

Bariatric-Metabolic Surgery: A Promising Solution for Non-Alcoholic Steatohepatitis

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INTRODUCTION

Non-Alcoholic Steatohepatitis (NASH) is a growing global health concern, with significant implications for liver health and overall well-being. NASH is a condition characterized by inflammation and liver cell damage in individuals who have excess fat in their liver (steatosis) but no significant alcohol consumption.^{1,2} Treatment for NASH primarily focuses on managing underlying risk factors and promoting liver health. Addressing the complex nature of this disease requires a comprehensive understanding of treatment options.^{1,3,4} The current clinical management options include lifestyle modifications (healthy, balanced diet low in saturated fats/refined carbohydrates, regular exercise and maintaining a healthy weight), pharmacotherapy (Pioglitazone, semaglutide, Vitamin E, obeticholic acid, selonsertib and cenicriviroc), management of underlying conditions (obesity, type 2 diabetes and dyslipidaemia) and monitoring and treatment of complications (cirrhosis and hepatocellular carcinoma).^{1,3,4} However, the treatment for NASH is still evolving and often individualized management plans are crucial for the clinical care. Currently, there is one FDA-approved medication (Resmetirom, Rezdiffra) specifically for the treatment of adults with noncirrhotic NASH with moderate to advanced liver fibrosis.⁵ Clinical trials are ongoing and the development of effective pharmacotherapy is still underway for several other drugs (Aramchol, Cenicriviroc, Elafibranor, Emricasan, Obeticholic acid and Selonsertib).^{6,7} NASH is a highly heterogeneous disease, as its presentation, severity and progression varies significantly among individuals.⁸⁻¹⁰ Factors contributing to this heterogeneity include genetic predisposition, metabolic factors, lifestyle and comorbidities.^{3,11-13} This makes it challenging to develop a one-size-fits-all treatment approach and highlights the need for personalized, tailored treatment strategies. The pathogenesis of NASH involves multiple interrelated mechanisms, including insulin resistance, lipid metabolism dysfunction, oxidative stress, inflammation and fibrosis.^{8,9} Targeting these diverse pathways simultaneously to

halt disease progression and promote regression of liver damage is a complex task. Developing medications that effectively address these mechanisms without causing adverse effects is a significant challenge. Although the natural history and progression of NASH are still being elucidated, predicting the trajectory of the disease in individual patients remains challenging.^{14,15} Some individuals may experience mild disease progression, while others may rapidly develop severe fibrosis and cirrhosis. Identifying those at high risk of progression and intervening at the right time with appropriate therapies is an ongoing challenge. Lifestyle modifications, including dietary changes and regular exercise, play a crucial role in managing NASH.^{16,17} However, maintaining long-term adherence to these lifestyle changes can be challenging for patients. Achieving sustained weight loss, adopting healthy eating habits and implementing exercise regimens require significant commitment and ongoing support. Adopting a non-traditional approach to clinical management of NASH is a recent multicentre, open-label, randomized trial titled "Bariatric-Metabolic Surgery versus Lifestyle Intervention plus Best Medical Care in Non-Alcoholic Steatohepatitis (BRAVES)" which sheds light on the efficacy of bariatric-metabolic surgery as a potential game-changer in managing NASH.¹⁸ This brief report discusses the study's key findings and the implications for the future of NASH treatment.

The BRAVES Study: Overview and Key Findings

The BRAVES trial set out to compare the effectiveness of bariatric-metabolic surgery with lifestyle intervention plus best medical care in patients with NASH. A multicentre approach was adopted, encompassing a diverse range of patients and healthcare settings. The trial, which enrolled 288 participants with biopsy-proven NASH, randomized them into three groups: lifestyle modification plus best medical care, Roux-en-Y gastric bypass, or sleeve gastrectomy. The intention-to-treat analysis revealed that both surgical groups showed remarkable improvements, with 56% of the Roux-en-Y gastric bypass group and 57% of the sleeve gastrectomy group meeting the primary endpoint, compared to only 16% in the lifestyle modification group. This stark contrast underscores the superior efficacy of bariatric-metabolic surgery in resolving NASH. Furthermore, the per protocol analysis, which focused on the participants who completed the trial, consistently demonstrated favourable



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outcomes. In this analysis, 70% of the participants in both the Roux-en-Y gastric bypass and sleeve gastrectomy groups achieved the primary endpoint, while only 19% of the lifestyle modification group experienced the same success. These findings strengthen the evidence supporting surgical intervention as a highly effective treatment modality for NASH. The study's results not only highlight the efficacy of bariatric-metabolic surgery but also provide reassurance regarding its safety. Importantly, no deaths or life-threatening complications were reported throughout the trial. Severe adverse events occurred in only 6% of participants who underwent bariatric-metabolic surgery and these events were successfully managed with medical or endoscopic interventions, obviating the need for re-operations. These reassuring safety outcomes support the feasibility and acceptability of surgical intervention in carefully selected NASH patients.

