Metabolic syndrome and the hepatorenal reflex

Michael D. Wider

Abstract

Insufficient hepatic O₂ in animal and human studies has been shown to elicit a hepatorenal reflex in response to increased hepatic adenosine, resulting in 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 O₂ 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 the loss of appetite or dietary restriction.

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

INTRODUCTION

Obesity is increasing rapidly on a global scale and is associated with comorbidities that require expensive medical care and limit life span,[12] including increased risk of all cause and cardiovascular disease mortality.[3-5] 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 stronger criteria for predicting risk of developing metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM).[6-12] 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, leaving upwards of 40% of these obese patients relatively healthy.[4] While obesity is a risk factor for MetS, the fact that not all obese patients develop MetS or T2DM[13-19] 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,
nephropathy with proteinuria, cardiovascular disease, obstructive sleep apnea, nonalcoholic fatty liver disease (NASH), and nonalcoholic steatohepatitis (NASH), polycystic ovary syndrome, and 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 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 the 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). 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 seen in MetS and that 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 for and against the role of gastrointestinal hormones including insulin and GLP-1 as well as the potential role of leptin and adipokines.

It is possible, if not probable, that there are multiple pathophysiologic mechanisms involved in the individual morbidities grouped into the classification of MetS. Those 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 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) that is relieved by bariatric surgery. Obese humans were variably observed in early studies to have elevated whole body sympathetic activity as indicated by urinary and plasma norepinephrine levels whereas later reports using the more accurate and refined techniques of microneurographic monitoring and norepinephrine spillover confirmed the tissue specific nature of the sympathetic outflow. The term “sympathetic overdrive” was coined to refer to the sympathetic overactivity that is widely accepted as playing a central role in the etiology of the comorbidities and though there are a number of theories as to the causes of overactivity, including insulin action in the brain, the etiology remains unclear.

Elevated sympathetic discharge following a meal has been reported in normal humans and animals 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. High mSNA leads to muscle vasoconstriction, increasing peripheral vascular resistance, and decreasing muscle glucose uptake, suggesting a role in the development of hypertension and insulin resistance. The nature of the sympathetic overdrive has been shown to be due to recruitment of previously silent fibers rather than an increase in the firing rate.

Although results of studies on the role of sympathetic nerve activity in relation to vascular response and insulin action are mixed, renal denervation and clonidine administration as well as angiotensin converting enzyme (ACE) inhibitors all of which reduce sympathetic outflow from the rostroventral lateral medulla (RVLM), have been shown to lower 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. [172-174]

HEPATORENAL REFLEX

The close functional relationship between the liver and kidney provides a potential mechanism for development of the sympathetic overdrive in response to a hepatorenal reflex. [175-177] 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. [178-182] 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. [176,182-189]

The reflex nature of the response to low hepatic blood flow is supported by the denervation of the liver and/or kidney that has been shown to decrease rSNA and improve renal blood flow and Na+ excretion. [180,187-191] Further, there is no histologic damage to the kidneys in HRS and kidneys from HRS donors resume normal function when transplanted. [180,192] Liver transplantation in HRS patients though sometimes associated with kidney damage from immunosuppresants [191] also results in the resumption of kidney function, indicating that the elevated rSNA is due to a neurologically mediated reflex. [180,190,195-199]

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. [196]

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. [180,191,195,197,199] 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. [180,200,201]

HEPATIC OXYGEN DELIVERY

Portal blood flow to the liver increases over 100% following a meal [236-245] depending on the type of nutrient. [239,246-249] but 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% [276-277] and postprandial O2 consumption by the gastric mucosa during secretory periods, along with the thick gastric muscle requirement for O2 during contraction, contribute significantly to lowering portal O2 following a meal. [277-276] Hepatic oxygen delivery is further compromised following a meal by increased hepatic artery resistance leading to lower arterial flow. This “hepatic arterial buffer response,” [250,251] 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. [253]

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 mm Hg in animals while perivenous Zone 3 O2 is 30–35 mm Hg. [256] The periporal to perivenous gradient of O2 and nutrient delivery results in both cell structure and metabolic differentiation from inflow to outflow areas of the lobule. [242,235] While the reduced postprandial O2 delivery is thought to be compensated for by increased O2 uptake by hepatocytes, 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 O2 gradient, [257-259] 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%.\textsuperscript{[259-263]} by impeding parenchymal microcirculation.\textsuperscript{[264-266]}

**RELATIVE HEPATIC HYPOXIA IN METABOLIC SYNDROME**

Low hepatic ATP and inorganic phosphate (P\textsubscript{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.\textsuperscript{[202-206]} The low hepatic ATP may be caused by the chronically decreased portal O\textsubscript{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]. How hepatic adenosine that should be washed out following a meal would cause a hepatorenal reflex however, is not clear. The “hepatic arterial buffer response” described above assumes constant adenosine secretion into the space of Moll but doesn’t address long term increased hepatic resistance from NAFLD that reduces portal flow, eventually limiting washout and increasing hepatic adenosine.

