

## Metabolic syndrome and the hepatorenal reflex

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# Metabolic syndrome and the hepatorenal reflex

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## Abstract

Insufficient hepatic O<sub>2</sub> in animal and human studies has been shown to elicit a hepatorenal reflex in response to increased hepatic adenosine, resulting in the stimulation of renal as well as muscle sympathetic nerve activity and activating the renin angiotensin system. Low hepatic ATP, hyperuricemia, and hepatic lipid accumulation reported in metabolic syndrome (MetS) patients may reflect insufficient hepatic O<sub>2</sub> delivery, potentially accounting for the sympathetic overdrive associated with MetS. This theoretical concept is supported by experimental results in animals fed a high fructose diet to induce MetS. Hepatic fructose metabolism rapidly consumes ATP resulting in increased adenosine production and hyperuricemia as well as elevated renin release and sympathetic activity. This review makes the case for the hepatorenal reflex causing sympathetic overdrive and metabolic syndrome in response to exaggerated splanchnic oxygen consumption from excessive eating. This is strongly reinforced by the fact that MetS is cured in a matter of days in a significant percentage of patients by diet, bariatric surgery, or endoluminal sleeve, all of which would decrease splanchnic oxygen demand by limiting nutrient contact with the mucosa and reducing the nutrient load due to loss of appetite or dietary restriction.

**Key Words:** Bariatric, cholesterol, diabetes, hepatorenal, metabolic syndrome, obesity, sympathetic

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## INTRODUCTION

Obesity is increasing rapidly on a global scale and is associated with comorbidities that require expensive medical care and limit the life span,<sup>[4,180]</sup> including increased risk of all cause and cardiovascular disease mortality.<sup>[26,120,180]</sup> Body mass index (BMI) has been widely used to indicate the level of obesity, though recent studies have found that abdominal or visceral adiposity (vs subcutaneous), as reflected in the waist-to-hip ratio or waist circumference, is a strong criteria for predicting the risk of developing metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM).<sup>[57,76,81,96,172,198,217,276]</sup> The incidence of MetS has been reported to be as low as 22% in overweight patients with a BMI of 25–30 and 60% in patients with a BMI of 30–35, with more than 40% of these obese patients relatively healthy.<sup>[180]</sup> While obesity is

a risk factor for MetS, the fact that not all obese patients develop MetS or T2DM<sup>[25,106,186,196,203,230,266]</sup> suggests that adiposity may not be etiologic.

While not all obese people develop MetS, the rising incidence of obesity is regarded as an epidemic due to the broad spectrum of associated comorbidities in many patients, including increased mortality, T2DM, glucose intolerance, insulin resistance, hypertension, dyslipidemia,

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nephropathy with proteinuria, cardiovascular disease, obstructive sleep apnea, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatotic hepatitis (NASH), polycystic ovary syndrome, and an increased risk of a number of cancers.

The term MetS, or originally Syndrome X, was proposed to foster a coherent clinical approach to management and therapeutic intervention. Though the diagnostic criteria for MetS has been variably defined in the literature, most definitions now include the presence of at least three of the following: Abdominal obesity, insulin resistance, hypertension, elevated fasting plasma glucose, high serum triglycerides, and low high-density lipoprotein levels. A requirement of insulin resistance and abdominal adiposity as part of the diagnostic criteria depends on the group or agency proposing the definition. There have been several attempts to develop a unified set of diagnostic criteria, and in 2009 the International Diabetes Federation, the American Heart Association, and the National Heart, Lung and Blood Institute developed a list of criteria that is now broadly accepted.

## METABOLIC SYNDROME ETIOLOGY

A large number of clinical studies have demonstrated that a significant percentage of patients with MetS have durable remission of comorbidities within days of bariatric surgery, calorie restriction (diet), or implantation of an endoluminal plastic sleeve that prevents nutrient contact with the proximal gastrointestinal mucosa, as discussed below. It is essential then to ask of any proposed etiologic factor whether, first, it is capable of causing the spectrum of comorbidities, and second, that it is rapidly eliminated by reducing nutrient contact with the proximal gut.

