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Editorial

Metabolic surgery and NASH: When you have the data but you can't prove it[☆]



NASH y cirugía metabólica: cuando tienes los datos pero no puedes demostrarlo

Since being established as a valid therapeutic option (even for the control of type 2 diabetes in patients with class I obesity), metabolic surgery (MS) is now facing one of its most exciting challenges: trying to demonstrate whether the beneficial effects on non-alcoholic fatty liver disease (NAFLD) and its possible evolution to nonalcoholic steatohepatitis (NASH) observed to date after bariatric surgery (BS) are sufficient to establish a new indication *per se*.

The justification for considering MS is threefold: on the one hand, loss of at least 10% of body weight is associated with improvements in both functional and histological parameters of NAFLD; on the other hand, MS improves two of the main axes of the pathophysiology of the disease: meta-inflammation and insulin resistance. Finally, MS considerably reduces cardiovascular risk, which is the main cause of death in these patients^{1,2}. However, until now, these associations have been based solely on observational studies that have not been specifically designed to assess the effect of MS on NAFLD. In contrast, the safety of this treatment in patients with borderline liver function may be questionable.

Furthermore, MS improves the lipid profile, insulin sensitivity and insulin secretion, reducing the loss of hepatocytes generated by the accumulation of short-chain fatty acids, which is characteristic of hepatic steatosis³. Also, the recent evidence that the loss of microbiome diversity has a prominent role in the etiopathogenesis of NAFLD and the restorative effect of the intestinal flora of MS and its relationship with the modification of bile acids. These findings

suggest that there is a set of biomolecular effects that are solid enough to justify surgical indication⁴.

The goal of NAFLD/NASH treatment is to improve histological parameters without having a negative impact on metabolic and cardiovascular comorbidities. Although the number of pharmacological therapies under development is growing exponentially, the results are not encouraging, and when they are acceptable, they are fundamentally related to weight loss. A weight loss of 5% is considered necessary to obtain some type of histological improvement, and that a loss of $\geq 10\%$ in weight is associated with NASH resolution and regression of fibrosis in most patients. However, less than half of patients are able to achieve this through medication and lifestyle changes⁵.

Bearing in mind that BS usually results in weight loss of more than 20% of total weight, it seems reasonable to think of it as a good option. Until now, the results of BS (non-metabolic) in patients with NAFLD/NASH have shown a clear improvement in analytical parameters, a decrease in steatosis up to 75%, a decrease in fibrosis between 50% and 75%, reduction of steatohepatitis between 75% and 80%, stopping the progression from NAFLD to NASH in 50% of patients, with NASH resolution rates of up to 60%^{6,7}. In addition, patients with NASH undergoing bariatric surgery demonstrate a clear reduction in the risk of hepatic and cardiovascular adverse effects compared to non-surgical management⁸.

Despite the fact that almost all surgical and non-surgical scientific societies recognize the beneficial effects of MS on the

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disease, no consensus has been reached about its suitability for specifically treating NAFLD/NASH. The main reason is probably the lack of clinical trials demonstrating its safety and its effectiveness.

The complications of BS have been reduced to a minimum. However, it is still a set of technically demanding procedures with possible harmful effects on liver function, both of nutritional origin and due to the impact on splanchnic hemodynamics and biliary enterohepatic circulation. In addition, the presence of portal hypertension and/or ascitic decompensation considerably multiplies the morbidity and mortality of any digestive surgical procedure⁹. Thus, currently and excluding techniques with a significant hypoabsorptive component, the presence of NAFLD/NASH in patients who are candidates for metabolic surgery should not be a contra-indication, except in cases of portal hypertension or decompensation¹⁰.

Regarding its effectiveness, from a theoretical point of view it seems logical to think that MS will provide good results; however, we still cannot say which patients it will help the most or if it really will be a strategy with a reasonable cost/benefit balance. Thus, in the absence of clinical trials, several studies have carried out simulations comparing MS with medical treatment and changes in lifestyle, taking into account all possible scenarios associated with the degree of obesity and the degree of liver dysfunction. These studies have shown that both life expectancy and quality of life improve to a greater extent in any type of patient when operated on. The small number of patients treated to avoid death due to liver failure or the development of cirrhosis stands out (less than 10), but even more striking is the fact that the strategy has a clearly favorable cost/benefit balance. The discussions of these studies repeatedly mention that conducting the necessary trials is unlikely in the near future in the context of privatized healthcare. However, they indicate that settings associated with public healthcare systems, such as ours, would be appropriate because quality surgery is performed and there are acceptable resources for research^{11,12}.

In short, the possibility of considering MS as an option to treat NAFLD/NASH seems both a reasonable and probably necessary alternative in the face of the imminent tsunami that threatens the until now reasonably calm shore of hepatologists, endocrinologists, and surgeons. To achieve this, we must mimic the same path that was followed with type 2 diabetes, by conducting clinical trials that demonstrate what the observational data to date seem to indicate. Surgical practice based on solid principles and high-quality evidence have greatly raised the scientific quality of bariatric and metabolic surgery, and its indication can never be sustained by foundations built on assumptions or preliminary data. To paraphrase Deaver's aphorism, let us work like surgeons, generally something more than a doctor, and never something less.

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Conflict of interests

The authors have no conflict of interest to declare.

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