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Review Article

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NON-ALCOHOLIC FATTY LIVER DISEASE AND DIABETES MELLITUSA TALE OF TWO SINS

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1. INTRODUCTION

Diabetes mellitus (DM) is a major global health problem with an increasing incidence and prevalence, particularly in developing and newly industrialized countries.[1] In 2014, 347 million people worldwide had diabetes and World Health Organization (WHO) projects that by the end of 2030, diabetes will be the seventh leading cause of death.[2] As per the International Diabetes Federation (IDF), in 2015, 69.1 million cases of diabetes have been reported in India.[3] A decade back the major focus of health agencies was on AIDS and tuberculosis, which has shifted to diabetes because of the increasing prevalence of diabetes and other non-communicable diseases world wide including the thrust for research. As the people are living longer and population is aging, the coexistence of NCDs are a real problem to focus that include diabetes and liver diseases. Increasing evidence now suggests that DM is associated with multiple liver diseases, an important one being, non-alcoholic fatty liver disease (NAFLD).[1]

NAFLD is defined as a group of liver disorders predominantly (though not exclusively) characterized by evidence of steatosis (fatty changes) on imaging or histology with or without ballooning degeneration and fibrosis in the absence of secondary causes of hepatic fat accumulation such as significant alcohol consumption, certain drugs or hereditary disorders. NAFLD is a spectrum ithat histologically include simple steatosis (non-alcoholic fatty liver, NAFL), steatohepatitis (non-alcoholic steato-hepatitis, NASH) and advanced fibrosis, which may evolve into cirrhosis and hepatocellular carcinoma. NAFLD is commonly associated with metabolic risk factors including obesity, diabetes mellitus and dyslipidemia as observed in insulin-resistant (IR) states.

NAFLD and diabetes display a bi-directional relationship and the concept of NAFLD being the "hepatic manifestation of the metabolic syndrome" is now outdated**.** Studies have shown that the prevalence of NAFLD is very high in patients with T2DM and in fact NAFLD is considered a risk factor for future development of T2DM.[5,6] This seems to be a classic chicken and egg story with no clear evidence of which comes first**.** However, it is increasingly becoming clear that both the diseases coexist together, have a common pathogenesis resulting in one disease increasing the severity of the other. An additional area of concern is the association between NAFLD and cardiovascular (CV) complications.[7] NAFLD can accelerate the development of dyslipidemia and affect cardiac structure and function. Patients with NAFLD have reduced life expectancy primarily due to increased cardiovascular complications and also progression to cirrhosis and hepatocellular carcinoma.[4]

This review eludes the scale of coexistence of NAFLD and diabetes, their common etiopathogenesis, and the treatment implications.

1. Epidemiology and prevalence

The presence of T2DM and varying diagnostic modalities impacts the prevalence and epidemiological features associated with NAFLD.[4] The reported prevalence of NAFLD across the world varies from 20–30% in Europe, 9 -30% in Japan and 5-24% in China. It affects 36.8% of Mediterraneans and 21.5% of Iranians with lowest figures reported from Singapore (5%).[8]

NAFLD diagnosed by ultrasonography in the general population was observed in 25%-30% and 2-4 times more common in men as compared to women. In contrast, in patients with T2DM, NAFLD is three times more common in patients with diabetes than non-diabetics with no gender differences.[4]

2. The interplay of pathogenesis between NAFLD and diabetes

The prevalence of diabetes in cirrhosis is 20-30% and more than two-third have glucose intolerance. There is a

substantial body of evidence indicating that the liver plays a pathogenic role in T2DM development and that the close interplay between T2DM and liver disease may result in a "vicious circle" eventually leading to an excess risk of liver-related and cardiovascular complications.[4]

Liver is the predominant site of insulin action and also insulin metabolism with 80% of gluconeogenesis and glucose uptake occurring in hepatocytes. NAFLD is associated with impaired glucose uptake that produces sustained hyperglycemia. (Reference: Nielsen et al. Am J Physiol Gastrointest Liver Physiol 288:G1135–G1143) It also contributes to both hepatic as well as systemic insulin resistance mediated by the release of multiple pro-inflammatory cytokines (IL-6, TNF-alpha), diabetogenic hepatokines (fetuin –A) and reactive oxygen species. If left uncorrected, insulin resistance will eventually lead to progressive pancreatic beta cell failure and diabetes in predisposed individuals.

