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Is There an Obesity Paradox in the Short Bowel Syndrome?: A Review

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Obesity complicates clinical outcomes of a variety of medical conditions, operative procedures, and overall health. The obesity paradox refers to the counterintuitive finding of a protective effect of obesity for a number of clinical conditions. This has been observed not only for specific complications, but for overall mortality. We have speculated there may be an obesity paradox in the short bowel syndrome (SBS), as observed in human adults and experimental murine models. A review of the existing literature in this field is presented here.

Keywords: *Intestinal Failure, Obesity, Obesity Paradox, Short Gut Syndrome, Short Bowel Syndrome, SBS, Surgery.*

OBESITY AND THE SHORT BOWEL SYNDROME

Obesity complicates clinical outcomes of a variety of medical conditions, operative procedures, and overall health. The obesity paradox refers to the counterintuitive finding of a protective effect of obesity for a number of clinical conditions.[1] This has been observed not only for specific complications, but for overall mortality. We have speculated there may be an obesity paradox in the short bowel syndrome (SBS), as observed in human adults and experimental murine models.

The short bowel syndrome (SBS) is a common cause of intestinal failure which results when the intestinal remnant is less than 200cm in length. This shortened intestinal remnant leads to malabsorption and the need for parenteral nutrition (PN). Even morbidly obese individuals can progress to develop the short bowel syndrome (SBS). This unexpected subgroup could be the result of weight loss surgeries or other comorbid conditions that impact the functionality of the gastrointestinal tract. In a preliminary study, it appeared that obesity may be a prognostic factor in the SBS.[2] Obesity can theoretically confer protective effects as a caloric and energy store buffer to make weaning from PN a possibility. However, these patients continued to have an increased risk of hepatobiliary complications and thus, potentially increased mortality. In the evaluation of a larger series of SBS patients, BMI >35 did not achieve statistical significance as a predictor of need for PN on multivariable analysis (OR 1.8, p<.057).[3]

The explanation for these observations remains unclear. Patients who have undergone gastric bypass (GBP) for obesity and develop the SBS do not maintain an increased body mass index (BMI) even if they have an elevated BMI when developing the SBS.[4] Interestingly, they remain at increased risk of hepatobiliary complications. This suggests that post GBP anatomy and physiology play a role, and that perhaps previous history of obesity is a factor. However, any advantages of gastric reconstruction on nutritional prognosis remains to be evaluated.

POTENTIAL MECHANISMS OF THE OBESITY PARADOX

The potential mechanisms of the nutritional advantage of obesity in the SBS has been evaluated in mice and rats conditioned with a high fat diet (**Table 1**).[5,6] Six months of high fat (40% fat) diet led to increased body weight and body fat while maintaining lean body mass. However, 50% proximal or distal intestinal resection in obese animals resulted in greater body weight and body fat loss than controls with no significant difference in lean body mass. There was no significant difference in postoperative food intake. Leptin, ghrelin, PPY, ghrelin, and GIP were all modulated by the loss of small bowel. Intestinal adaptation after resection was not different between obese versus non-obese rats. A subsequent study with 75% intestinal resection and longer follow-up again failed to demonstrate improvement in lean body mass in the obese rats.[7]

BODY COMPOSITION & THE SHORT BOWEL SYNDROME

The existence of an obesity paradox remains controversial.[8,9] This may relate, in part, to the use of BMI to define obesity as opposed to using body composition. Normal weight individuals can have elevated body fat.[10] Overweight and obese individuals can be malnourished or have sarcopenia in the setting of their excess weight. BMI can be elevated due to increased fat free mass.[11] Timing of BMI measurements related to the condition being studied may also be important. The duration of obesity may be a factor as weight loss might occur due to chronic illness.

Individuals with the SBS also frequently exhibit less fat-free mass and more percent body fat. Mean percent body fat was 35% in adult SBS patients compared to 30% in healthy controls.[12] There are similar findings in children with intestinal failure. In mice intestinal resection is associated with similar abnormal body composition and finding of a resection–related metabolic syndrome.[13] Sarcopenia is present in 72% of intestinal failure patients and inflammatory activity is a risk factor.[14] In line with this, oral energy intake has been positively correlated with increased non-adipose body mass, while conversely, malnutrition has been associated with reduced muscle mass.[15,16]

ADAPTATION & INFLAMMATION

Massive small intestine loss in a murine model yielded an anomalous constellation of impaired glucose metabolism, increases in systemic inflammation, intestinal paracellular permeability, abnormal body composition, lymphatic remodeling, and profound hepatic steatosis; a sort of novel resection-associated metabolic syndrome that developed independently of parenteral nutrition.[6] Subsequent single cell analysis revelated a phenomenon of proximalization of the distal remnant tissues status post proximal small bowel resection.[17] Moreover, increased adaptation was seen after distal small bowel resection in both remnant small bowel and colon.[18].

Inflammatory cascade regulation was also interrogated and found to be positively modulated by intact nonsense mediated decay signaling in the distal resection mice, and upregulation of the protein kinase R-like endoplasmic reticulum kinase pathway of the unfolded protein response.[19,20] These changes were found to be driven by bile acid pool manipulation secondary to disrupting enterohepatic circulation, a healthier overall pool of bile acids, and enhanced de novo bile acid production in the distal resection mice. Hepatoprotection was able to be conveyed to mice undergoing proximal small bowel resection with the supplementation of tauroursodeoxycholic acid, a known cellular chaperone.[21] Summarily, these distinct profiles of hepatic injury presence and prevention lend credence to the idea of a multifaceted metabolic response to massive intestinal loss, that may be driven by a combination of bile acid metabolism, inflammatory regulation, and enterohepatic circulation.

CONCLUSION

The obesity-short bowel syndrome paradox persists as a prime example of the ever-unraveling knot of medical knowledge. While the detrimental effects of excess fat on every organ system have been well established, its protective attributes cannot be ignored either. Further, the observance of pathologies typically associated with obesity such as parenteral nutrition independent liver injury being present in the setting of the short bowel syndrome supports the notion of complex interactions yet to be elucidated (**Table 1**). The obesity paradox of the short bowel syndrome exists as a complex, incompletely understood physical reaction to intestinal loss.

Table 1

Potential Mechanisms of an Obesity Advantage in SBS
Greater energy stores[22]
Adaptive hyperphagia[22]
Enhanced intestinal adaptation (i.e. crypt/villous growth)[6]
Improved intestinal absorption[6]
Altered intestinal microbiome[6]
Change in hormonal indices[7]
Enhanced energy metabolism[7]
Alterations in enterohepatic circulation[21]
Bile acid pool modulation[19]
Proximalization of distal intestine (i.e. villous generation)[18]
Alterations in cellular signaling of regulatory feedback[17]
Increased intestinal paracellular permeability[23]
Presence of inflammatory mediators[20]
Lymphatic remodeling[24]

Table 1. Potential mechanisms of an obesity advantage in the short bowel syndrome.

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