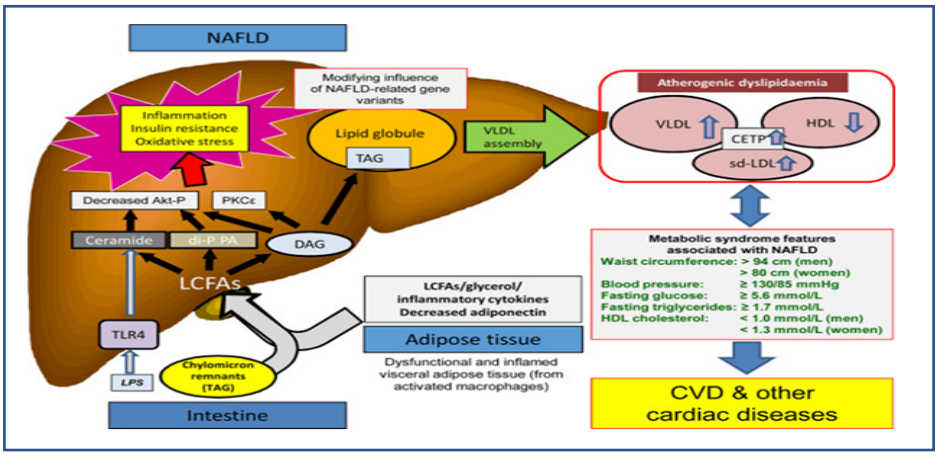

Figure 5: The Linkage between a Fatty Liver Disease that is not caused by Alcohol (NAFLD) with CVD and also the Factors Responsible for the Diseases.

The link between hepatic steatosis and blood triglycerides was stronger in people with moderate steatosis than in people with severe steatosis as shown in Figure 5. As the authors thought, this could show that VLDL can't take in triglycerides (Bornfeldt, Linton, Fisher, & Guyton, 2021). People who are likely to get hepatic steatosis were looked at. In contrast to our earlier research, which found a strong link between fats in the liver. The Hoorn Prandial research revealed no association among ALT or subsequent sugar (as determined by proton-magnetic resonance-spectroscopy) or triglycerides. Hoorn Prandial didn't find a strong connection between these two parameters. Even though there was a strong link between liver fat and glucose and insulin levels after a meal, this link was weaker (Tushuizen et al, unpublished data). These results show that the second method, not ALT, may be a better way to measure the amount of fat in the liver after meal alterations (Park et al., 2018).

Conclusions

More and more evidence points to a link between fatty liver disease not caused by alcohol intake (NAFLD) and risk factors for cardiovascular disease (CVD), such as symptoms of atherosclerosis that haven't reached the clinical stage yet and overt CVD events. These people are more prone to get heart disease, so they need medical care and maybe even therapy. Long-term research on the benefits of treating NAFLD is needed to find out if doing so lowers or gets rid of the risk of diabetes or heart disease or if it doesn't. At present time, the data firmly supports the view that NAFLD is a "multisystem" illness that has a negative impact on numerous extrahepatic organ systems, including the cardiovascular system. NAFLD worsens hepatic and peripheral insulin intolerance, leads to atherogenic dyslipidemia, and causes the onset of systemic creation of cytokines that are pro-inflammatory and hepatokines, that have the potential to promote the onset of T2DM. The liver is essential for the pathophysiology of T2DM because it leads significantly to the onset of insulin intolerance. The higher the prevalence of NASH in T2DM patients the greater chance of the development of additional problems, such as liver cirrhosis and hepatocellular cancer, that are becoming more common.

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