The theories proposed to explain the dramatic impact of surgical intervention include neuroendocrine, immunologic, and hormonal influences from the proximal gut (foregut theory) and distal gut (hindgut theory).<sup>[131,188,191,259]</sup> The challenge to these theories is in the diverse mix of comorbidities and the dramatic effect of simply removing part of the stomach and/or duodenum. There are no known hormones or even cytokine cascades associated with inflammation that would cause the specific complex of issues observed in MetS, which would be eliminated in a matter of days by something as simple as a sleeve gastrectomy.

It is not the intent of this review to argue the value or relevance of the extensive body of work and related theories for the etiology of MetS but rather to propose an etiologic mechanism based on nutrient contact with the gastrointestinal mucosa in patients with immediate resolution. There are a number of excellent reviews detailing the evidence both for and against the role of gastrointestinal hormones including insulin and

GLP-1,<sup>[42,110,124,155,194]</sup> as well as the potential role of leptin and adipokines.<sup>[33,60,155,179,206]</sup>

It is possible, if not probable, that there are multiple pathophysiologic mechanisms involved in the individual morbidities grouped into the classification of MetS. Patients whose comorbidities are resolved in a matter of days, however, may have a unique mechanism related to nutrient contact. The diversity of morbidities and the immediate resolution in up to half of the patients indicates a rapidly acting physiologic mechanism with the potential for broad impact that points to neurologic origin.

## SYMPATHETIC OVERDRIVE

Obesity and the related T2DM and MetS have been shown to have a high correlation with elevated sympathetic nerve activity in the kidney (rSNA) and muscles (mSNA)<sup>[34,50,53,86-89,91,92,95,134-136,143,150,182,228,235]</sup> that is relieved by bariatric surgery.<sup>[228,274]</sup> Obese individuals were variably observed in early studies to have elevated whole body sympathetic activity as indicated by urinary and plasma norepinephrine levels,<sup>[264]</sup> while later reports using the more accurate and refined techniques of microneurographic monitoring and norepinephrine spillover confirmed the tissue-specific nature of the sympathetic outflow.<sup>[22,47,68,90]</sup> The term “sympathetic overdrive” was coined to refer to the sympathetic overactivity<sup>[191,150,182]</sup> that is widely accepted to play a central role in the etiology of the comorbidities,<sup>[22,135,136,245-247,257]</sup> and though there are a number of theories as to the causes of overactivity, including insulin action in the brain,<sup>[70,136]</sup> the etiology remains unclear.

Elevated sympathetic discharge following a meal has been reported in normal humans and animals<sup>[47,70,257]</sup> and may lead to sustained overdrive in response to repetitive and/or excessive eating. Obese, hypertensive patients as well as animal models of MetS caused by high fructose and high fat diets exhibit elevated rSNA and mSNA as well as uric acid and angiotensin II (Ang II) levels compared to lean controls.<sup>[54,62,71,104,133,152,204,215,216]</sup> High mSNA leads to muscle vasoconstriction, increasing peripheral vascular resistance, and decreasing muscle glucose uptake,<sup>[68]</sup> suggesting a role in the development of hypertension and insulin resistance. The nature of the sympathetic overdrive has been shown to be due to the recruitment of previously silent fibers rather than an increase in the firing rate.<sup>[80,133]</sup>

Although results of studies on the role of sympathetic nerve activity in relation to vascular response and insulin action are mixed,<sup>[61,67,68,113,116,122,142,153,181,192]</sup> renal denervation<sup>[117,52,148]</sup> and clonidine administration,<sup>[84,105,209,210]</sup> as well as angiotensin converting enzyme (ACE) inhibitors,<sup>[8,14,23,145,271]</sup> all of which reduce sympathetic

outflow from the rostroventral lateral medulla (RVLM), have been shown to reduce blood pressure and improve insulin sensitivity and lipid levels in MetS and T2DM. Further, renal denervation and ACE inhibitors reduce kidney and circulating Ang II, decreasing AT1 receptor activation in the RVLM as well as limiting the Ang II enhancement of norepinephrine secretion and reuptake in the kidney.<sup>[59,117,269]</sup>

