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Review Article

Which treatment for type 2 diabetes associated with non-alcoholic fatty liver disease?

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ABSTRACT

Type 2 diabetes (T2DM) and nonalcoholic fatty liver disease (NAFLD) are highly prevalent in the community, and share common pathogenic mechanisms. There is also evidence that T2DM may be favored by hepatic fat accumulation; in turn the presence of T2DM is a risk factor for liver disease progression. The treatment of T2DM has considerably changed in the past few years; new drug classes, promoting glucose-lowering through mechanisms different from classical insulin-sensitizing or insulin-secreting action, have been added to continuing lifestyle intervention. Metformin and pioglitazone may be safely used in the presence of liver fat, whereas sulfonylureas and insulin itself have been associated with NAFLD progression and adverse outcome. Drugs acting on the incretin axis and on Na-glucose co-transport at renal tubular level offer new hopes for a tailored treatment able to reduce the burden of hepatic triglyceride accumulation and liver disease progression.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2DM) are frequently associated as part of the metabolic syndrome [1,2]. In patients with T2DM, the prevalence of NAFLD is around 70% by ultrasound techniques [3], whereas in the general population the presence of NAFLD predicts the development of T2DM [3]. This association is likely to result from common pathogenic mechanisms: insulin resistance with compensatory hyperinsulinemia progressing to beta-cell dysfunction and T2DM as well as to defective lipid metabolism and hepatic triglycerides accumulation [2].

In addition, both diseases contribute to increase the number and the severity of complications. NAFLD *per se* is a well-known cardiovascular risk factor [4], and has been associated with an increased prevalence of micro and macro vascular complications in both type 1 and type 2 diabetes [5,6] and with chronic kidney disease (CKD) [7]. On the other hand, diabetes is a marker of NAFLD progression to nonalcoholic steatohepatitis (NASH), fibrosis, progression to liver cirrhosis and eventually to hepatocellular carcinoma [8,9].

T2DM and NAFLD are highly prevalent in the community, and being aware of this ominous association as well as approaching this combination by an appropriate therapy might significantly improve the prognosis of both conditions, also reducing the burden on National Heath Services. Continuing lifestyle intervention aimed at weight loss by healthy diet and habitual physical activity is the mainstay of treatment in NAFLD patients who are overweight or obese, particularly in the presence of diabetes [10], but also drugs may play a role in disease progression. The pharmacological approach to T2DM has considerably changed in the past few years and it is no longer confined to metformin and sulfonylureas. A tailored therapy may be proposed among the different therapeutic options, balancing the benefits with potential risks, and taking into account the adverse effects of medications as well as the patients' health status [11]. The presence of NAFLD in a patient with diabetes might be a reason for selecting specific therapeutic options. In the present article we will review the available data on the effects of the various therapeutic approaches of NAFLD on the presence and evolution of T2DM, with particular attention to the most recent glucose-lowering drugs.

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2. Lifestyle intervention

Considering the common pathogenic mechanisms, any therapeutic approach to NAFLD and T2DM must include a continuing education on the benefits of healthy diet and habitual physical activity. Following the experience of the Diabetes Prevention Program [12] and the seminal experience showing that a similar cognitive-behavioral therapy may reduce the burden of NAFLD [13,14], a large Cuban study on 293 patients with histologically proven NASH provided evidence that weight loss, achieved through a 52-week lifestyle modification program, leads to a significant improvement in the histologic features of NASH [15]. All patients who lost ≥10% of their baseline weight experienced a significant reduction in nonalcoholic activity score; 90% had NASH resolution, and 45% showed fibrosis regression [15]. One third of cases had pre-diabetes, and another 33% had overt diabetes, and weight loss is likely to produce a significant impact also on the metabolic control of T2DM. In obese subjects undergoing "bariatric surgery", weight loss is accompanied by long-term T2DM remission in a large proportion of cases [16], which prompted to define the surgical approach as "metabolic surgery". However, similar data are achieved by weight loss induced by strict adherence to a very-low calorie diet followed by behavior therapy, also in non-recent-onset, insulin-treated T2DM [17]. These data strengthen the need for a continuing intervention to facilitate lifestyle changes in combined NAFLD-T2DM cases, as part of the treatment to reduce the burden of the metabolic syndrome [18].

3. Drug treatment

Whenever lifestyle is not sufficient to achieve a satisfactory metabolic control, pharmacologic treatment should be instituted through drugs acting at different levels (Fig. 1). They all have positive and negative effects, both on the liver and in different organs (Table 1).

