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Fatty liver for diabetics

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Introduction:

The complex and intricate relationship between diabetes and nonalcoholic fatty liver disease (NAFLD) has been the subject of extensive research and clinical observations over the years. This connection was first suggested in 1884 when Pepper noted fatty infiltration in the liver of a patient, which laid the groundwork for further investigations into the interplay between liver disease and metabolic disorders. This early observation set the stage for a deeper understanding of how conditions such as diabetes, particularly type 2 diabetes mellitus (T2DM), interact with liver pathology. In 1938, Connor made further significant contributions by documenting the presence of fatty liver in diabetic patients and proposing that it could potentially lead to cirrhosis in these individuals. This pivotal observation suggested that the liver was not just an incidental organ in the pathophysiology of diabetes, but a central player in the progression of the disease(Bhatt et al.,2015).

In the modern context, type 2 diabetes mellitus (T2DM) and obesity have become leading contributors to the global rise in chronic metabolic diseases. According to recent estimates by the World Health Organization (WHO), approximately 422 million individuals worldwide are affected by T2DM, which equates to a prevalence rate of about 8.8%. This sharp rise in diabetes cases has coincided with an alarming increase in obesity rates, which are recognized as one of the primary drivers of insulin resistance and the subsequent development of metabolic disorders, including NAFLD. Research has shown that 70–80% of diabetic patients are also affected by NAFLD, underscoring the strong and consistent association between these two conditions. NAFLD, characterized by the accumulation of fat in the liver without the presence of excessive alcohol consumption, is now considered one of the most common liver disorders worldwide. This fatty liver condition is often asymptomatic in its early stages, but as it progresses, it can lead to more severe liver complications such as nonalcoholic steatohepatitis (NASH), advanced liver fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC), a life-threatening form of liver cancer (Hazlehurst et al.,2016).

The progression from simple hepatic steatosis (fatty liver) to more severe forms of liver disease, such as NASH and cirrhosis, is closely linked to chronic inflammation. In diabetic patients, the presence of

NAFLD is often compounded by insulin resistance, which exacerbates liver inflammation and promotes fibrotic changes in the liver. The risk of developing severe liver disease, including cirrhosis and HCC, is significantly elevated in individuals with both diabetes and NAFLD. This combination of metabolic disturbances poses a substantial threat to liver health and highlights the critical importance of early detection and intervention. The presence of NAFLD in diabetic patients serves as an early warning sign for the potential development of more serious liver complications. If left undiagnosed and untreated, diabetic NAFLD can lead to irreversible liver damage and death, making it a pressing issue in public health (Mavrogiannaki et al.,2013).

Given the strong association between diabetes and NAFLD, it is essential for healthcare providers to incorporate routine screening for NAFLD in the management of diabetic patients. Screening should be as integral to diabetic care as evaluations for other common diabetes-related complications, such as microvascular and macrovascular diseases. The implementation of regular screening for NAFLD in diabetic patients could significantly reduce the incidence of severe liver outcomes, as early identification allows for timely interventions that can slow or even halt the progression of liver disease. By monitoring liver health regularly, endocrinologists and primary care providers can work together to implement targeted therapies and lifestyle modifications that can prevent the escalation of liver damage (Leite et al.,2014).

One of the challenges in the management of diabetic NAFLD is the lack of definitive diagnostic tests. Current diagnostic standards rely heavily on imaging techniques, such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI), to detect fatty liver, along with liver enzyme tests to assess liver function. However, these methods are not always able to differentiate between simple fatty liver and more advanced forms of NAFLD, such as NASH. Liver biopsy remains the gold standard for diagnosing NASH and assessing the degree of liver fibrosis, but it is invasive and not routinely performed. As a result, there is a growing interest in developing non-invasive diagnostic tools, such as blood biomarkers and advanced imaging technologies, that can provide a more accurate and less invasive means of diagnosing and staging NAFLD in diabetic patients (Noureddin et al.,2015).

In terms of treatment, managing NAFLD in diabetic patients involves a multi-faceted approach, focusing on both lifestyle modifications and pharmacological interventions. Lifestyle changes, particularly improvements in diet and physical activity, are foundational in the management of both diabetes and NAFLD. Weight loss has been shown to have a beneficial effect on liver function and can significantly reduce liver fat accumulation. A reduction of just 5-10% of body weight can lead to marked improvements in liver histology, including a reduction in liver fat content and inflammation. Physical activity, particularly aerobic exercise, has been shown to improve insulin sensitivity and reduce liver fat, further underscoring the importance of regular exercise in managing both conditions.

