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COMMENTARY

Improvement of hepatic steatosis and fibrosis in diabetes: Which bariatric procedure is more appropriate?

The non-alcoholic fatty liver disease (NAFLD) epidemic poses a major public health issue globally, affecting around 25% of the population worldwide, and has a close association with type 2 diabetes, liver failure, hepatocellular carcinoma, and liver-related morbidity and mortality[1]. Moderate weight loss is effective for histologic improvement of nonalcoholic steatohepatitis, and the reversal of fibrosis. Bariatric surgery effectively promotes weight loss and reduces metabolic syndrome and hepatic steatosis in most patients[2,3]. However, the current knowledge comparing the effects of different bariatric procedures in improving steatohepatitis and fibrosis were largely drawn from observational studies and remains inconsistent[2], with a lack of robust evidence from randomized controlled trials.

Recently, Seeberg *et al.*[4] reported, in *Annals of Internal Medicine*, promising results from a single-center, randomized controlled trial comparing the 5 week and 1 year effects of two bariatric procedures, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), in terms of the effects on different stages of NAFLD, hepatic steatosis, and hepatic fibrosis. In this study, magnetic resonance imaging (MRI) and enhanced liver fibrosis (ELF) tests were used to assess hepatic steatosis and liver fibrosis among patients with severe obesity and type 2 diabetes. The study included 100 patients (65% female; mean age, 47.5 years; mean body mass index, 42.0 kg/m^2) with type 2 diabetes, who were randomly assigned (1:1 ratio) to RYGB or SG from 2013 to 2018. The results showed that the liver fat fraction declined similarly after SG (19.7%) and RYGB (21.5%) from surgery to the 1-year follow-up, and the ELF score remained stable in 77% of patients, but fibrosis became worse in 18% of patients at 1 year, with no substantial between-group differences.

The authors made several observations. First, metabolic surgery improved hepatic steatosis in patients with type 2 diabetes regardless of the type of procedure, which confirms the findings of many observational studies on the role of weight loss in the development of hepatic steatosis. Bariatric surgery affecting NAFLD might be through weight loss and *via* mechanisms leading to improved glucose homeostasis, lipid metabolism, reduced inflammatory activity, and hepatic and peripheral insulin sensitivity as well. Second, the findings in terms of the effects on liver fibrosis were inconclusive. Regarding fibrosis, several cohort studies have demonstrated improvements in inflammation and fibrosis, whereas others have reported worse fibrosis after metabolic surgery[5]. In this study, both SG and RYGB showed similar effects, with the ELF score category remaining stable in 77%, worsening in 18%, and improving in 5% of patients. Although the mean ELF scores were similar at baseline and at 5 weeks, it was increased at 1 year. Fibrosis is a wound healing response in which damaged areas are encapsulated by an extracellular matrix or scar. The higher ELF score observed could indicate a greater likelihood of more severe fibrosis at 1 year after surgery. Fibrosis develops at various rates in almost all patients with chronic liver injury, depending in part on the cause of the liver disease and host factors. Hepatic stellate cell (HSC) activation, the cellular sources of the extracellular matrix, and the roles of chemokine, adipokine, neuroendocrine, angiogenic, and nicotinamide adenine dinucleotide phosphate oxidase signaling in the pathogenesis of hepatic fibrosis have been investigated in the pathway from extracellular matrix stiffness to fibrogenesis. Together with the contribution of innate immunity and the complexity of gene regulation in HSCs and myofibroblasts, these have yielded a comprehensive and nuanced picture of the progression and regression of fibrosis. This single-center, short-term, randomized controlled trial was not able to reach conclusive findings on the effects of metabolic surgery on the pathogenesis of fibrosis. Short-term findings with only 1 year of follow-up might be one reason. In this study, the ELF test results suggested a slight worsening of liver fibrosis at 1 year after surgery, but further research on the long-term progression or regression of fibrosis is warranted. Other factors, including genetic and epigenetic factors, inflammation, other comorbidities, and gut microbiota should also be further included in the consideration. Finally, from baseline to the 1 year follow-up, there was a general improvement in all measured liver enzymes in both groups. However, a significant 1 year reduction in alanine aminotransferase levels was seen in the SG group only, and a significantly higher aspartate aminotransferase: alanine aminotransferase ratio was observed after SG compared with RYGB, despite the fact that 1 year weight loss was significantly higher after RYGB than after SG (between-group difference, 8.4 kg [95% confidence interval, 0.3–16.4 kg]). This indicates that

*Correspondence
Weiping Jia
Tel.: +86-21-24056058
Fax: +86-21-24058713
E-mail address: wpjia@sjtu.edu.cn
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SG may have a better effect on NAFLD than RYGB.

In 2020, the International Consensus Panel and the Asian Pacific Association for the Study of the Liver suggested that the nomenclature of NAFLD should be updated to metabolic-associated fatty liver disease (MAFLD). MAFLD is a chronic liver disease characterized by pathological hepatocyte fat and is associated with metabolic dysfunction and inflammation caused by genetic or epigenetic susceptibility, insulin resistance, or environmental factors. Compared with NAFLD, patients with MAFLD tend to have more severe inflammatory liver damage and even progressive fibrosis. Currently there is no recognized drug treatment, and weight loss is still the core treatment method. Compared with other treatment methods, metabolic surgery has an undisputed greater effect on weight loss and remission of diabetes. The effects of different bariatric procedures on the improvement of MAFLD also need further investigation.

The results of this ongoing Oseberg study[4] with a single-center randomized controlled trial design showed that both bariatric procedures including RYGB and SG reduced the development of hepatic steatosis effectively. However, the effects of these procedures on fibrosis still need long-term investigation and further consideration of other influencing factors and comorbidities. Metabolic surgery offers an opportunity to treat these metabolic comorbidities, and should also be considered as one of the treatment options for patients.

Weiping Jia
Department of Endocrinology and Metabolism, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Key Clinical Center for Metabolic Disease, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Diabetes Institute, Shanghai, China

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