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Review Article

A CORRELATION BETWEEN NAFLD AND T2DM**¹Prof. Venkatesh J.S, ²Dr.Santhosh Uttangi, ³Joshina Johnson, ⁴Juby Johnson, ⁵Kundan Singh, ⁶Jomin Varghese**¹Professor and HOD, M. Pharma, Pharmacy Practice, SCS College of Pharmacy, Harapanahalli, Karnataka, India, 583131² Assistant Professor, Pharm D SCS College of Pharmacy, Harapanahalli, Karnataka, India, 583131³Pharm D intern, SCS College of Pharmacy, Harapanahalli, Karnataka,India, 583131⁴Pharm D intern, SCS College of Pharmacy, Harapanahalli, Karnataka, India,583131⁵Pharm D intern, SCS College of Pharmacy, Harapanahalli, Karnataka, India,583131⁶ Pharm D intern, SCS College of Pharmacy, Harapanahalli, Karnataka,India, 583131**Abstract:**

Lifestyle changes play a crucial role in managing NAFLD/NASH. Balancing physical activity with a healthy diet is key, as sedentary behaviour and poor dietary patterns are linked to insulin resistance, T2DM, and NAFLD development. The intricacies of this relationship involve both the type of diet and the quantity of food consumed. Losing weight is seen to be the most crucial aspect of managing NAFLD. It has been demonstrated that a weight-neutral Mediterranean diet improves insulin sensitivity and lowers liver steatosis. Vitamin E may show some benefits in patients with biopsy-proven NASH (Nonalcoholic Steatohepatitis) without diabetes, but individual responses can vary. Some antihyperglycemic medications used for treating type 2 diabetes have shown benefits in reducing liver fat and improving liver histology.

Early recognition of non-alcoholic fatty liver disease (NAFLD) and its extrahepatic manifestations is crucial for clinicians. Timely identification can be key in managing patients, especially in the context of preventing and addressing type 2 diabetes mellitus (T2DM).

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INTRODUCTION:

Indeed, the rise in diabetes prevalence, especially Type 2 diabetes, is closely linked to factors like overweight and sedentary lifestyles. The impact on the liver's role in energy homeostasis further complicates the situation, emphasizing the need for lifestyle interventions and awareness campaigns to address this global health concern (1). Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of conditions characterized histologically by macrovesicular hepatic steatosis and occurs in those who do not consume alcohol in amounts generally considered to be harmful to the liver. (2). Nonalcoholic fatty liver disease (NAFLD) encompasses two main conditions: (1) nonalcoholic fatty liver (NAFL) marked by steatosis alone, and (2) nonalcoholic steatohepatitis (NASH) characterized by steatosis, inflammation, and hepatocyte ballooning, potentially progressing to liver fibrosis (LF), cirrhosis, hepatocellular carcinoma (HCC), and necessitating liver transplantation in severe cases. Regular monitoring and lifestyle interventions are crucial for managing NAFLD (3). Nonalcoholic fatty liver disease (NAFLD) is indeed a significant health concern, linked to factors such as metabolic syndrome, obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia. Addressing these underlying issues is crucial for managing and preventing NAFLD (4-6). Recently, it has been recognized that NAFLD represents an important burden of disease for patients with type-2 diabetes mellitus. Individuals with type-2 diabetes not only have a high prevalence of NAFLD, up to 70% (7) but also seem to have an increased severity of disease. (8-10) It has been reported that fatty liver influences the severity of hepatic insulin resistance in type-2 diabetes mellitus. (11) The hepatic fat content predicts the amount of daily insulin needed to maintain adequate glycemic control. (12) The prevalence of NAFLD in type 2 diabetes mellitus ranges from 34 - 94% around the Globe (13).

Studies revealed that among NASH patients, 30–40% have advanced liver fibrosis at the time of presentation, while 10–15% have established cirrhosis (14). The rapidly growing incidence of NAFLD is causing an increase in non-communicable diseases (NCDs), such as cardiovascular disease, cancer, diabetes, and obesity (15). The evolving understanding of the relationship between NAFLD and T2DM underscores a bidirectional and mutual association, emphasizing the need for clinicians to screen, diagnose, and treat T2DM in patients with NAFLD to mitigate both short- and long-term complications. This review aims to synthesise current literature on the incidence of T2DM in NAFLD patients and the prevalence of NAFLD in those with

T2DM, focusing on recent key studies.

PREVALENCE OF NAFLD IN PATIENTS WITH T2DM

The prevalence of NAFLD (Non-Alcoholic Fatty Liver Disease) varies based on diagnostic methods and obesity levels. It's commonly associated with T2DM, with estimates suggesting higher prevalence in those with diabetes/glucose intolerance compared to the general population. (16,17) T2DM patients have high prevalences of the more severe stages of NAFLD, 78% for NASH and 34–60% for advanced fibrosis. (18) Type-2 diabetic patients have a high prevalence of ultrasonographic NAFLD and its presence is associated with obesity, mainly abdominal, hypertriglyceridemia and high-normal ALT levels. Non-alcoholic fatty liver disease in diabetic patients may develop and progress independent of the diabetes progression itself. (19) When we discuss about the findings related to magnetic resonance spectroscopy (MRS) and its association with hepatic triglycerides (TGs) in individuals with Type 2 Diabetes Mellitus (T2DM). Additionally, the connection between prediabetes, T2DM, and Non-Alcoholic Fatty Liver Disease (NAFLD) severity, progression, fibrosis, and hepatocellular carcinoma (HCC) development is highlighted. (20,21)

PREVALENCE OF T2DM IN NAFLD PATIENTS

It's true that limited studies have focused on assessing the prevalence of prediabetes/diabetes in NAFLD patients. Further research could provide a more comprehensive understanding of the relationship between these conditions. Among 118 patients with non-alcoholic fatty liver disease (NAFLD) in a San Antonio, Texas research, 85% had prediabetes and 30% had type 2 diabetes (T2DM); the controls did not know they had impaired glucose metabolism.