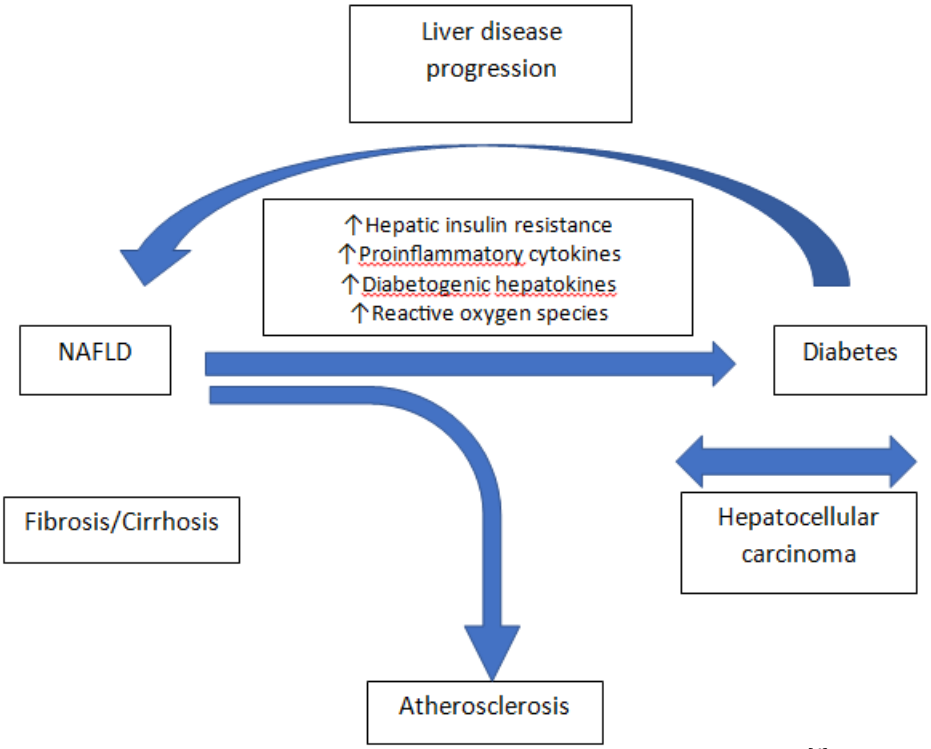

Figure 1: Interplay of pathogenesis between DM and NAFLD.[4]

3. Diagnosing NAFLD in T2DM

The spectrum of NAFLD is similar in diabetic and non-diabetic individuals, and it develops from simple steatosis to advanced fibrosis, cirrhosis and hepatocellular carcinoma.[5] NAFLD is a diagnosis of exclusion after other known etiologies of chronic liver diseases like drug-related steatosis, viruses and alcohol. Most patients with non-cirrhotic NAFLD are asymptomatic in the beginning with incidental detection of raised liver enzymes or fatty liver on ultrasound or during work-up for dyspeptic symptoms, malaise or fatigability.[9]

NAFLD is diagnosed by serology, imaging and histopathology. Liver enzymes may be elevated, but normal aminotransferases do not exclude the diagnosis of NAFLD in T2DM individuals. Ultrasound is a reliable imaging technique that helps to confirm the presence of fatty liver with a sensitivity of 60%-94% and a specificity of 66%-95% for detecting steatosis and is used to grade the disease severity. Its main limitation is that it is operator dependent and cannot detect mild steatosis (5%-30%). However, the gold standard for the diagnosis of NAFLD is liver biopsy. However, it is sparingly used in clinical practice outside of research settings due to its invasive nature along with the risk of complications.[5,9]

The other modalities that have been used for diagnosis include Doppler fluxometry, ultrasonographic fatty liver indicator (USFLI), computed tomography, magnetic resonance (MR) imaging, MR spectroscopy. Another novel method to diagnose and quantify steatosis is the controlled attenuated parameter (CAP). CAP is a software that can be used simultaneously with liver transient elastography available by Fibroscan.[9]

Severity of NAFLD can be assessed either non-invasively by using various biomarkers used either singly or in combination, or with the help of imaging and liver biopsy. Since serum biomarkers are not available routinely, are costly, and lack standardization, the severity assessment is usually based on imaging and liver biopsy. Patients with NAFLD should be further evaluated for the presence of hypertension, dyslipidemia and IGT,. In addition, all patients should also be

screened for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (anti-HCV). Further work-up including autoimmune markers, TTg (tissue transglutaminase) IgA for celiac disease, serum iron profile, and serum ceruloplasmin is required in few patients based on clinical suspicion.[9]

4. Treatment of NAFLD in T2DM

There are various therapeutic options available ranging from non-pharmacological options like weight loss, physical exercise to pharmacological options including various drugs like ursodeoxycholic acid (UDCA), vitamin E, pentoxifylline etc.[9] However, till date there is no particular drug approved for treatment of NAFLD in patients with T2DM.[13]

4.1 Non- pharmacological options

4.1.1 Lifestyle modification/weight reduction

All patients with NAFLD irrespective of their body weight should be advised lifestyle modifications in the form of regular exercise and those with obesity are advised weight reduction of atleast 5%.[9] The efficacy of lifestyle modification along with UDCA were assessed by Duseja et al, in 100 patients with NAFLD. 74% patients achieved a biochemical response after 6 months.[9]