Pharmacological interventions have also shown promise in the treatment of diabetic NAFLD. Medications that improve insulin sensitivity, such as metformin and thiazolidinediones (TZDs), have been shown to reduce liver fat and improve liver function in some patients. Additionally, newer agents, such as glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, have been found to have beneficial effects on both glycemic control and liver health. While these medications have not been specifically approved for the treatment of NAFLD, their use in managing diabetes has led to improvements in liver outcomes, making them an attractive option for treating diabetic patients with NAFLD (Stefan et al.,2022).

In more severe cases of NAFLD, particularly those involving significant liver fibrosis or cirrhosis, bariatric surgery may be considered. Bariatric surgery, such as gastric bypass or sleeve gastrectomy, has been shown to produce significant weight loss and improvements in insulin sensitivity, which can lead to marked improvements in liver histology. This surgical intervention may be particularly beneficial for patients with morbid obesity who have not responded to other treatments.

Emerging therapeutic strategies, including novel pharmacologic agents and combination therapies, hold promise for the future treatment of NAFLD, particularly in the context of diabetes. Clinical trials investigating the use of antifibrotic agents, such as obeticholic acid and selonsertib, are underway, and these treatments may offer hope for slowing or reversing the progression of liver fibrosis in diabetic patients. Additionally, research into the microbiome's role in liver disease suggests that gut health may

play a critical role in the development and progression of NAFLD, opening the door for potential microbiome-targeted therapies in the future (Targher et al.,2022).

Ultimately, a comprehensive and individualized approach is required to manage diabetic NAFLD effectively. This approach should include early screening, regular monitoring, lifestyle interventions, pharmacological treatments, and, in some cases, bariatric surgery. The goal is not only to improve liver health but also to enhance overall metabolic control and quality of life for diabetic patients. With ongoing research into the pathophysiology of NAFLD and its relationship with diabetes, there is hope that more effective and targeted treatments will emerge, reducing the burden of these interconnected conditions on public health worldwide. By focusing on both prevention and early intervention, healthcare systems can better manage the growing prevalence of diabetes and NAFLD, ultimately improving patient outcomes and reducing the long-term costs associated with liver disease and diabetes complications (Lee et al.,2019).

