Alcohol misuse is a major contributory factor to the global burden of disease, and the numbers of alcohol-related deaths are growing in many countries. Scotland experiences the highest levels of alcohol-related harm to health within the United Kingdom, with alcohol-specific death rates 5 times higher in areas with the worst socioeconomic deprivation compared to those with the least. In response to this, Scotland introduced minimal unit pricing (MUP) for alcohol, with a threshold of £0.50 (~$0.61) per unit instigated in May 2018. Previous evidence had indicated that the implementation of alcohol MUP reduced population-level alcohol sales by 3%.

Wyper et al explored the impact of introducing this policy on alcohol-specific hospitalizations and deaths in Scotland, including subgroup analysis across different demographic and socioeconomic groups. The study design was a controlled interrupted time-series regression, with data from England (where no MUP has been introduced) used as a control group. The pre-intervention time series was January 2012 to April 2018, whereas the intervention time series was the 32 months from policy instigation in May 2018 through December 2020.

Across Scotland, MUP was associated with a 13.4% reduction (95% confidence interval [CI] −18.4% to −8.3%; $P = 0.0004$) in deaths fully attributable to alcohol misuse, and a 4.1% decrease (95% CI −8.3% to 0.3%; $P = 0.064$) in hospitalizations. Of note, while there was an overall 7.3% reduction (95% CI −9.5% to −4.9%; $P < 0.0001$) in hospitalizations for chronic causes attributable to alcohol, there was a 9.9% increase (95% CI −1.1% to 22.0%; $P = 0.08$) in hospitalization from acute causes. Alcohol-related liver disease was one of the conditions mostly markedly showing reductions in both hospitalization and deaths after policy introduction. On subgroup analysis, men and those aged 35 to 64 years achieved the greatest harm reduction associated with MUP. Further analysis by socioeconomic status noted a significant reduction in hospitalization for 3 of the bottom 4 socioeconomic deciles, and in deaths for all 4 bottom deciles.

In summary, the implementation of the MUP policy significantly reduced alcohol-specific deaths and hospitalizations, most notably for those of lower socioeconomic status. The observed worsening of acute outcomes for hospitalization attributable to alcohol was unexpected and may relate to reduced food consumption or switching to consumption of higher alcohol-by-volume products in response to the financial implications of the policy. Such a finding suggests the need for accessible medical and psychological services to support those with alcohol dependence to coincide with MUP policy introduction. Furthermore, whether MUP policies can be introduced successfully in other places remains to be seen, with relevant factors including the level of government support to alcohol purveyors regarding instigation of the policy, the framework for policy enforcement, and the acceptance and support of the alcohol industry.

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The author discloses no conflicts.

Enterochromaffin Cells: Small in Number but Big in Impact

Bayrer JR, Castro J, Venkataraman A, et al. Gut enterochromaffin cells drive visceral pain and anxiety. Nature 2023;616(7955):137–142.

Enterochromaffin (EC) cells, a subtype of enteroendocrine cells in the GI tract, store and release 5-HT in response to both mechanical and chemical stimuli. The released 5-HT can then activate 5-HT_3 receptors on spinal afferent nerves and transmit nociceptive signals to the spinal cord. Given the close proximity of EC cells to mucosal afferent nerves, a sub-type of spinal afferent nerves that respond to deformation of the mucosa, it was unknown whether communication between mucosal afferent nerves and EC cells contributes to visceral pain.

A recent study by Bayrer et al addressed this question. In ex vivo experiments, selective activation of EC cells increased mucosal afferent nerve sensitivity to both mechanical and non-mechanical stimuli via 5-HT release acting at 5-HT_3 receptors. Conversely, selectively inhibiting release of neurotransmitter from EC cells blocked this sensitizing effect. While distension-responsive nerves have been implicated in driving visceral pain, in vivo experiments demonstrated that EC cell activation induced visceral hypersensitivity to colorectal distension, an effect not observed when EC cells were silenced. When EC cells were stimulated daily for 3 weeks, visceral hypersensitivity persisted 3 days after cessation of EC cell stimulation. Altogether, this suggests that mucosal afferent nerves interacting with EC cells can modulate both acute and persistent visceral pain.

Interestingly, sex differences were observed within the EC cell–mucosal afferent nerve circuit. Activation of EC cells sensitized nerves and induced visceral hypersensitivity to colo-rectal distention in males but not females. However, silencing EC cells appeared to have a larger proportional reduction in the baseline response to colo-rectal distention in females. This may suggest that EC cell–mucosal afferent nerve communication is more tonically active in females, whereas there is a larger range of activation of this circuit in males.