In another study reported by Promrat et al, patients were randomly assigned to receive either diet, exercise, and behavioral strategies or to a control group (2:1 ratio). Liver biopsies were performed pre-and post study with a follow up period of 2 years. The lifestyle intervention group had significant improvements in histology at 48 weeks, with 67% improving their NAFLD activity score to ≤2. There was improvement in hepatic steatosis, lobular inflammation, parenchymal inflammation, and ballooning injury in the interventional group; but results showed no improvement in fibrosis in either group. A statistically siginificant decerase in weight and liver enzymes were observed in the intervention arm.[14]

Jin et al, reported a study in which 120 patients were encouraged to lose 5% of their body weight by diet and exercise. Over an average of 10 weeks, 92 patients lost weight (on average 3 kg), 15 gained weight and the remainder maintained their weight. One hundred and three liver biopsies showed improvement, 82 of these were in those who had lost weight. Further analysis also showed that these improvements were greatest in those who were younger and had the largest decrease in BMI and cholesterol.[14]

4.2 Pharmacological interventions

4.2.1 Biguanide

Insulin sensitizing drugs like metformin have been evaluated for their effect on NAFLD both in diabetic and non-diabetic population as insulin resistance is sine-quo-non-for NAFLD,. Metformin improves insulin sensitivity and also regulates lipid metabolism therefore could have a positive impact on both NAFLD and T2DM.[15]

A meta-analysis to evaluate metformin efficacy given over 4 to 12 months in NAFLD patients involving 417 participants from nine studies (Table 2)[15] revealed a significant improvements were observed in aminotransferases [alanine aminotransferase (ALT) (mean difference (MD), -8.12 U/l; P=0.03), aspartate aminotransferase (AST) (MD, -4.52 U/l; P=0.04)], insulin sensitivity [homeostasis model assessment of IR (HOMA‑IR) (MD, -0.61; P=0.005)] and body mass index (BMI) (MD, -0.82 kg/m^2; P=0.04). Six of these studies were on NAFLD and three on NASH. However, metformin did not improve the condition of NAFLD or NASH in patients with the histological spectrum of steatosis, inflammation, hepatocellular ballooning and fibrosis.[15]

Table 2: Details of included studies.

Study author and year	Number of patients	Metformin dose (g/day)	Comparator	Duration (months)
Bugianesi et al, 2005	82[a]	2	Diet	12
Akyüz et al, 2007	36[a]	0.85	Diet + exercise	12
Garinis et al, 2010	50	1	Diet (1300)	6
Haukeland et al. 2009	48	2.5-3	Placebo	6
Idilman et al, 2008	49[a]	1.7	Diet + exercise	12
Nar and Gedik, 2009	34	1.7	Diet + exercise	6
Shields et al, 2009	19	0.5-1	Placebo+ Diet + exercise	12
Sofer et al, 2011	63	0.85-1.7	Placebo	4
Uygun et al, 2004	36	1.7	Diet (1600-1800)	6

[a]Patients in trial arms of interest only.

Data from India showed a similar results where the biochemical response to metformin 500mg tid for 6 months in NAFLD patients was studied. There was a significant improvement in ALT in all patients. with ALT normalization in 56% of the patients.[16]

However, currently there is uncertainty regarding the role of metformin in the treatment of NAFLD and is not approved for this indication.

4.2.2 Sulphonylureas (SUs)

Sulphonylureas (SU) act upon the sulphonylurea receptor-1 subunit of the inward-rectifying potassium channel of the β-cells of the pancreas, causing the channel to close, which leads to cellular depolarisation,

resulting in the opening of voltage gated Ca2 + channels and consequent insulin release. There are no prospective data examining their use in NAFLD with co-existent diabetes. Some retrospective data exist suggesting that the prevalence of fibrosis in diabetic patients with NAFLD is higher in individuals treated with SUs. However, no adjustment was made for glycemic control or diabetes duration.[17]

In four randomized, double-blind studies with duration of one year, liver enzymes were analyzed in over 3700 T2DM patients after treatment with sulphonylurea (gliclazide) and other antidiabetic agents. Treatment with gliclazide was associated with a modest increase in liver enzymes between 3 to 13% in these patients.[18]

Knowing the fact that SUs are associated with a gain in weight and is metabolised extensively by the liver, it is unlikely to be an attractive treatment option for diabetic patients with NAFLD.[17]

4.2.3 Thiazolidinediones (TZDs)

TZDs are second line oral agents for glucose control in T2DM that decrease insulin resistance.[19] In comparison with metformin, both TZDs (rosiglitazone and pioglitazone) increase peripheral glucose disposal and improve whole-body insulin sensitivity during hyperinsulinemic euglycemic clamp in patients with T2DM. In addition to the favorable effects of TZDs on glycemic control, TZDs decrease fasting FFA concentration and hepatic fat accumulation.[20] Several clinical trials have shown that TZDs treatment prevents subsequent events, such as an increase in oxidative stress, lipid peroxidation and proinflammatory cytokines that contribute to the progression of NAFLD to NASH.[20]