Reduced hepatic oxygen in rat and mouse hepatocytes has been shown to increase the dephosphorylation of AMP to adenosine, even 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.\textsuperscript{[227-230]} 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.\textsuperscript{[231]} Further, extracellular ATP is exclusively metabolized to adenosine by ecto-5’ nucleotidase.\textsuperscript{[232]} Regardless of the dominant pathway, adenosine A1 receptors have been shown to be responsible for the activation of the hepatorenal reflex\textsuperscript{[188,191,195,197,198]} and AMP, inosine\textsuperscript{[233,234]} and adenosine 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.\textsuperscript{[148,164,207-211]} Although the results of both animal and human studies are variable,\textsuperscript{[213]} high fructose diet is widely used to produce MetS in animals that is not observed in fructokinase A and C knockout mice.\textsuperscript{[214]} Extrahepatic cells do not express fructokinase and extrahepatic hexokinase has a high Km 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\textsubscript{i} from ATP and causing increased adenine nucleotide production leading to hyperuricemia [Figure 1].\textsuperscript{[212]}

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\textsubscript{i} concentrations.\textsuperscript{[204]} Further, the hyperuricemia observed in both humans and animal models of MetS\textsuperscript{[215-221]} has been shown to be a very sensitive index of hepatic ATP depletion\textsuperscript{[225]} and T2DM patients do not tolerate large doses of fructose due to impaired ATP recovery following an intravenous fructose challenge.\textsuperscript{[203,226]}

**BARIATRIC SURGERY IMPACT ON HEPATIC O\textsubscript{2}**

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 and MetS, even if at a variable rate and durability, though remission has been reported in a number of publications to be durable and immediate prior to significant weight loss.

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.

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, as well as variants of these techniques including laparoscopic approach.

Both gastrectomy and diversion of the stomach and/or proximal intestine from nutrient contact would significantly lower splanchnic \( O_2 \) demand resulting in increased portal \( O_2 \) that may result in increased ATP production, as suggested by the fact that hyperuricemia is reduced following bariatric surgery. The decreased uric acid indicates reduced adenine nucleotide metabolism and nucleotide production and theoretically limits the hepatorenal reflex.

While the stomach and duodenum are not removed in a gastric bypass or RYGB, reduced acid secretion and gastrin release that would lead to \( O_2 \) consumption by the excluded stomach in humans has been reported. 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.

![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 \( O_2 \) delivery to the liver, potentially enhancing hepatic ATP production and reducing adenine nucleotide accumulation and the hepatorenal reflex.](image)

![Figure 3: Reduced blood flow in the gastric artery and gastric vein following gastrectomy has the potential to improve \( O_2 \) delivery to the liver by decreasing low \( O_2 \) 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.](image)
The reduced contribution of low O₂ gastric vein blood to portal flow and the increased hepatic arterial flow following gastrectomy would be expected to significantly improve hepatic O₂ 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 O₂ consumption, improving hepatic O₂ 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 O₂ 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 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+ retention, glucose intolerance, nephropathy with proteinuria, cardiovascular disease, NAFLD, and increased risk of cancer. Bariatric surgery, diet, and endoluminal sleeve limit contact of nutrient with the gastrointestinal mucosa as well as decreasing appetite, resulting in increased splanchnic O₂ delivery to the liver and preventing the hepatorenal reflex. Why 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.

Financial support and sponsorship

Nil.

Conflict of interest

The author and his institution did not receive any funding or other monetary support for any aspect of the submitted work. The author has received no payment for services and has no financial relationships or intellectual property relevant to the work. The author has no other relationships that would influence or give the appearance of potentially influencing the work.