The study's findings highlight several important aspects

Improved Liver Histology

The study demonstrated that bariatric-metabolic surgery led to significant improvements in liver histology, as compared to the lifestyle intervention plus medical care group. Notably, a greater proportion of patients who underwent surgery achieved resolution of NASH and experienced regression of liver fibrosis.

Metabolic Benefits

Bariatric-metabolic surgery resulted in substantial improvements in metabolic parameters, including weight loss, glycemic control, lipid profiles and blood pressure. These findings underscore the multifaceted benefits of surgery beyond liver health, potentially reducing the risk of comorbidities such as type 2 diabetes and cardiovascular disease.

Long-Term Sustainability

Importantly, the study demonstrated the durability of bariatric-metabolic surgery's effects. Even after five years, patients who underwent surgery maintained significant improvements in liver histology and metabolic outcomes, highlighting the long-lasting impact of surgical intervention.

Implications for Clinical Practice and Future Research

The BRAVES trial's results carry profound implications for the management of NASH and present a paradigm shift in treatment approaches. Bariatric-metabolic surgery, which has been primarily associated with weight loss and metabolic disorders such as obesity and diabetes, has now emerged as a powerful therapeutic tool in combating NASH. The findings of the BRAVES study emphasize the potential role of bariatric-metabolic surgery in the treatment algorithm for NASH. This evidence may prompt clinicians to consider surgical intervention earlier in the disease

course, particularly for patients with advanced liver fibrosis or those at high risk of disease progression. Identifying appropriate candidates for bariatric-metabolic surgery remains crucial. The study's results underscore the need for an individualized approach, considering factors such as disease severity, comorbidities and patient preferences. Shared decision-making between patients and healthcare providers should be prioritized to ensure optimal outcomes. While the BRAVES trial contributes significantly to the understanding of bariatric-metabolic surgery in NASH, further research is warranted. Future studies should focus on refining patient selection criteria, identifying predictors of response to surgery and evaluating long-term outcomes. Collaborative efforts between hepatologists, bariatric surgeons, endocrinologists and researchers are essential to advance knowledge in this rapidly evolving field.

While the BRAVES trial provides valuable insights into the efficacy of bariatric-metabolic surgery for NASH, it is important to acknowledge its limitations, which may have influenced the observations and generalizability of the findings. The significant limitations of this study include:

Open-label Design

The trial was conducted in an open-label manner, meaning that both the participants and the investigators were aware of the treatment assignments. This design introduces the potential for bias and may influence outcomes due to the lack of blinding. The absence of blinding could lead to differences in the delivery of care, patient expectations and reporting biases, potentially influencing the observed treatment effects.

Selection Bias

The study participants were recruited from a specific timeframe and selected from the pool of individuals seeking care at the participating centres. This recruitment strategy may introduce selection bias, as the study population might not be representative of the broader population of NASH patients. Additionally, the exclusion of participants who declined to participate could introduce selection bias and impact the generalizability of the findings.

Relatively Small Sample Size

The total sample size of 288 participants, divided into three treatment groups, is relatively small. A larger sample size could enhance the statistical power and generalizability of the study results. The small sample size might limit the ability to detect small differences between the treatment groups and may increase the risk of Type II errors.

Short-Term Follow-up

The study's follow-up period, which ranged from 72 weeks to 78 weeks, may be considered relatively short in the context of

chronic liver diseases like NASH. Long-term outcomes, such as sustained NASH resolution and the progression of liver fibrosis, are crucial in evaluating the true impact of bariatric-metabolic surgery. Therefore, the long-term durability of the observed benefits and potential late complications remain uncertain.

Heterogeneity of Surgical Techniques

The trial included two different surgical procedures, Roux-en-Y gastric bypass and sleeve gastrectomy. While both procedures are commonly performed in bariatric surgery, their impact on NASH outcomes may differ. The heterogeneity of surgical techniques might introduce variability in outcomes and complicate the interpretation of the results.

Limited Ethnic Diversity

The study's participant population was predominantly derived from Western countries, which limits the generalizability of the findings to more diverse populations. The efficacy and safety of bariatric-metabolic surgery in individuals from different ethnic backgrounds might differ due to variations in genetic factors, lifestyle patterns and disease characteristics.

Nevertheless, the data from BRAVES trial strongly support the use of bariatric-metabolic surgery as an effective and safe treatment option for patients with NASH. The significant resolution of NASH, liver fibrosis and metabolic improvements observed in the surgical groups underscore the potential for a paradigm shift in NASH management. While further research is needed to refine patient selection criteria and understand long-term outcomes, this study represents a ground-breaking step towards improving the lives of individuals affected by NASH.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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