EC cells were also implicated in anxiety-like behavior. Selective activation or silencing this small subpopulation of cells was anxiogenic, suggesting that anxiety-like behavior is quite sensitive to changes in EC cell activity. No sex differences were observed.

This study not only highlights the role of EC cells and 5-HT in visceral hypersensitivity, but also reveals a new role

for an EC cell–mucosal afferent nerve circuit. Further studies are needed to tease out the sex differences observed in the animal model. For example, in irritable bowel syndrome (IBS), a disorder of gut-brain interaction with a female predominance that has abdominal pain as a major symptom, it is unknown whether there are differences in the activity of this EC cell–nerve circuit compared with healthy individuals. Furthermore, clinical studies suggest that 5-HT_3 receptor antagonists provide benefit in females with IBS, but it is unknown whether this is due to sex differences of this EC cell–nerve circuit in general or sex differences in this circuit specific to IBS. In addition, psychological disorders, such as anxiety, are associated with IBS. Therefore, future studies will need to study the impact of changes in anxiety-like behavior on the sensation of pain when targeting EC cells.

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The author discloses no conflicts.

Bariatric Surgery for the Treatment of NASH—An Old Solution to a Newer Problem?

Verrastro O, Panunzi S, Castagneto-Gissey L, et al. Bariatric-metabolic surgery versus lifestyle intervention plus best medical care in nonalcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial. The Lancet 2023;401(10390):1786–1797.

Non-alcoholic steato-hepatitis (NASH), the progressive form of non-alcoholic fatty liver disease, is among the most common causes of end-stage liver disease and is the second most common indication for liver transplantation. Despite its increasing prevalence and morbidity, no NASH-directed pharmacotherapies are approved. Although weight loss is a primary intervention to treat NASH, few comparative effectiveness analyses on dietary, pharmacologic, and surgical weight loss interventions on NASH outcomes exist.

The BRAVES trial addresses this in an open-label, multicenter, randomized study comparing the impact of surgical vs medical weight loss interventions on histologic NASH and fibrosis. Two hundred eighty-eight obese participants with histologically confirmed NASH were randomized to receive lifestyle and medical intervention (diet, exercise, liraglutide, pioglitazone, and vitamin E), sleeve gastrectomy, or Roux-en-Y gastric bypass (RYGB) before liver biopsy at 1-year follow-up. Importantly, both surgical bariatric interventions yielded a higher probability of histologic NASH resolution and weight loss compared with medical and lifestyle intervention. In addition, RYGB was more likely to improve glucose homeostasis and lipid profiles versus medical and lifestyle intervention, and to specifically improve fibrosis by at least 1 stage among patients with advanced F2-F3 NASH, independently from co-morbid type 2 diabetes.

These results are particularly important in the context of a burgeoning pharmacologic pipeline and increasing glucagon-like peptide 1 (GLP-1) receptor agonist use, owing to their efficacy in body weight and liver fat reduction. However, despite this efficacy, the GLP-1 agonist semaglutide did not reduce histologic fibrosis compared with placebo (N Engl J Med 2021;384:1113–1124). In contrast, obeticholic acid improves fibrosis without significant effects on NASH (The Lancet 2019;394(10215):2184–2196), whereas FGF21 agonists improve both fibrosis and NASH without clinically meaningful weight reduction (Nat Med 2021;27:1262–1271). Finally, the impact of newer agents on NASH and fibrosis, such as the glucose-dependent insulinotropic polypeptide and GLP-1 receptor co-agonist, tirzepatide, has not yet been demonstrated.

Bariatric surgery is invasive, requires recovery time, and poses some risk for short- and long-term complications, such as gastroesophageal reflux disease, dumping syndrome, and nutritional deficiencies. These remain relevant considerations and barriers for many patients. In addition, the heterogeneity of interventions in the comparison arm makes it difficult to declare superiority of RYGB over any one specific medical and lifestyle intervention. Finally, as the frontier for noninvasive options in the treatment of obesity and metabolic syndrome expands, ongoing comparisons between bariatric-metabolic surgery and newer pharmacologic therapies are critical. However, in light of such future considerations, the BRAVES study offers evidence for improved NASH and fibrosis, glucose and lipid homeostasis, and greater weight reduction following RYGB as compelling justification for RYGB compared with lifestyle and medical intervention.

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The authors disclose no conflicts.