In a proof of concept study, 55 patients with impaired glucose tolerance and liver biopsy–confirmed NASH were assigned to 6 months of treatment with a hypocaloric diet (a reduction of 500 kcal per day in relation to the calculated daily intake required to maintain body weight) plus pioglitazone (45 mg daily) or a hypocaloric diet plus placebo. Diet plus pioglitazone, as compared with diet plus placebo, significantly improved glycemic control and glucose tolerance (P<0.001), normalized liver aminotransferase levels (Figure 2) and increased hepatic insulin sensitivity (by 48% vs. 14%, P = 0.008). Administration of pioglitazone, was associated with improvement in histologic findings with regard to steatosis (P = 0.003), ballooning necrosis (P = 0.02), and inflammation (P = 0.008). Subjects in the pioglitazone group had a greater reduction in necroinflammation (85% vs. 38%, P = 0.001), but the reduction in fibrosis did not differ significantly from that in the placebo group (P = 0.08).[21]

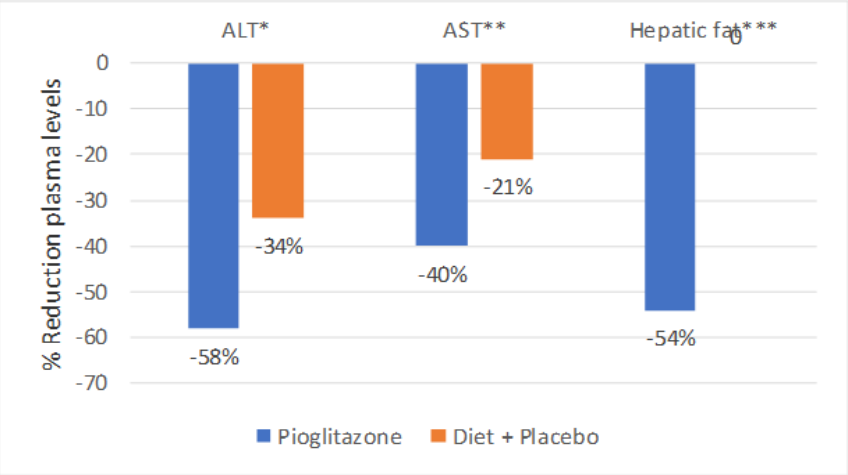

Figure 2: Effect of pioglitazone in T2DM patients with NAFLD after six months of treatment.
* P<0.001, ** P=0.04, *** P<0.001, AST- aspartate aminotransferase, ALT- alanine aminotransferase

A novel TZD, lobeglitazone was recently investigated in drug-naïve or metformin-treated T2D patients with NAFLD in a multicenter, open-label, exploratory clinical trial. Lobeglitazone once daily with 0.5 mg for 24 weeks reduced intrahepatic fat content, as assessed by transient liver elastography, and improved glycemic, liver, and lipid profiles in these patients. However, further randomized controlled trials using liver histology as an end point are necessary to evaluate the efficacy of lobeglitazone for NAFLD treatment.[22]

TZDs are linked with safety concern especially regarding an association between increased cardiovascular risk with rosiglitazone and its use has been restricted.[2] In certain countries, drugs from this class are banned.[23] Furthermore, while treating NAFLD with pioglitazone, weight-gain, edema, and worsening of pre-existing congestive heart failure should be kept in mind as potential adverse effects. Further studies will be needed to determine the long-term safety profile of TZDs.[9]

4.2.4 Sodium–glucose cotransporter 2 inhibitors (SGLT2i)

SGLT2 inhibitors are oral antidiabetic drugs that promote the urinary excretion of glucose by blocking its reabsorption in renal proximal tubules.[24] Control of hyperglycemia by inhibition of proximal tubule glucose reabsorption is actively being investigated as a potential approach for NAFLD in patients with T2DM. A reduction in intrahepatic triacylglycerol accumulation would be expected from a decrease in substrate supply to the liver by the combined effects of normoglycemia plus modest weight loss and enhanced insulin sensitivity.[7]