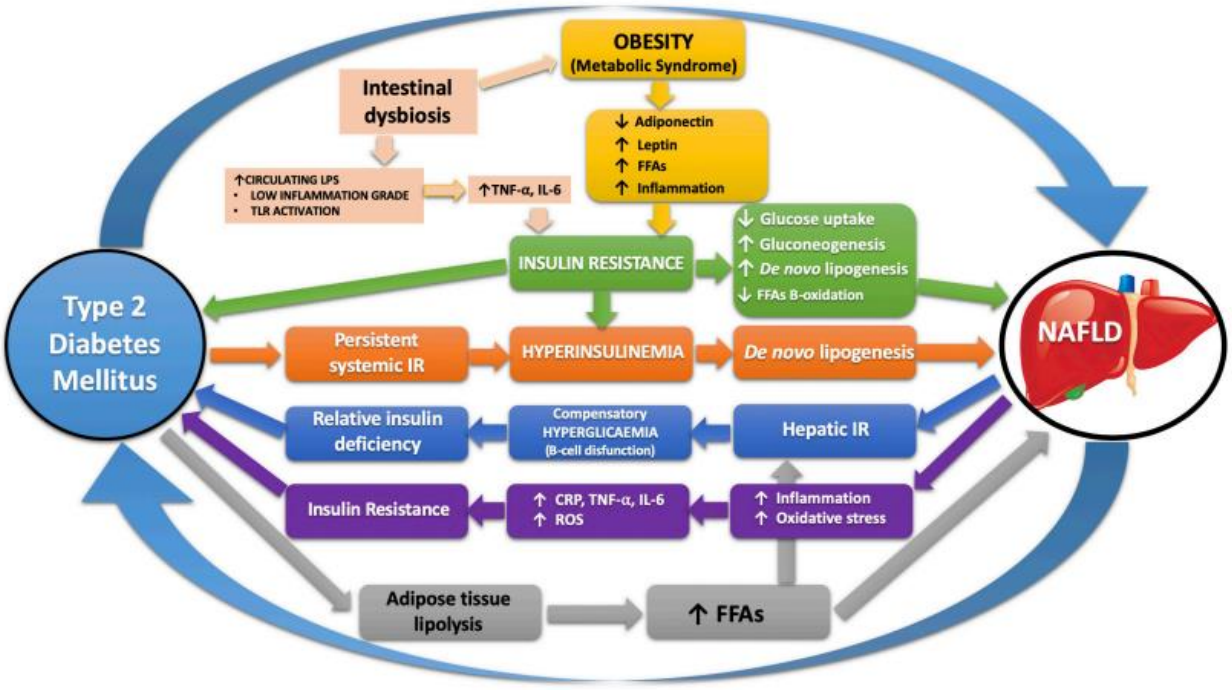

Figure 1: Schematic representation of the pathophysiological mechanisms shared between NAFLD and T2DM that connect the two sides of the coin. LPS: lipopolysaccharides; CRP: C reactive protein; TNF-α: tumor necrosis factor; IL-6: inteleukine-6; ROS:reactive oxygen species; TLR: toll like receptor

Liver steatosis (NAFLD):

Hepatic steatosis, commonly known as fatty liver, is a condition characterized by the accumulation of fat in more than 5% of liver cells (hepatocytes). This imbalance arises when the liver's ability to metabolize fatty acids is exceeded by their influx and storage. A significant component of this fat accumulation is triglycerides, also called triacylglycerols, which are formed when glycerol binds to three fatty acid chains instead of hydroxyl groups.

The liver synthesizes triglycerides using the enzyme acyl-CoA synthetase, which converts free fatty acids (FFAs) into an active form known as acyl-coenzyme A (Acyl-CoA). This process depends on L-glycerol 3-phosphate, a byproduct of glycolysis. Fatty acids reach the liver through three main routes. First, they can originate from lipolysis, where triglycerides in peripheral adipose tissue are broken down, releasing FFAs into the bloodstream. Second, the liver itself can produce FFAs through a process called de novo lipogenesis, which involves converting excess carbohydrates into fatty acids. Third, dietary fats are absorbed in the intestines and transported to the liver as part of chylomicrons, which are lipid-rich particles (Noureddin et al.,2015).

Once inside liver cells, fatty acids have two primary metabolic fates. They can be oxidized in the mitochondria through beta-oxidation, a process that generates ATP or produces ketone bodies during periods of fasting or insulin deficiency. Alternatively, they can be esterified into triglycerides. These triglycerides are then either stored within hepatocytes as lipid droplets or packaged with apolipoproteins and secreted into the bloodstream as very low-density lipoproteins (VLDL).

In the context of type 2 diabetes mellitus (T2DM), hepatic steatosis is strongly associated with insulin resistance (IR). Insulin resistance increases the flow of FFAs to the liver by promoting lipolysis in adipose tissue while impairing normal fatty acid metabolism. As a result, triglyceride synthesis is enhanced, leading to excessive fat accumulation in the liver. Over time, this process contributes to the development of nonalcoholic fatty liver disease (NAFLD), which may progress to more severe forms such as nonalcoholic steatohepatitis (NASH), characterized by inflammation and fibrosis, and in some cases, cirrhosis.

Further research into the biochemical and pathophysiological mechanisms underlying hepatic steatosis is essential, particularly in patients with diabetes. Understanding these pathways could facilitate the development of targeted therapies to reduce triglyceride synthesis, improve fatty acid metabolism, and prevent the progression of liver disease in this high-risk population.

IR:

Since the late 1980s, the strong association between insulin resistance (IR), hyperinsulinemia (elevated blood insulin levels), glucose intolerance, dyslipidemia (low HDL cholesterol levels), and hypertension has been widely recognized. Hyperinsulinemia, driven by increased insulin secretion from pancreatic beta cells in response to IR, plays a key role in glycemic compensation and maintaining plasma free fatty acid (FFA) levels within normal ranges. Metabolic syndrome (MS), a condition defined by abdominal obesity, insulin resistance, dyslipidemia, and hypertension, is associated with a range of health issues. These include a pro-thrombotic state, nonalcoholic fatty liver disease (NAFLD), and reproductive disorders. Insulin resistance, often triggered by overeating, obesity, and genetic predisposition, is closely linked to the development of NAFLD. Lipotoxicity, resulting from IR, exacerbates liver disease progression, potentially leading to nonalcoholic steatohepatitis (NASH). Recent studies highlight the critical role of fibroblast growth factor (FGF)-21, a hormone-like protein, in the pathogenesis of IR and NAFLD. FGF-21, which is highly expressed in the liver, regulates energy metabolism, lipid processing, and glucose synthesis. Its expression is controlled by the peroxisome proliferator-activated receptor (PPAR)-α pathway. A deficiency in FGF-21 or resistance to its effects can impair glucose tolerance and contribute to the metabolic dysfunctions associated with obesity, type 2 diabetes, insulin resistance, and NAFLD. Elevated circulating levels of FGF-21 in these conditions are linked to both hepatic and peripheral insulin resistance. Evidence from animal and human studies indicates a strong correlation between blood FGF-21 levels and liver fat content. Experimental research further suggests that altered FGF-21 signaling contributes to the development and progression of NAFLD. Interestingly, therapeutic interventions using FGF-21 mimetics have shown promise in improving

NAFLD, according to recent reports. These findings propose FGF-21 as a potential biomarker for diagnosing NAFLD and monitoring its progression. Additionally, it represents a novel therapeutic avenue, offering a targeted approach to mitigating the effects of insulin resistance and associated liver dysfunctions. Further research is needed to fully understand the mechanisms of FGF-21 in metabolic regulation and its potential clinical applications.

T2DM:

Hyperglycemia, resulting from insulin resistance (IR) and relative insulin insufficiency, is a defining feature of type 2 diabetes mellitus (T2DM), a metabolic disorder. A key factor in the onset of T2DM is the inability of pancreatic beta-cells to adapt to insulin resistance by producing sufficient insulin, leading to hyperinsulinemia. It is evident that insulin resistance plays a pivotal role in the development of T2DM, as the pathophysiology of the condition stems from the beta-cells' inability to compensate for the increased demand for insulin due to resistance. Under normal conditions, beta-cells counteract insulin resistance by increasing insulin secretion, thereby maintaining normal glucose levels. However, when insulin resistance becomes more pronounced, glucose concentrations rise because the pancreas cannot produce enough insulin to meet the body's needs. As the pancreatic beta-cells' capacity to maintain hyperinsulinemia diminishes, available evidence supports the notion that insulin resistance may be a primary factor contributing to the development of type 2 diabetes. Nonetheless, there is a growing recognition that insulin resistance might also serve a protective role, particularly in safeguarding vital tissues from the harmful effects of chronic nutritional excess. Some have suggested that insulin resistance may function as a protective mechanism for cardiovascular tissues against damage caused by excessive calorie intake. This challenges the view that insulin resistance is solely detrimental. While insulin resistance remains a key biomarker of metabolic dysfunction, it may not always be the underlying cause of metabolic disturbances in conditions like metabolic syndrome (MS). Therefore, it is important to consider that insulin resistance during MS might merely be an epiphenomenon rather than a direct cause. If insulin resistance does have an adaptive protective role, efforts to treat it aggressively without considering this potential function could inadvertently be harmful.

This evolving understanding calls for a shift in how we view insulin resistance and the underlying causes of type 2 diabetes. It also necessitates a reconsideration of how we approach the treatment of individuals with metabolic syndrome, type 2 diabetes, and related disorders. A more nuanced perspective is required to ensure that treatment strategies align with the complex role of insulin resistance in these conditions.

Association of NAFLD with diabetes mellitus (DM):

The incidence of non-alcoholic fatty liver disease (NAFLD) is increasing globally. Over the past two decades, the proportion of the US population affected by NAFLD has risen, as demonstrated by a population-based analysis from the US National Health and Nutrition Examination Survey. Epidemiological studies have shown varied results, but a global median prevalence of 20% or higher is plausible, with even greater rates observed in Asia. Hepatitis A, B, and C, autoimmune hepatitis, hemochromatosis, and hypothyroidism can coexist with hepatic steatosis and steatohepatitis. However, the primary drivers behind the increasing prevalence of NAFLD are the epidemiological and pathophysiological links to type 2 diabetes (T2DM) and obesity. The prevalence of NAFLD among overweight individuals with type 2 diabetes is estimated to exceed 70%. In children with type 2 diabetes, NAFLD is responsible for 20% of cases where alanine aminotransferase (ALT) levels are more than twice the normal value (Stefan et al.,2022).