## HEPATORENAL REFLEX

The close functional relationship between the liver and kidney provides a potential mechanism for the development of sympathetic overdrive in response to a hepatorenal reflex.<sup>[98,99,236]</sup> Much of the information supporting the existence of the hepatorenal reflex has been developed from studies of hepatorenal syndrome (HRS) in decompensated cirrhosis, initially attributed to a baroreflex response to hypotension associated with infection.<sup>[9,10,218,241,263]</sup> However, studies in both humans and animals have documented an immediate decrease in renal blood flow, glomerular filtration rate, and urine flow, as well as increased sodium retention in response to increased intrahepatic pressure or reduced liver blood flow due to the reflex activation of rSNA.<sup>[24,44,98,103,112,127,129,130,160]</sup>

The reflex nature of the response to low hepatic blood flow is supported by denervation of the liver and/or kidney that has been shown to decrease rSNA and improve renal blood flow and Na<sup>+</sup> excretion.<sup>[79,127,129,159,160,263]</sup> Further, there is no histologic damage to the kidneys in HRS, and kidneys from HRS donors resume normal function when transplanted.<sup>[126,263]</sup> Liver transplantation in HRS patients, though sometimes associated with kidney damage from immunosuppressants,<sup>[258]</sup> also results in the resumption of kidney function, indicating that the elevated rSNA is due to a neurologically mediated reflex.<sup>[79,126,158,258]</sup>

Regardless of the cause of the elevated mSNA and rSNA observed in HRS and cirrhosis, it has been shown, as stated above, that acute reduction of blood flow or increased hepatic resistance in animals and humans causes rapid stimulation of rSNA resulting in renal vasoconstriction and reduced kidney function with stimulation of the RAS. Intraportal glutamine and serine have also been shown to increase rSNA by causing hepatocyte swelling that reduces sinusoidal blood flow. Cutting the vagal hepatic nerves or spinal transection prevented the effect on rSNA in these experiments and unilateral renal denervation prevented the effect only in the denervated kidney, firmly demonstrating the reflex nature of the response.<sup>[137]</sup>

Hepatic adenosine has been identified as a potential factor in stimulating the hepatorenal reflex in that

infusion into the portal vein in animals results in an immediate increase in rSNA and a reduction in renal blood flow that is prevented by liver denervation and intraportal, but not intravenous, A1 adenosine receptor blockers.<sup>[101,156-160]</sup> The compounding effect of RAS stimulation caused by renal ischemia in response to rSNA is well established, with elevated Ang II resulting in broad activation of sympathetic outflow capable of generalized overdrive.<sup>[55,152,163]</sup>

## HEPATIC OXYGEN DELIVERY

Portal blood flow to the liver increases over 100% following a meal<sup>[51,77,85,93,102,167,175,238,252,256]</sup> depending on the type of nutrient,<sup>[102,164,197,232,233]</sup> however, the portal hemoglobin saturation can be very low due to increased oxygen demand from gut secretory and contractile activity. Splanchnic oxygen consumption has been observed in normal humans to increase in the first hour following a mixed meal by over 50%<sup>[29,147,272]</sup> and postprandial O<sub>2</sub> consumption by the gastric mucosa during secretory periods, along with the thick gastric muscle requirement for O<sub>2</sub> during contraction, contribute significantly to lowering portal O<sub>2</sub> following a meal.<sup>[37,128,165,184]</sup> Hepatic oxygen delivery is further compromised following a meal by increased hepatic artery resistance leading to lower arterial flow. This “hepatic arterial buffer response”<sup>[28,63,69,140,141]</sup> has been postulated to account for the relatively constant hepatic vein outflow despite the increased portal inflow following meals. Adenosine secretion into the space of Moll is assumed to be constant and to cause arterial vasodilation. The increased portal flow following a meal is thought to wash out the adenosine, resulting in increased arterial resistance and balancing hepatic perfusion.<sup>[69,111]</sup>