At the level of muscle, liver, and adipose tissue, insulin sensitivity was impaired in patients with NAFLD to a similar degree, whether they had prediabetes or T2DM. Only adipose tissue IR worsened in T2DM and correlated with the severity of muscle and hepatic IR and steatosis by MRS. (22) The rising prevalence of Type 2 Diabetes Mellitus (T2DM) in Non-Alcoholic Fatty Liver Disease (NAFLD) is concerning, and it's important for clinicians to stay informed about this trend for effective patient management. Regular updates on research and continuing education can help bridge awareness gaps in clinical practice.

PATHOGENESIS WHICH RELATES T2DM AND NAFLD

The link between non-alcoholic fatty liver disease (NAFLD) and increased risk of type 2 diabetes mellitus (T2DM) often involves factors from expanded visceral adipose tissue, including free fatty acids, hormones, and proinflammatory adipocytokines. These elements contribute to atherogenesis and the development of insulin resistance, forming a complex interplay in the progression of these conditions. (23,24) Both T2DM and NAFLD patients typically experience an increase in circulating insulin levels in response to peripheral tissue demands to overcome insulin resistance. Elevated insulin levels ought to prevent fat tissue lysis; yet, in these individuals, due to the existence of fat tissue insulin resistance, this doesn't happen. (25,26) Advanced forms of non-alcoholic fatty liver disease (NAFLD) can contribute to increased insulin resistance, creating a cycle that involves elevated free fatty acid influx into the liver. Insulin resistance in adipose tissue heightens the release of free fatty acids (FFAs) and inflammatory cytokines. This contributes to metabolic dysfunction and can lead to various health issues. (27)

The gut and liver have a close relationship in metabolism. The liver receives nutrients from the gut via the portal vein, playing a key role in processing and regulating substances absorbed by the digestive system. This connection is crucial for maintaining metabolic balance and overall health. The interplay between proteolytic and saccharolytic fermentation metabolites can impact gut barrier function and the immune system, influencing liver metabolism and fat accumulation. This connection is crucial in understanding the progression of NAFLD (Non-Alcoholic Fatty Liver Disease) and its link to insulin resistance and type 2 diabetes, particularly in individuals with obesity. (28)

A range of proatherogenic, proinflammatory, and diabetogenic mediators may be released by the livers of NAFLD patients, all of which play significant roles in the development of type 2 diabetes. (29,30) Certainly, polymorphisms in genes like APOB, APOC3, and MTP can contribute to the risk of Type 2 Diabetes Mellitus (T2DM) and Non-Alcoholic Fatty Liver Disease (NAFLD) due to their involvement in lipid metabolism. These variations may influence lipid levels and metabolic processes, impacting susceptibility to these conditions. (31) Environmental factors play a significant role in the development of non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM). High fat diet, sedentary lifestyle, and exposure to certain chemicals can contribute to the onset and progression of these conditions. A healthy lifestyle

can help migrate these risk factors (32,33,34)

MANAGEMENT

lifestyle changes play a crucial role in managing NAFLD/NASH. Balancing physical activity with a healthy diet is key, as sedentary behaviour and poor dietary patterns are linked to insulin resistance, T2DM, and NAFLD development. The intricacies of this relationship involve both the type of diet and the quantity of food consumed (35,36). Losing weight is seen to be the most crucial aspect of managing NAFLD. It has been demonstrated that a weight-neutral Mediterranean diet improves insulin sensitivity and lowers liver steatosis (37) Vitamin E may show some benefits in patients with biopsy-proven NASH (Nonalcoholic Steatohepatitis) without diabetes, but individual responses can vary (38,39). Some antihyperglycemic medications used for treating type 2 diabetes have shown benefits in reducing liver fat and improving liver histology. These effects can contribute to better overall metabolic health in individuals with diabetes. (37) Steatohepatitis has improved with Thiazolidinediones, like pioglitazone and rosiglitazone, they have been considered in the context of liver conditions, particularly non-alcoholic fatty liver disease (NAFLD).

The potential benefits include improved insulin sensitivity and liver function. However, their use should be carefully assessed based on individual health considerations (40-44)

CONCLUSION:

For individuals with type 2 diabetes and elevated liver enzymes to be assessed for nonalcoholic steatohepatitis (NASH) and liver fibrosis, as per the 2019 ADA Standards of Care guidelines. Our review discusses the prevalence, common pathophysiology, and management. Early recognition of non-alcoholic fatty liver disease (NAFLD) and its extrahepatic manifestations is crucial for clinicians. Timely identification can be key in managing patients, especially in the context of preventing and addressing type 2 diabetes mellitus (T2DM).

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