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance in the body's target tissues and inadequate insulin secretion by beta cells in the pancreatic islets. Both genetic and environmental factors are thought to contribute to these abnormalities. Over 40 known gene variants have been identified, each contributing slightly to the overall risk of T2DM, suggesting a multifactorial genetic predisposition. Many of these genes are involved in pathways related to beta cell growth or function, although the molecular mechanisms linking them to T2DM remain unclear. Environmental factors, particularly a lack of physical activity and a high-calorie diet, are significant contributors to both obesity and insulin resistance.

Obesity and type 2 diabetes have been on the rise for decades, driven by changes in dietary patterns and physical activity levels, often associated with increased urbanization. According to the International Diabetes Federation, nearly 90% of the 400 million people with diabetes worldwide have type 2 diabetes. Additionally, 316 million people are at high risk of developing type 2 diabetes due to slightly elevated fasting or postprandial glucose levels. Individuals with pre-diabetes or active T2DM are also more likely to develop NAFLD (Targher et al.,2022). Many individuals with non-alcoholic fatty liver disease (NAFLD) also present with additional clinical features that align with the diagnostic criteria for metabolic syndrome, beyond the association with impaired glucose metabolism. Metabolic syndrome is characterized by five abnormalities: increased waist circumference or waist-to-hip ratio, impaired glucose tolerance or overt diabetes, elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, and high blood pressure. It is widely recognized that the presence of any three of these abnormalities constitutes metabolic syndrome. A study of 304 patients with NAFLD found that metabolic syndrome was present in 88% of those with steatohepatitis. In addition to impaired glucose metabolism, the other components of metabolic syndrome, such as hypertension, increase the risk of cardiovascular diseases, with hypertension potentially worsening microvascular issues in diabetes (Targher et al.,2022).

In addition to its links with diabetes and metabolic syndrome, NAFLD itself may independently contribute to an increased risk of cardiovascular disease. Research involving over 2,000 adults with type 2 diabetes over 6.5 years revealed an almost twofold increase in the risk of cardiovascular disease in individuals with NAFLD. This relationship persisted even when adjusting for other factors like age, sex, smoking status, diabetes duration, hemoglobin A1c levels, or LDL cholesterol. Similarly, a separate study on individuals with type 1 diabetes mellitus (T1DM) also found an independent association between NAFLD and cardiovascular disease. Furthermore, there is emerging evidence that NAFLD may be a contributing factor to diabetic retinopathy and chronic kidney disease (Lee et al.,2019).

Further research is needed to fully understand the causal role of NAFLD and its strength in relation to these long-term complications of diabetes.

Detecting fatty liver in diabetics by ultrasound:

Two-dimensional shear wave elastography (2D-SWE), point shear wave elastography (pSWE), and transient elastography (TE) are all non-invasive techniques (NIT) utilized for screening and assessing the severity of Non-Alcoholic Fatty Liver Disease (NAFLD). Among these, TE is particularly popular due to its widespread availability and ability to serve as a point-of-care test. It can effectively assess hepatic steatosis and liver stiffness—two key indicators of liver fibrosis. Given its high accuracy, elastography has become a cost-effective, non-invasive alternative to liver biopsy, gaining increasing support as a reliable tool for evaluating liver damage in various chronic liver diseases, including NAFLD. This endorsement is reflected in practice guidelines provided by the Brazilian Society of Hepatology and the Brazilian College of Radiology(Garg et al.,2018).

the Screening for Undiagnosed Non-Alcoholic Fatty Liver Disease and Non-Alcoholic Steatohepatitis (SUNN) study, even asymptomatic high-risk patients should undergo NAFLD screening. A study by Eskridge et al. showed that 16% of participants had both steatosis and fibrosis, while 57% had steatosis without fibrosis, using TE and Controlled Attenuation Parameter (CAP) measurements. However, the study's findings on steatosis may be somewhat exaggerated due to the application of a cut-off value of ≥238 dB/m. The European Association for the Study of the Liver (EASL) recommends using a CAP value >275 dB/m for diagnosing hepatic steatosis, though there is no universal consensus on these cut-off values. For more precise staging, TE can be used with cut-offs of 297, 317, and 333 dB/m for stages S0, S1, and S2, respectively (Ahn et al.,2014)