While hepatic perfusion is relatively constant over the day, the distribution of blood supply and hence oxygen delivery to the hepatic parenchyma in normal humans and animals results in what is termed “metabolic zonation” involving a periportal Zone 1 (portal inflow) to perivenous Zone 3 (outflow to the hepatic vein). Hepatic oxygen levels vary across the lobule with mixed portal and arterial blood in the Zone 1 periportal region reported to be 60–65 mmHg in animals whereas perivenous Zone 3 O<sub>2</sub> is 30–35 mmHg.<sup>[115,262]</sup> The periportal to perivenous gradient of O<sub>2</sub> and nutrient delivery results in both cell structure and metabolic differentiation from inflow to outflow areas of the lobule.<sup>[200,201]</sup> While the reduced postprandial O<sub>2</sub> delivery is thought to be compensated for by increased O<sub>2</sub> uptake by hepatocytes,<sup>[63,139,146]</sup> it would present a significant challenge to hepatic metabolism, especially in Zone 3.

Oxygen delivery to the liver is compromised in obesity by hepatocyte swelling from lipid accumulation. Intracellular lipid follows the same perivenous distribution as the

intrahepatic zonal  $O_2$  gradient,<sup>[100,119,144]</sup> suggesting that fatty acid metabolism is initially compromised by the diminished oxygen in zone 3. Because fatty acid transport out of cells is an energy dependent process, the low hepatic ATP in MetS would be expected to diminish transport as well as lowering beta oxidation, resulting in lipid accumulation. NAFLD can eventually lead to NASH that has been shown to reduce sinusoidal blood flow up to 50%<sup>[15,64,72,205,239]</sup> by impeding parenchymal microcirculation.<sup>[107,226,227]</sup>

## RELATIVE HEPATIC HYPOXIA IN METABOLIC SYNDROME

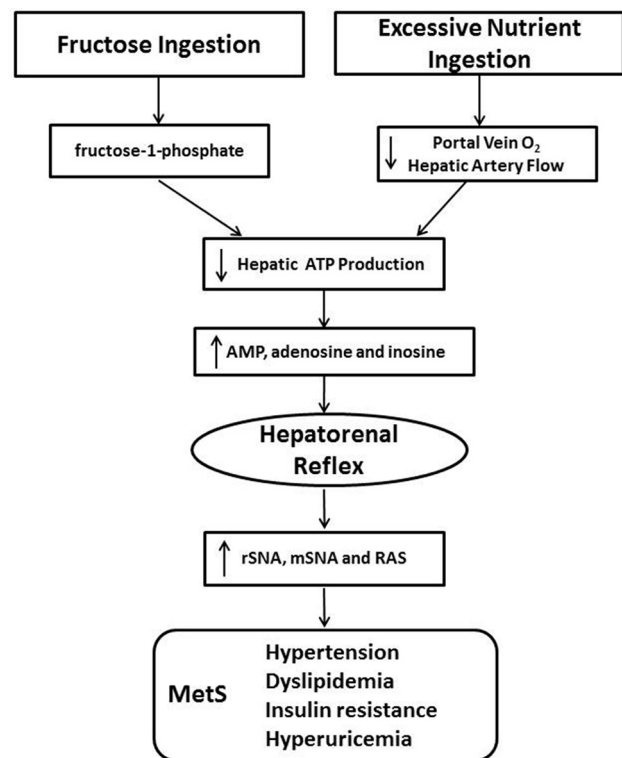
Low hepatic ATP and inorganic phosphate ( $P_i$ ) have been reported in MetS and T2DM patients but not in BMI matched, healthy controls and is associated with NAFLD, hepatic insulin resistance, and hyperuricemia.<sup>[46,125,169,222,251]</sup> The low hepatic ATP may be caused by the chronically decreased portal  $O_2$  delivery from exaggerated mesenteric oxygen demand associated with excessive eating. The limited ATP production could result in increased hepatic adenosine, potentially stimulating the hepatorenal reflex and increasing the sympathetic outflow that results in MetS [Figure 1]. However, how hepatic adenosine which should be washed out following a meal would cause a hepatorenal reflex following food ingestion is not clear. The “hepatic arterial buffer response” described above assumes constant adenosine secretion into the space of Moll, however, fails to take into account changes in hepatic energetics in response to decreasing  $O_2$  delivery, especially in the face of increased alimentary  $O_2$  demand.