In patients with diabetes, levels of plasma aminotransferases decrease during treatment with SGLT2i. Recently, pooled data from four 26-week placebo-controlled studies of canagliflozin (n = 2313) and two 52 week active-controlled studies of canagliflozin vs sitagliptin (n =1488) found significant reductions in plasma ALT with canagliflozin 300 mg compared with placebo or sitagliptin. Reductions in ALT, AST, alkaline phosphatase and gamma-glutamyl transferase, and increases in bilirubin were seen with canagliflozin 100 and 300mg versus placebo (nominal P<0.001 for ALT, AST and gamma-glutamyl transferase [both doses]; P<0.001 for alkaline phosphatase and P=0.015 for bilirubin [canagliflozin 300mg only]) at week 26 and with canagliflozin 300mg versus sitagliptin 100mg (nominal P<0.001 for ALT, AST, gamma-glutamyl transferase and bilirubin, and P<0.01 for alkaline phosphatase) at week 52.[25] Changes in AST/ALT were fully explained by the reduction in HbA1c and body weight.[7]

Future studies are needed to define the role of SGLT2 inhibitors in the management of patients with NAFLD and T2DM, but seems an attractive option because of weight reducing effect.[7]

4.2.5 Glucagon-like peptide-1 (GLP-1) analogs

The biological activities of GLP-1 agonists include glucose-dependent insulin secretion, suppression of postprandial glucagon to reduce hepatic glucose release and slowing of gastric emptying.[2] In addition to glycemic control, GLP-1 analogues are an effective treatment for obesity including in non-diabetic individuals and have been granted a license for use as weight loss therapy by both Food and Drug Administration and European Medicines Agency.[17] There is also evidence that GLP-1 agonists have beneficial effects on the liver, including suppression of hepatic lipogenesis and stimulation of lipid oxidation.[2]

The presence of GLP-1 receptors on human hepatocytes is controversial with conflicting data. Whilst the underpinning mechanisms remain to be fully elucidated in humans, the GLP-1 agonist liraglutide in a dose of 1.8 mg has been shown to be safe and well tolerated in a meta analysis of six 26-week studies conducted in patients with type 2 diabetes. The use of liraglutide was associated with a reduction in ALT.[17,26] A meta-analysis of two GLP-1 agonists, liraglutide and exenatide, in populations with and without diabetes, was conducted including data on liver enzyme tests from 12 of the 25 trials. The dose of liraglutide given in most trials was 1.2 or 1.8 mg/day; one trial of obese individuals without diabetes also used doses of 2.4 and 3 mg/day. The doses of exenatide used were 10 to 20 µg/day or 2 mg/week. It was found that after atleast 20 weeks of treatment, ALT concentrations decreased with liraglutide (–2.2 U/L, –3.6 to –0.9) but not with exenatide (1.1 U/L, –0.6 to 2.8).[2,27]

Liraglutide has been shown to be an effective treatment for those with NASH, both with and without diabetes in a placebo controlled study with improvement in liver biopsy at 52 weeks as the primary outcome. Furthermore, in a 12 week study incorporating hyperinsulinemic–euglycemic clamps, liraglutide 1.8 mg has been shown to improve hepatic and adipose insulin sensitivity. Contrary to this data, a 12-week intervention with liraglutide did not improve liver fat on magnetic resonance spectroscop.[17,28]

The Liraglutide Effect and Action in Diabetes (LEAD) program assessed the efficacy and safety of liraglutide therapy on liver parameters in comparison with placebo controls in a meta-analysis performed using data from six 26-wk, phase-III and randomized controlled trials in patients with T2DM. In this program, 2241 (50.8%) patients had an abnormal elevation of plasma ALT levels at baseline. Liraglutide dose-dependently reduced the ALT levels in these patients, with similar adverse effects between the liraglutide and control groups. Additionally, in a sub-study of LEAD-2 where hepatic steatosis was measured by computerized tomography scan, once-daily subcutaneous injection of liraglutide (1.8 mg) showed a trend towards improving hepatic steatosis compared with placebo (liver-to-spleen attenuation ratio: 0.10 vs 0.00; P= 0.07). However, this difference became smaller after adjusting for reduction in body weight and HbA1c.[29]

Similarly, the effects of exenatide on blood glucose, body weight and hepatic enzymes in 117 patients with T2DM and concomitant NAFLD was evaluated. Patients were treated with exenatide or metformin, for 12 weeks. All the patients underwent lifestyle interventions. In Group A, exenatide injection was administrated from week 1 to week 4 at 5 µg (bid), and from week 5 to week 12 at 10 µg (bid) in patients (n = 49) and in Group B (n = 68), metformin was initially administered at 0.5 g (bid). The dose of metformin was adjusted to a maximum of 2.0 g/d on the basis of FPG and 2-h PPG. After 12 weeks of treatment, there were no marked differences in HbA1c, FPG, homeostatic model assessment- IR (HOMA-IR), triglycerides, high-density lipoproteins cholesterol (HDL-C), low density lipoproteins cholesterol (LDL-C) between two groups. However, body weight (76.09 ± 9.85 vs. 77.22 ± 10.15, P = 0.02), body mass index (BMI) (25.87 ± 1.48 vs. 26.91 ± 1.79, P = 0.02), waist-to-hip ratio (WHR) (0.95 ± 0.05 vs. 0.96 ± 0.04, P = 0.01, AST/ALT (0.81 ± 0.17 vs. 0.69 ± 0.15, P = 0.00), high-sensitivity C-reactive protein (hs—CRP)