Transient Elastography (TE) and Liver Fibrosis Staging: TE, developed in 2003 by Sandrin et al., is a non-invasive imaging technique that plays a significant role in liver fibrosis staging. TE measures liver stiffness through Liver Stiffness Measurement (LSM), which correlates well with histologically confirmed liver fibrosis in patients with NAFLD. The Fibroscan® instrument (Echosens, Paris, France), which performs TE, is not part of standard ultrasound-based systems but has demonstrated high feasibility, with both M and XL probes being 93.5% feasible for liver stiffness measurement. The M probe is suitable for individuals with normal weight, while the XL probe is used for those who are overweight (Sawaf et al.,2020).

TE is especially useful for detecting advanced fibrosis (stages F3–F4), even in asymptomatic individuals who may be at risk of developing severe complications such as portal hypertension and chronic liver disease. As such, these patients are often classified under the term "compensated advanced chronic liver disease" (cACLD). TE results greater than 15 kPa suggest cACLD, while measurements between 10 and 15 kPa require further confirmation. This ability to identify at-risk patients before the onset of symptoms is a significant advantage in managing liver disease progression .

Clinical Applications and Future Research: The TE technique has found widespread application, from assessing the prevalence of type 2 diabetes in NAFLD patients to screening for hepatic steatosis and fibrosis in those with suspected NAFLD. It has also become an essential tool in monitoring patients undergoing treatment for liver conditions, both pharmacologic and non-pharmacologic, to track improvements over time. Studies have shown that individuals with diabetes and steatosis are particularly prone to developing fibrosis. However, many studies using TE to investigate NAFLD and its associated risk factors have often relied on non-diabetic cohorts for validation. This suggests the need for further research to separate the risks associated with diabetes from those related to other factors, such as body mass index (BMI). More precise cut-off values need to be established for populations with diabetes to improve diagnostic accuracy (De Franchis et al.,2015).

Research conducted at a tertiary center in Lebanon, for example, demonstrated that more than 58% of patients had NAFLD, and 20% had type 2 diabetes. A significant proportion of these patients (almost 50%) also had metabolic risk factors. These findings underline the importance of using TE as a tool for assessing fibrosis and monitoring disease progression in populations with chronic liver diseases, particularly in those with NAFLD and diabetes (Sporea et al.,2016).

Elastography techniques such as TE, 2D-SWE, and pSWE represent valuable non-invasive tools for diagnosing and monitoring NAFLD, with TE standing out as an accessible and reliable method. Although further research is necessary to refine diagnostic cut-offs and better understand the relationship between diabetes, obesity, and liver disease, these methods offer an important step forward in the management of liver fibrosis, improving patient care and outcomes (Panel et al.,2021).

Pathophysiological links between NAFLD and type 2 diabetes (T2DM)

Obesity is the primary driver of insulin resistance, which plays a crucial role in the pathophysiology of non-alcoholic fatty liver disease (NAFLD), though the exact mechanisms remain incompletely understood. Insulin resistance, largely caused by post-receptor abnormalities in insulin signaling pathways, worsens as the body accumulates fat due to excessive calorie intake, obesity-related lipid metabolism alterations, adipose tissue inflammation, and ectopic fat deposition (Bhatt et al.,2015).

When free fatty acid concentrations in the bloodstream rise, typically due to insulin's impaired ability to regulate lipolysis in adipose tissue, the liver receives an increased supply of these fatty acids. This supply drives the liver to produce excess triglycerides, while insulin resistance-related disruptions in hepatic fatty acid oxidation further exacerbate the accumulation of liver fat. In conditions like prediabetes or overt diabetes, elevated glucose levels contribute additional substrates for triglyceride production, further compounding hepatic fat storage. Insulin resistance also impairs the secretion of very low-density lipoproteins (VLDL), which worsens the accumulation of fat in the liver.

A euglycemic insulin clamp study identified insulin resistance as a potential underlying mechanism for NAFLD even in non-obese individuals who do not have diabetes, suggesting its role beyond obesity and diabetes. However, insulin resistance is most often observed in conjunction with obesity and caloric excess, both of which are closely linked to the onset and progression of NAFLD (Bhatt et al.,2015).