Reduced hepatic oxygen in rat and mouse hepatocytes has been shown to increase the dephosphorylation of AMP to adenosine, though adenosine is not always an intermediate in adenine nucleotide metabolism. AMP is catabolized by AMP deaminase to inosine monophosphate in the inosine pathway, which would circumvent the production of adenosine.<sup>[21,254,255,261]</sup> AMP deaminase in rat brain extracts, however, is inhibited at ischemic ATP concentrations resulting in AMP breakdown to adenosine almost exclusively through the adenosine pathway.<sup>[18]</sup> Further, extracellular ATP is exclusively metabolized to adenosine by ecto-5' nucleotidase.<sup>[277]</sup> Regardless of the dominant pathway, adenosine A1 receptors have been shown to be responsible for the activation of the hepatorenal reflex<sup>[101,157-160]</sup> and AMP,<sup>[207]</sup> inosine<sup>[11,170]</sup> and adenosine<sup>[138]</sup> all activate A1 receptors.

This proposed theory of decreased hepatic ATP leading to increased adenosine formation and ultimately MetS is further supported by experimental models where MetS is induced by a high fructose diet.<sup>[3,13,27,35,49,105,152]</sup> Though

the results of both animal and human studies are variable,<sup>[242]</sup> high fructose diet is widely used to produce MetS in animals that is not observed in fructokinase A and C knockout mice.<sup>[109]</sup> Extrahepatic cells do not express fructokinase and extrahepatic hexokinase has a high  $K_m$  for fructose, restricting almost all fructose metabolism to the liver. Fructose is transported into hepatocytes by Glut2, bypassing the need for insulin and is cleared by the liver close to 100% in the first pass. Once in the hepatocytes, it is rapidly phosphorylated to fructose 1-P, consuming  $P_i$  from ATP and causing increased adenine nucleotide production, leading to hyperuricemia [Figure 1].<sup>[253]</sup>

Interestingly, BMI has been reported to be inversely correlated with hepatic ATP in normal humans and multiple regression analysis has identified waist circumference as an independent predictor of hepatic ATP flux and  $P_i$  concentrations.<sup>[222]</sup> Further, the hyperuricemia observed in both humans and animal models of MetS<sup>[38,40,41,75,219,237]</sup> has been shown to be a very sensitive index of hepatic ATP depletion,<sup>[185]</sup> and T2DM patients do not tolerate large doses of fructose due to impaired ATP recovery following an intravenous fructose challenge.<sup>[2,125]</sup>



**Figure 1:** The postulated etiologic mechanisms is supported by the fact that excessive eating and fructose ingestion, both of which can result in MetS, have the potential to reduce hepatic ATP production, increasing levels of adenine nucleotides that are known to stimulate the hepatorenal reflex and theoretically lead to MetS

## BARIATRIC SURGERY IMPACT ON HEPATIC O<sub>2</sub>

If a hepatorenal reflex in response to relative hepatic hypoxia is the primary stimulus to sympathetic overdrive and subsequent MetS, then the question of why bariatric surgery, diet, or endoluminal sleeve should correct the hypoxia is central to understanding the role they play in remission. The excessive eating that leads to obesity produces a constant state of increased splanchnic oxygen demand and decreased hepatic artery blood flow that may be significantly corrected by limiting nutrient exposure to the stomach and intestines.