(2.18 ± 0.34 vs. 2.69 ± 0.53, P = 0.01), and 2-h PPG (10.31 ± 3.17 vs. 12.05 ± 4.03, P = 0.036) were markedly reduced, and adiponectin increased dramatically in the exenatide group when compared with the metformin group. The ALT, AST and γ-GT reductions are represented in figure 3. However, liver histology was not conducted in this study.[30]

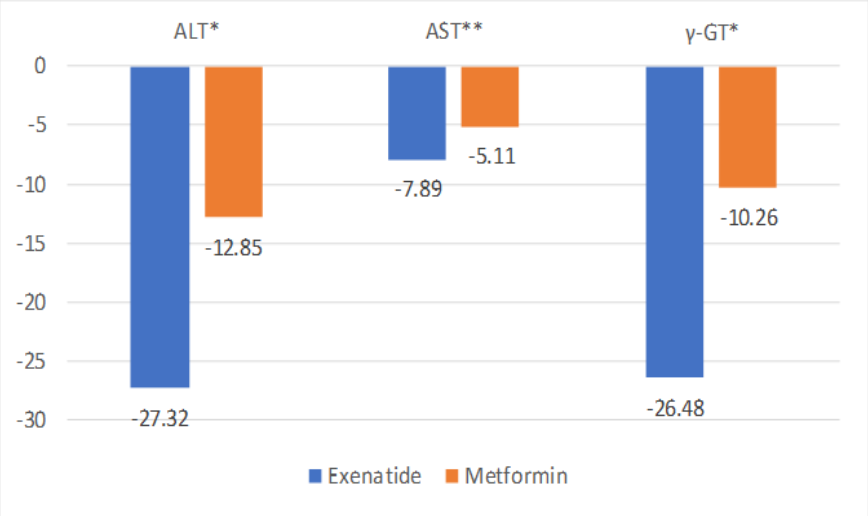

Figure 3: Effect of Exenatide in T2DM patients with concomitant NAFLD after 12 weeks of treatment

* P ≤ 0.01, ** P ≤ 0.05, AST- aspartate aminotransferase, ALT- alanine aminotransferase, γ-GT- serum gamma glutamyl transferase.

GLP-1 may be an effective option for the treatment of NAFLD amongst patients with diabetes, however, future studies, of long-term treatment with GLP-1 and a large sample size are required to confirm their effects on T2DM patients with NAFLD.

5.2. 6 Dipeptidyl peptidase-4 (DPP-4) inhibitors

Dipeptidyl peptidase 4 inhibitors may play a potential role in the treatment of NAFLD in T2DM. The reason for this hypothesis are first, DPP-4 inhibitors are known to improve insulin resistance, a key metabolic abnormality encountered by patients with NAFLD. Second, patients with nonalcoholic steatohepatitis have increased DPP-4 activity, which has been found to correlate positively with the histopathologic grade and degree of liver steatosis. Finally, data from experimental studies suggest that DPP-4 inhibitors can reduce liver inflammation and steatosis.[31]

In experimental studies, linagliptin (10 mg/kg) was found to alleviate liver steatosis and structural changes in the hepatic microvasculature and lymphatic roots in a model of NAFLD with diabetes.[32] In another experimental study, saxagliptin (daily dose of 10 mg/kg) for 8 weeks significantly reduced blood glucose and HOMA-IR, improved the liver function, lowered the liver weight, liver index (P<0.01) and slightly lowered the body weight and blood lipids (P>0.05); AST level was similar between the normal control group and saxagliptin intervention group (P>0.05).[33] In a preclinical study, treatment with teneligliptin improved hepatic steatosis and inflammation, as evaluated by the NAFLD activity score. Serum ALT and intrahepatic triglyceride levels were significantly decreased in teneligliptin-treated group (p < 0.05).[34]

The role of sitagliptin in NAFLD is controversial. In 30 NAFLD patients with T2DM, sitagliptin (50mg/body/day) for 4 months has been reported to significantly decrease not only plasma glucose and HBA1c but also AST and ALT.[7,35] However, in another recent study, 12 patients with biopsy proven NASH were randomized to sitagliptin (100 mg daily) (n = 6) or placebo (n = 6) for 24 wk. No significant reduction of liver fibrosis was seen as measured by liver biopsy with sitagliptin (mean difference between sitagliptin and placebo arms, 0.40, P = 0.82).[36]