Beyond the association between diabetes and an increased risk of NAFLD, some evidence suggests that NAFLD itself may elevate the risk of developing type 2 diabetes mellitus (T2DM). In a follow-up study conducted 11 years later, patients with NAFLD were more likely to develop diabetes and metabolic syndrome compared to those without diabetes at baseline. When diabetes develops in the context of pre-existing insulin resistance and obesity, it may independently contribute to the progression of NAFLD, eventually leading to cirrhosis. In a study of over 400 NAFLD patients, diabetes was found to be more common among those with moderate to severe liver fibrosis. Therefore, both the prevalence of NAFLD in individuals with diabetes and the effect of diabetes on the progression of NAFLD to non-alcoholic

steatohepatitis (NASH) are critical to understanding the relationship between diabetes and NAFLD (Bhatt et al.,2015).

Type 1 Diabetes Mellitus (T1DM) and Liver Disease

Unlike type 2 diabetes, obesity is not considered a major contributing factor to the development of type 1 diabetes mellitus (T1DM), as it is an autoimmune disorder. However, many individuals with T1DM are overweight or obese, reflecting the broader trend of increasing obesity within the general population. The risk of developing non-alcoholic fatty liver disease (NAFLD) tends to rise with the degree of obesity, as measured by body mass index (BMI), in people with T1DM. While poorly controlled T1DM can lead to disturbances in glucose and lipid metabolism, it is not fully established whether individuals with T1DM have a higher prevalence of NAFLD compared to non-diabetic individuals with similar obesity levels.

In the context of liver abnormalities in T1DM, it is essential to distinguish glycogen hepatopathy from NAFLD. The Mauriac syndrome, which involves excessive glycogen deposition in the liver and hepatomegaly, was initially described shortly after insulin therapy became widely available for the treatment of T1DM. This syndrome is characterized by hyperlipidemia, growth failure, delayed sexual maturation, a Cushingoid appearance, and hepatic glycogen accumulation, and is believed to result from poor metabolic control during childhood diabetes.

Even in the absence of the full spectrum of Mauriac syndrome, glycogen hepatopathy is becoming more commonly recognized in individuals with poorly managed T1DM. This condition manifests in both children and adults, marked by an excess of glycogen in hepatocytes, leading to hepatomegaly, mildly elevated transaminase levels, and sometimes symptoms such as nausea, vomiting, and abdominal discomfort. The underlying pathogenic mechanism appears to involve high blood glucose levels and insulin together, which reduce glycogen breakdown (glycogenolysis) while simultaneously enhancing glycogen synthesis in the liver.

A definitive diagnosis of glycogen hepatopathy requires liver biopsy, as ultrasound imaging cannot reliably differentiate it from NAFLD. Importantly, when blood glucose control improves, the symptoms of glycogen hepatopathy—such as hepatomegaly and elevated transaminases—usually resolve relatively quickly, in contrast to the more persistent nature of NAFLD. Additionally, while NAFLD can be associated with long-term liver damage and progression to more severe liver conditions, glycogen hepatopathy tends to improve upon improved diabetes management (Targher et al.,2022).

Prevention and Treatment of Fatty Liver Disease in Diabetes

Obesity and Weight Management

The treatment and prevention strategies for non-alcoholic fatty liver disease (NAFLD) in individuals with type 2 diabetes closely mirror those used for the general population. One of the most effective ways to prevent NAFLD is achieving and maintaining a healthy weight. Additionally, weight loss remains the most effective approach to reversing the progression of existing NAFLD in overweight or obese individuals.

A safe and effective way to manage and treat NAFLD is through lifestyle changes that promote weight reduction. For obese individuals, a 7-10% reduction in body weight is often recommended, which can be achieved through a combination of a balanced, calorie-restricted diet and increased physical activity. Diets high in meat and sugary beverages have been linked to a higher risk of NAFLD, and there is growing concern that a high-fructose diet may further increase this risk. Weight loss has been shown to improve insulin levels, liver function, and overall quality of life for individuals with NAFLD. A safe weight loss rate for those with NAFLD is up to 1 kilogram per week, as rapid weight reduction can exacerbate liver disease, as evidenced by a study of 41 patients over 8 months (Hazlehurst et al.,2016).

For individuals at risk of NAFLD, alcohol consumption should also be limited or avoided. Alcohol abuse is known to worsen liver disease in those with NAFLD, and its elimination can help reduce liver damage.