3.1. Metformin

The molecular mechanisms of metformin action are complex and involve several biochemical events; in summary, metformin acts by decreasing hepatic glucose production, mainly by inhibiting gluconeogenesis [19,20]. Based on clinical trials, metformin is suggested as the first line pharmacological treatment for T2DM [21], in association with lifestyle modification. The UK Prospective Diabetes Study (UKPDS) reported that intensive glucose control with metformin decreased the risk of cardiovascular complications and death in overweight diabetic patients [22,23]. Moreover metformin was associated with less weight gain and fewer hypoglycemic episodes compared to insulin and sulfonylureas. Early studies reported a beneficial effect of metformin in NAFLD on steatosis and necroinflammation [24–26], but a specific effect of metformin on liver fat accumulation is difficult to establish given the large weight loss reported in these studies. More recent randomized controlled trials reported negative results in both children [27] and adults [28]. On this basis, both the US and the European Guidelines on NAFLD management do not support metformin use in the treatment of NAFLD [29,30]. Although randomized controlled trials (RCTs) suggested that the benefits of metformin on NAFLD are probably not greater than those expected with weight loss from diet and exercise, metformin has some potential advantages in the real life as it helps increasing weight loss, reducing insulin resistance, and possibly lowering the risk of hepatocellular carcinoma in obese patients with T2DM [31,32].

Metformin may be safely used in subjects with normal renal function. In the presence of an estimated glomerular filtration rate (eGFR) below 45 mL/min, metformin administration must be reduced, and possibly stopped whenever eGFR drops below 30. Its use needs caution in the elderly, where eGFR may decrease rapidly for complicating diseases [33].

3.2. Thiazolidinediones

Thiazolidinediones (TZDs) are a second line treatment for T2DM [21]. They modulate the transcription factor PPAR-γ and influence insulin action, glucose and lipid metabolism, inflammation and adipose tissue biology [34]. PPAR-γ agonists – namely pioglitazone – might be used with some caution considering safety concerns (weight gain, salt and water retention leading to an increased risk of congestive heart failure, altered bone metabolism and bone fractures), and the possible risk of bladder cancer [35,36], whereas it decreases the risk of other cancers and of hepatocellular carcinoma in particular [37]. TZDs remain a good pharmacologic option for patients with T2DM and NAFLD; a 6-month placebo-controlled trial of pioglitazone in biopsy-proven NASH with pre-diabetes or T2DM reported a significant improvement of hepatic steatosis and necroinflamation and a trend for reduced fibrosis [38]. Conflicting results have been reported in long-term studies on fibrosis scores [36,39], but international guidelines support the use of pioglitazone in patients with NASH with cautious recommendations for long-term use [29,30]. Of note, pioglitazone is not approved by most national agencies outside T2DM, and its use outside indication needs patients' consent.

3.3. Sulfonylureas

Few data are available on sulfonylureas and NAFLD. In a cross-sectional study of 346 T2DM subjects with biopsy-proven NAFLD (NASH, 57%; significant fibrosis, 48%), advanced liver disease was more common in subjects treated with sulfonylureas (odds ratio (OR), 2.04; 95% confidence interval (CI), 1.10–3.74). Notably, the use of statins was associated with a reduced risk of NASH and significant fibrosis [40]. A few studies suggest that insulin secretagogues (sulfonylureas) are also associated with an increased risk of hepatocellular carcinoma [31,32].

The impending risk of hypoglycemia [41] and the risk of adverse cardiovascular outcomes [42] would suggest limiting the use of sulfonylureas to very few cases [21].

3.4. Insulin

Insulin is a second or third line treatment for T2DM [21]. Being NAFLD characterized by significant insulin resistance, high doses of insulin are frequently needed, particularly in morbid obese subjects. High doses of exogenous insulin may negatively influence the evolution of NAFLD; as for insulin secretagogues (sulfonylureas), the use of insulin has been associated with a higher risk of NASH (OR, 2.24; 95% CI, 1.11–4.54) [40] and an increased risk of hepatocellular carcinoma in T2DM [31,32].

3.5. Dipeptidyl peptidase-4 (DPP-4) inhibitors

DPP-4 inhibitors activate the GLP-1 pathway by inhibiting the enzyme involved in GLP-1 degradation. DPP-4 inhibitors increase the glucose-induced biosynthesis and secretion of insulin with low risk of hypoglycemia and inhibit glucagon secretion. Health agencies have so far approved sitagliptin, vildagliptin, alogliptin, linagliptin and saxagliptin for the treatment of T2DM. Sitagliptin decreased steatosis in animal models [43], but conflicting results have been reported on sitagliptin effects on liver fat content in humans (measured by magnetic resonance spectroscopy or imaging) [44–46]. In a randomized trial comparing sitagliptin to placebo