Vildagliptin was also studied in 44 diabetic patients with mild steatosis on stable metformin therapy. After six months of intervention mean fasting plasma glucose concentration decreased over the study period with vildagliptin vs placebo by −1.0 mmol/L (P = .018), and there was a positive correlation between these decrements and liver triglyceride in the vildagliptin group at 3 months (r = 0.47; P = .02) and 6 months (r = 0.44; P = .03). Plasma alanine aminotransferase fell from 27.2 ± 2.8 to 20.3 ± 1.4 IU/L in the vildagliptin group (P = .0007), and there was a correlation between the decrements in alanine aminotransferase and liver triglyceride (r = 0.83; P < .0001). Insulin sensitivity during the euglycemic clamp was similar in each group at baseline (3.24 ± 0.30 vs 3.19 ± 0.38 mg/kg/min) and did not change (adjusted mean change of 0.26 ± 0.22 vs 0.32 ± 0.22 mg/kg/min; P = .86). The reductions in mean

fasting TGY, serum ALT and mean body weight at the end of six months are shown in figure 4.[37]

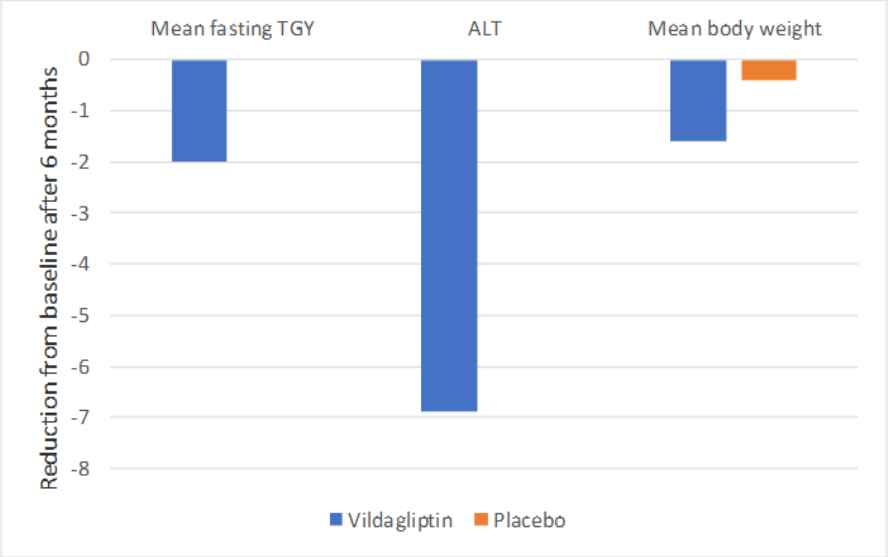

Figure 4: Effects on vildagliptin in T2DM patients with NAFLD after 6 months of treatment.

TGY- triglyceride, ALT- alanine aminotransferase.

Mashitani T, et al. reported that alogliptin may have efficacy against NAFLD progression in NAFLD patients with T2DM. In ultrasonographically diagnosed NAFLD patients, alogliptin 25 mg/day was administered for 12 months. NAFIC scores [non-alcoholic steatohepatitis (NASH), ferritin, insulin and type IV collagen 7S] markedly decreased but remained >2 points in 10 patients, indicating that NASH may have persisted in these patients.[38]

Further studies will be needed to determine whether DPP-4 inhibitors have sustained beneficial effects on NAFLD or NASH.[19]

5.2.7 Insulin therapy

Studies evaluating the effect of insulin therapy in T2DM patients with NAFLD are conflicting. In 459 T2DM patients with biopsy proven non-alcoholic fatty liver disease, the prevalence of advanced fibrosis was higher in patients treated with insulin.[39]

On the contrary in a small study of 14 patients, insulin therapy was associated with positive changes in the hepatic fat content. Liver fat content decreased from 17 ± 3 to 14 ±3% ($P < 0.05$). The change in liver fat content was significantly correlated with that in hepatic insulin sensitivity ($r = 0.56$, $P < 0.05$). Body weight increased by 3.0 ± 1.1 kg ($P < 0.05$). Of this, 83% was due to an increase in fat-free mass ($P < 0.01$).[40]

In another study, newly diagnosed T2DM patients were started with insulin in combination with metformin. The average hepatic TG content in these 19 subjects was 11.83%±7.61% (range 0.93% to 23.16%)] and correlated with BMI (r=0.567). Three months of treatment reduced hepatic steatosis by 45%, with 75% of the study subjects achieving a normal level.[41]
Further studies are required to validate the effect of insulin therapy in the management of NAFLD in diabetes patients.