Surgical restructuring of the gut referred to as “bariatric” or “metabolic” surgery includes a number of approaches that were originally focused on weight loss and were designed to either reduce the nutrient load or limit absorption by the small intestine. While these procedures restructure the gut in various ways, all of them result in comorbid disease remission including T2DM<sup>[1,20,36,39,108,118,154,162,166,168,171,173,189,193,202,212-214,221,224,231,249,265,275]</sup> and MetS<sup>[7,30,32,45,121,132,174,177,183,199,225,243,250,260,270,274,275]</sup> even if at a variable rate and durability<sup>[12,31,48,78,82,83,97,108,114,168,208,221,224,243,244,267,275]</sup> though remission has been reported in a number of publications to be durable<sup>[1,39,168,178,191]</sup> and immediate prior to significant weight loss.<sup>[20,74,161,187,188,190,195]</sup>

The one common facet to all the procedures is that they reduce nutrient load and contact with the proximal gastrointestinal mucosa by diversion of nutrient flow and loss of appetite. Further, the surgical placement of a plastic, endoluminal sleeve in the gastroduodenal lumen, preventing proximal mucosal contact with nutrient, has been shown to result in rapid remission, suggesting that mucosal contact is etiologic.<sup>[5,43,56,58,65,66,94,149,211,220,223]</sup>

Bariatric procedures include gastroplasty, biliopancreatic diversion, duodenal switch, biliopancreatic diversion with duodenal switch, Roux-en-y gastric bypass (RYGB), sleeve gastrectomy, vertical gastric banding and adjustable gastric band,<sup>[123,177,234,248,268]</sup> as well as variants of these techniques including laparoscopic approach.<sup>[16,19,132,168,173,199,240,249,260]</sup>

Both gastrectomy and diversion of the stomach and/or proximal intestine from nutrient contact would significantly lower splanchnic O<sub>2</sub> demand resulting in increased portal O<sub>2</sub> that may result in increased ATP production, as suggested by the fact that hyperuricemia is reduced following bariatric surgery.<sup>[6,176,229]</sup> The decreased uric acid indicates reduced adenine nucleotide metabolism and nucleotide production and theoretically limits the hepatorenal reflex [Figure 2].

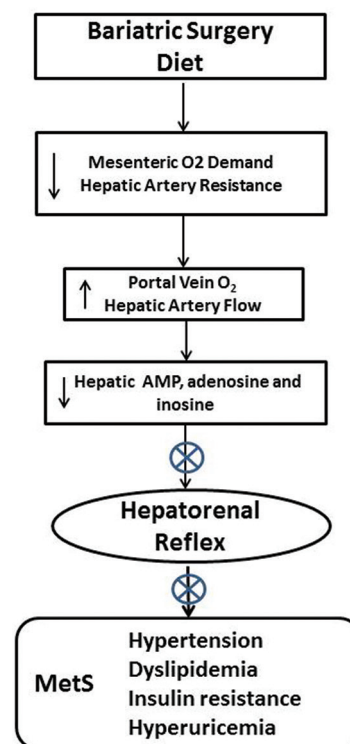
While the stomach and duodenum are not removed in a gastric bypass or RYGB, reduced acid secretion and gastrin release that would lead to O<sub>2</sub> consumption by the excluded stomach in humans has been reported.<sup>[151]</sup> Further, removal of a significant portion of the stomach

in a sleeve gastrectomy may increase hepatic artery flow by reducing gastric steal from the celiac artery. The reduced contribution of low O<sub>2</sub> gastric vein blood to portal flow and the increased hepatic arterial flow following gastrectomy would be expected to significantly improve hepatic O<sub>2</sub> delivery [Figure 3].