In the last few years, the U.S. Food and Drug Administration (FDA) has approved three medications for obesity treatment, which may also be considered for individuals struggling to lose weight through lifestyle changes. These include a combination of lorcaserin and phentermine/topiramate, naltrexone and bupropion, and lorcaserin alone. However, there is limited evidence regarding the impact of these medications specifically on NAFLD (Hazlehurst et al.,2016).

Bariatric Surgery

For patients who have not succeeded in losing weight through diet and lifestyle modifications, bariatric surgery may be an option. A meta-analysis of 15 trials indicated significant improvements in liver function after bariatric surgery, with 65.5% of patients experiencing reduced fibrosis and 91% showing improvement in steatosis. Additionally, NASH (non-alcoholic steatohepatitis) was resolved in about 70% of cases. Most of these studies focused on the Roux-en-Y gastric bypass procedure, which was effective in promoting significant weight loss and improving liver health.The improvement in liver function and histology after gastric bypass surgery may be mediated by several molecular mechanisms. In one study, hepatic variables such as transforming growth factor-β1, α-smooth muscle actin, and interleukin 8 were significantly improved in severely obese patients with NAFLD. These findings suggest that bariatric surgery, particularly Roux-en-Y gastric bypass, can be an effective treatment for obese individuals with NAFLD due to its substantial weight reduction benefits and positive effects on liver function ((Mavrogiannaki et al.,2013).

Pharmacological Interventions for Type 2 Diabetes and Non-Alcoholic Fatty Liver Disease

Maintaining consistently low blood glucose levels is critical in managing type 2 diabetes, as it is associated with a reduced risk of both short-term and long-term complications. However, regardless of the presence of non-alcoholic fatty liver disease (NAFLD), the primary goal in managing type 2 diabetes should always be to achieve adequate glucose control.

A Japanese study involving 39 individuals with type 2 diabetes and NAFLD found that reducing hemoglobin A1c and using insulin were both associated with improvements in hepatic fibrosis over a median period of 2.4 years between liver biopsies. Notably, the reduction in hemoglobin A1c was more

strongly linked to a decrease in hepatic fibrosis than insulin usage. However, further research is required to definitively determine whether better blood glucose control, irrespective of weight changes, can prevent or reverse NAFLD in individuals with type 2 diabetes. The effects of certain non-insulin pharmacological treatments for blood glucose management in type 2 diabetes on NAFLD remain insufficiently studied. This gap in research underscores the need for more investigation into how these medications may impact the progression or treatment of NAFLD (Leite et al.,2014).

Prospects for the future:

Patients at increased risk due to diabetes should not undergo routine screening for non-alcoholic fatty liver disease (NAFLD) unless there is clear evidence of liver disease, such as elevated liver transaminases. This approach stems from the uncertainty surrounding the most effective treatments for NAFLD and the lack of evidence-based guidelines for routine NAFLD screening. Moving forward, it will be crucial to continually assess the cost-effectiveness of screening as new data emerge regarding the impact of certain anti-diabetes medications, weight loss therapies, and other agents like statins on NAFLD. Screening for NAFLD should only be considered if there are cost-effective pharmaceutical options available with favorable adverse event profiles. This is especially important given that the progression from simple steatosis (NAFL) to non-alcoholic steatohepatitis (NASH) with inflammation and fibrosis appears to occur at a relatively low rate. However, since patients with NASH are at higher risk for advanced liver diseases, such as hepatocellular carcinoma or liver failure, screening for NASH may still prove cost-effective, even if the medications used for treatment are more expensive or have more significant side effects. Therefore, developing better noninvasive screening techniques for NASH and exploring innovative treatments after diagnosis are critical areas of focus. The high prevalence of obesity in type 2 diabetes and the role of insulin resistance in the development of both diabetes and NAFLD contribute to the increased risk of liver disease in individuals with T2DM. Preliminary evidence suggests that several pharmaceuticals used to treat type 2 diabetes may also show promise in managing NAFLD. As a result, individuals with type 2 diabetes should be a central focus of future research efforts aimed at improving NAFLD screening and treatment options.

Conclusion:

the relationship between Type 2 diabetes and NAFLD is complex and interdependent. Early diagnosis, comprehensive management strategies, and research into novel treatment options are essential to improve patient outcomes and reduce the impact of these conditions on individuals and healthcare systems globally. Through targeted interventions and improved care, the progression of these diseases can be better managed, ultimately improving the quality of life for affected individuals.

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