5.3 Bariatric surgery

Bariatric surgery is an effective treatment for obesity and has been shown to markedly improve and even remit diabetes as well as improve histological features in NAFLD.[17] In a prospective study with 381 severely obese adults followed-up for 5 years after surgery significant improvements in steatosis, ballooning, NAS and resolution of NASH were observed, at the end of first year. After 5 years, levels of fibrosis increased, but 95.7% of patients maintained a grade 1 fibrosis. As none of the patients had advanced fibrosis at entry, the effect of bariatric surgery on liver fibrosis could not be evaluated.[2]

In a meta-analysis that evaluated the influence of bariatric surgery on liver histology in adults with NAFLD, Mummadi et al found that steatosis, NASH, and fibrosis improved or completely resolved in a significant proportion of patients. At this moment, there is still no clear evidence indicating foregut bariatric surgery as an established option to specifically treat NASH, but it may provide benefit in NAFLD treatment in otherwise eligible obese individuals.[2]

6. Future or ongoing trials

Table 3 illustrates ongoing trials in patients with NAFLD associated with diabetes.[42]

Table 3: Future or ongoing trials.

Study title	Status/phase	Intervention	Primary outcome
The Effect of Empagliflozin on NAFLD in Asian Patients With Type 2 Diabetes	Recruiting / phase 4	Empagliflozin	Change in histological Grade as evaluated with Non-alcoholic Steatohepatitis Clinical Research Network Scoring System (liver biopsy) Change in serum FGF 2 (blood test)
Effects of Ipragliflozin on Excessive Fat in Type 2 Diabetes Patients With Non-alcoholic Fatty Liver Disease Treated With Metformin and Pioglitazone	Completed/ phase 4	Ipragliflozin vs metformin with pioglitazone	changes in visceral fat area
Adding Exenatide to Insulin Therapy for Patients With Type 2 Diabetes and Non-Alcoholic Fatty Liver Disease	Completed/ phase 4	Exenatide	Hepatic steatosis assessed non-invasively by MRS
A 24 Week, Multicenter, Prospective, Open-labeled, Single-arm, Exploratory Phase 4 Clinical Trial to Evaluate the Safety and Efficacy of Lobeglitazone in Decreasing Intrahepatic Fat Contents in Type 2 Diabetes With NAFLD	Completed/ phase 4	Oral administration of Lobeglitazone	changes from baseline in controlled attenuation parameters
Antidiabetic Effects on Intrahepatic Fat	Completed/ phase 4	Liraglutide Metformin Gliclazide	Intrahepatic fat change from baseline by quantitative ultrasound
Fatty Liver Study in Patients With Type II Diabetes	Recruiting/ phase 4	DPP4 inhibitor Pioglitazone Lantus insulin	Change in hepatic lipid content from baseline visit to six month follow up visit Comparison of the hepatic lipid content measurement taken by MRI at baseline and at the 6 month follow up visit
SGLT2 Inhibitor Versus Sulfonylurea on Type 2 Diabetes With NAFLD	Recruiting/ phase 4	Tofogliflozin Glimepiride	The improvement in histologic features of NAFLD at 48 weeks

7. Diabetes and NAFLD a difficult to treat scenario

Diabetes and NAFLD are reciprocal risk factors and when they occur together, an increasing body of data demonstrates that diabetes is more difficult to manage and that NAFLD is more likely to progress. Studies examining the treatment effect of anti-diabetic medications are also extremely heterogeneous with current evidence suggesting only limited disease modifying effects across different classes of agent. Many of these studies have focused on the accumulation of intrahepatic lipid measured either with ultrasound or more recently with MRS. Whilst reducing intrahepatic lipid is important and biologically relevant, studies examining future therapies may be better targeted to more severe NAFLD, including NASH with fibrosis and cirrhosis, as it is at this end of the disease spectrum where there are significant increases in both liver and cardiovascular mortality.[17] Similarly, co-existing liver disease is an important cause of death (2.5 fold higher risk) in T2DM patients.[43] Vica versa, diabetes is believed to be the key factor that leads to the genesis and progression of NAFLD. Insulin resistance in diabetes leads to increased lipolysis in peripheral adipose tissue and increased uptake of fatty acids by hepatocytes. Further, hyperinsulinemia resulting from insulin resistance also increases glycolysis and decreases apolipoprotein B-100 production, and hence export of fatty acids as very low density lipoproteins (VLDL). The end result is an increase in fatty acids and triglycerides in the hepatocytes leading to steatosis and NAFLD.[44]

8. CONCLUSION

Patients with DM and NAFLD are prone to the most severe stages of liver diseases and to cardiovascular and liver related outcomes. The major challenge is to identify these patients by accurate non-invasive methods. Many

algorithms and new imaging methods are available but they still need to be validated in this specific population.[2] Early data suggest that some of the pharmacological agents commonly used for glycemic management and dyslipidemia in T2DM may also be efficacious in treating NAFLD.[19] The ideal treatment should be one that is effective for both NASH and diabetes, but at present is far-fetched thought and not yet available. Given the importance of cardiovascular and liver outcomes in diabetic patients, effective interventions are urgently required in order to prevent progression to these co-existing life-threatening and prevalent complications.[2]

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