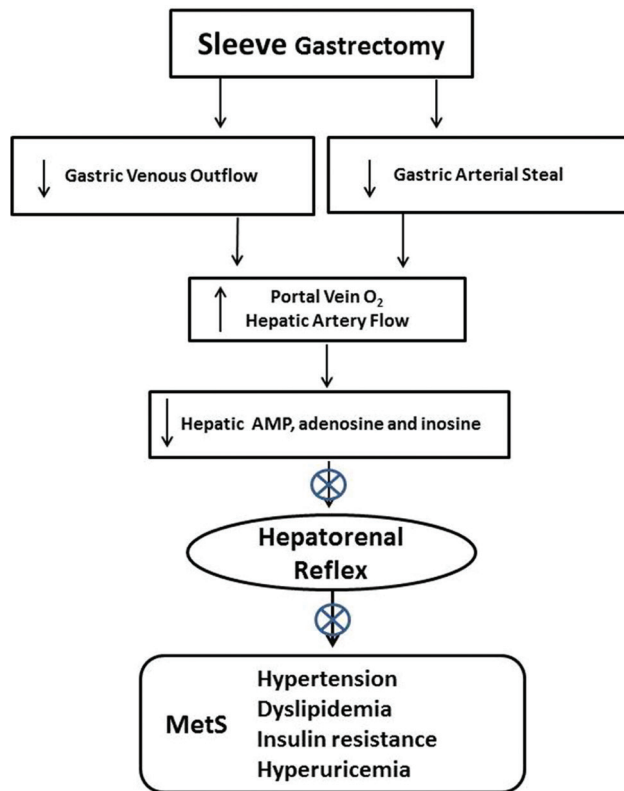
The immediate resolution of MetS following surgery or endoluminal sleeve would also be significantly impacted by the decreased appetite following bariatric surgery, which is a common problem requiring lifelong counseling and follow-up to insure adequate nutrition and vitamin intake. The reduced eating would further limit splanchnic O<sub>2</sub> consumption, improving hepatic O<sub>2</sub> delivery and increasing ATP production.

## CONCLUSIONS

This review postulates that excessive and/or repetitive eating that produces obesity causes a state of chronic, relative hypoxia in the liver due to lowered O<sub>2</sub> in portal blood, reduced hepatic artery flow, and increased hepatic resistance from lipid accumulation and hepatocyte swelling. The resulting low hepatic ATP production leads to the accumulation of adenine nucleotides in the liver that stimulates the hepatorenal reflex



**Figure 2:** Decreasing the contact of nutrient with the proximal gut by diet or bariatric surgery (including endoluminal sleeve placement) would be expected to reduce enteric oxygen consumption and improve O<sub>2</sub> delivery to the liver, potentially enhancing hepatic ATP production and reducing adenine nucleotide accumulation and the hepatorenal reflex



**Figure 3: Reduced blood flow in the gastric artery and gastric vein following gastrectomy has the potential to improve O<sub>2</sub> delivery to the liver by decreasing low O<sub>2</sub> gastric vein contribution and increasing hepatic artery flow by limiting gastric arterial steal from the celiac artery, theoretically allowing increased hepatic ATP production and reducing adenine nucleotide accumulation and the hepatorenal reflex**

producing sympathetic overdrive. Elevated sympathetic outflow has been shown to cause insulin resistance, hypertension, and dyslipidemia and is implicated in other related morbidities such as ventricular hypertrophy, Na<sup>+</sup> retention, glucose intolerance, nephropathy with proteinuria, cardiovascular disease, NAFLD, and an increased risk of cancer. Bariatric surgery, diet, and endoluminal sleeve limit the contact of nutrients with the gastrointestinal mucosa as well as decreasing appetite, resulting in increased splanchnic O<sub>2</sub> delivery to the liver and preventing the hepatorenal reflex. The fact that some obese patients develop MetS while others do not indicates that MetS is not caused by excess adiposity, but begs the question of what is different between these cohorts, both of which eat excessively and hence should have relative hepatic hypoxia. Vascular anatomy, metabolic response, 2,3-DPG levels, or sensitivity to the hepatorenal reflex are some of the potential areas for further investigation.

### Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

### Informed consent

Does not apply.

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### Conflicts of interest

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