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Opinion

Glycemic control, the unconsidered outcome in the treatment of nonalcoholic fatty liver disease

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NAFLD is the most common chronic liver disease (CLD) in the world affecting around one third of the population, and 55 % of individuals with diabetes mellitus (DM) [1]. NASH is the severe manifestation of the disease, since it causes steatosis, portal inflammation, ballooning necrosis, and fibrosis, which can progress to cirrhosis and hepatocellular carcinoma (HCC), making NASH the most common indication for liver transplantation in USA and Europe. NAFLD is closely related to metabolic syndrome (MS), which is a constellation of abnormalities, such as obesity, arterial hypertension, dyslipidemia, and DM. It has been known for years that type 2 DM (T2DM) is a major risk factor for the development NAFLD [2], and the progression of liver fibrosis, and is significantly associated to liver complications and mortality [3]. On the other hand, some clinicians have hypothesized that DM and NAFLD are both consequences of prolonged adipose tissue and hepatic insulin resistance, and that subclinical NAFLD likely precedes diabetes in most cases, as it has been demonstrated in lean subjects with NAFLD [4]. The pathophysiologic mechanisms of liver injury, such as inflammation and fibrosis due to T2DM and other metabolic abnormalities, are complex [5] and will not been discussed here.

Currently, no pharmacological agent has been approved by the FDA for the treatment of NAFLD. Therefore, an intensive pharmacotherapy research is ongoing, which has focused mainly on agents that act on specific molecular targets switched to liver inflammation and/or fibrosis mechanisms, such as: a) modulators of bile acid agents, such as FXR agonists (obeticholic acid), LXR α inhibitors (oltipraz), FGF19, and 21 analogues (adalfermin and pegbelfermin); b) modulators of lipid metabolism, such as ACC inhibitors (firsocostat), SCDI inhibitors (aramchol), diacylglycerol acyltransferase 2 inhibitors, THRβ selective agonists (resmetirom); c) antifibrotic agents such as CCR2 and 5 inhibitor (cenicriviroc), and others as selonsertif and simtuzumab; and e) antidiabetic agents, such as metformin, DPP4 inhibitors (sitagliptin), GLP-1 agonists (liraglutide), SGLT2 inhibitors (dapagliflozin, canagliflozin), and PPAR agonists (pioglitazone and rosiglitazone), among others. [6]. However, these therapeutic studies have yielded limited and conflicting results and some of them are still in early phases of study. Moreover, glycemic control has not been contrasted with histological changes of NASH in the few studies using antidiabetic drugs [7,8].

In a very recently published study performed in USA by Angelopoulos et al. [9] with 713 biopsy-confirmed NAFLD patients, 49% with DM, 51.3% with advanced fibrosis/cirrhosis, and 69.6% with NASH, glycemic control was assessed through glycated hemoglobin (HbA1c) measurements performed for several years preceding liver biopsy. It was found that high HbA1c levels were associated to ballooned hepatocytes, steatosis, and increased fibrosis. Patients with moderate glycemic control had significantly higher severity of ballooned hepatocytes and liver fibrosis than those with good glycemic control. The authors concluded that optimizing glycemic control may be a

Abbreviations: T2DM, Type 2 diabetes mellitus; NAFLD, Nonalcoholic fatty liver disease; NASH, Nonalcoholic steatohepatitis; HCC, Hepatocellular carcinoma; DPP-4, Dipeptidyl peptidase 4; GLP-1R, Glucagon-like peptide 1 receptor; SGLT-2, Sodium-glucose co-transporter 2; PPAR, Peroxisome proliferator activated receptor; FXR, Farsenoid X receptor; LXRα, Liver X receptor α; FGF, Fibroblast growth factor; ACC, Acetyl CoA carboxylase; SCDI, Steroyl-CoA desnaturase; THRβ, Thyroid hormone receptor β; CCR, Chemokine receptors

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means of modifying risk of NASH-related inflammation, and fibrosis progression.

Other studies have obtained similar findings. Hamaguchi et al. [10], in a Japanese study with 39 NAFLD patients who had undergone consecutively liver biopsies in a median follow up of 2.4 years, observed, in a multivariate analysis, that decreased HbA1c and the use of insulin were significantly associated with improvement of liver fibrosis independently of age, sex, and body mass index (BMI). The authors concluded that tight glycemic control may prevent histological progression of NASH. However, this study was limited by the low number of patients and by the fact that histological inflammation markers were not included in the assessment.

Other studies evaluating the impact of glycemic control on NAFLD have used noninvasive methods for assessing liver fibrosis. Tanaka et al. [11] in a study with 1935 NAFLD subjects found, in multivariate analysis, that an HbA1c level ≥6.5% was significantly associated to potential liver fibrosis assessed by Fib-4 ($p = 0.017$, hazard ratio = 1.7). The prevalence of NAFLD and liver fibrosis of NAFLD increased according to glycaemia up to 8.0% HbA1c. In a Chinese cross-sectional study performed by Yu CH et al. [12] on 1630 NAFLD patients, a strong association between HbA1c levels and the risk of fibrosis assessed by NAFLD fibrosis Score was observed using a multivariate analysis (OR; 2.69, 95%CI: 1.60−4.53, $p < 0.001$). This association remained significant, even in subjects without diabetes mellitus.

In the above described studies, the antidiabetic pharmacological and/or lifestyle changes regimen in patients who achieved glycemic control , were not described. It has been demonstrated that at least 7 −10% of weight loss induces improvement in NAFLD activity score (NAS) and their components (steatosis, lobular inflammation, and ballooning), as well as fibrosis. Improvement of fasting plasma glucose and insulin sensitivity may explain in part the beneficial effects of weight loss and physical exercise. [13].

The effects of glycemic control on histological parameters (particularly fibrosis) of patients with NAFLD had not been demonstrated. The important results of these pioneering studies guarantee the execution of prospective studies with large number of NAFLD patients with intermittent and regular assessment of glycemic control along with sequential histological evaluation, which more clearly determines its effects on the natural history of NAFLD, including clinical surrogates (cardiovascular and liver-related complications, and mortality). It is important to remember that maintaining a tight glycemic control is also essential to prevent both macrovascular and microvascular complications driving to reduction in cardiovascular complications. If the results of these studies are confirmed, they will probably lead to expanding the primary outcomes of pharmacological treatment of NAFLD, and certainly prioritize the objective of obtaining a tight glycemic control with highly effective antidiabetic medication and accessory measures (such as life style changes) as the relevant endpoint in diabetic and possibly non-diabetic patients.

Finally, although HbA1c is considered the “gold standard” for glycemic control in DM, it has some limitations in patients with CLD. Its sensitivity and specificity are lower in patients with moderate to severe anemia and hepatic impairment due to the curvilinear relationship between HbA1c and erythrocyte turnover as a result of hemorrhage, hemolysis caused by splenomegaly, and impaired erythropoiesis [14]. Therefore, in future studies, in addition of HbA1c, other complementary methods especially those evaluating variability of glycemia such as, self-monitoring, flash or continuous glucose monitoring should be included [15].

Declaration of Competing Interest

The authors have not conflicts of interest

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