REFERENCES

1. Abbatini P, Rizzello M, Casella G, Alessandri G, Capoccia D, Leonetti F, et al. Long term effects of laparoscopic sleeve gastrectomy, gastric bypass, and adjustable gastric banding on type 2 diabetes. Surg Endosc 2010;24:1005–10.
2. Abdelmalek MF, Lazo M, Horska A, Bonekamp S, Lipkin EW, Balsubramanayam A, et al. Fatty Liver Subgroup of Look AHEAD Research Group. Higher dietary fructose is associated with impaired hepatic adenosine triphosphate homeostasis in obese individuals with type 2 diabetes. Hepatology 2012;56:952-60.
3. Abdulla MH, Sattar MA, John EJ. The relation between fructose induced metabolic syndrome and altered renal hemodynamics and excretory function in the rat. Int J Nephrol 2011;2011:934659.
4. Aguilera M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States 2003-2012. JAMA 2015;313:1973-4.
5. Aguirre V, Stylopoulos N, Grimbau R, Kaplan LM. An endoluminal sleeve induces substantial weight loss and normalizes glucose homeostasis in rats with diet-induced obesity. Obesity 2008;16:2585-92.
6. Alexandreides TK, Skroibus G, Kallventzos F. Resolution of diabetes mellitus and metabolic syndrome following Roux-en-Y gastric bypass and a variant of biliopancreatic diversion in patients with morbid obesity. Obes Surg 2007;17:176-84.
7. Ali MR, Fuller WD, Rasmussen J. Detailed description of early response of metabolic syndrome after laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis 2009;5:346-51.
8. Alkhurafouf J, Nalinikumari K, Corry D, Tuck M. Long-term effects of the angiotensin converting enzyme inhibitor captopril on metabolic control in non-insulin-dependent diabetes mellitus. Am J Hypertens 1993;6 (Pt 1):337-43.
9. Arroyo V, Fernandez J, Ginès P. Pathogenesis and treatment of hepatorenal syndrome. Semin Liver Dis 2008;28:81-95.
10. Arroyo V, Fernandez J. Management of hepatorenal syndrome in patients with cirrhosis. J Nat Rev Nephrol 2011;7:517-26.
11. Asaifile-Lopes N, Wengert M, de Sá Pinheiro AA, Leão-Ferreira LR, Caruso-Neves C. Inhibition of renal Na⁺-ATPase activity by inosine is mediated by an ATP receptor-induced inhibition of the cAMP signaling pathway. Arch Biochem Biophys 2009;489 (1-2):76-81.
12. Astiarraga B, Gastaldelli A, Muscelli E, Baldi S, Camastra S, Mari A, et al. Biliopancreatic diversion in nonobese patients with type 2 diabetes: Impact and mechanisms. J Clin Endocrinol Metab 2013;98:2765-73.
13. Axlensen LN, Lademann JB, Petersen JS, Holstein-Rathslo NH, Ploug T, Prats C, et al. Cardiac and metabolic changes in long-term high fructose-fat fed rats with severe obesity and extensive intramyocardial lipid accumulation. Am J Physiol Regul Integr Comp Physiol 2010;2998 (1):R560-70.
14. Baba T, Kodama T, Ishizaki T. Effect of chronic treatment with enalapril on metabolic syndrome beyond SYMPLICITY. Cardiovasc Revascular Med 2013;14:229-35.
15. Barsotti C, Ipata PL. Metabolic regulation of ATP breakdown and of adenosine production in rat brain extracts. Int J Biochem Cell Biol 2004;36:221-25.
16. Batcheilder AJ, Williams R, Sutton C, Kharma A. The evolution of minimally invasive bariatric surgery. J Surg Res 2013;183:559-66.
17. Barbash IM, Waksman R. Sympathetic renal denervation; hypertension and mechanisms. J Clin Endocrinol Metab 2013;98:2765-73.
18. Bellanger DE, O'Neil CE. Early resolution of type 2 diabetes seen after Roux-en-Y and vertical sleeve gastrectomy. Diabetes Technol Ther 2012;14:30-4.
19. Belloni FL, Elkin PL, Giannotio B. The mechanism of adenosine release from hypoxic rat liver cells. Br J Pharmacol 1985;85:441-6.
20. Berne C, Fagius J, Niklasson F. Sympathetic response to oral carbohydrate administration. J Clin Invest 1989;84:1403-9.
21. Bikkin EC, Boyraz M, Taşkın N, Akçay A, Ulucan K, Akyol MB, et al. Effects
of ACE inhibitors on insulin resistance and lipid profile in children with metabolic syndrome. J Clin Res Pediatr Endocrinol 2013;5:164-9.

24. Blanchart A, Rodriguez-Puyol D, Santos JC, Hernandez L, Lopez-Novoa JM. Effect of chronic and progressive hepatic outflow blockade on renal function in rats. J Lab Clin Med 1987;109:718-23.

25. Boonchaya-anant P, Apovian CM. 2014 Metabolically healthy obesity—does it exist? Curr Atheroscler Rep 2014;16:441-6.

26. Borrell LN, Samuel L. Body mass index categories and mortality risk in US adults. Am J Public Health 2014;104:512-9.

27. Bremer AA, Stanhope KL, Graham JL, Cummings BP, Wang W, Saville BR, et al. Fructose-fed rhesus monkeys: A nonhuman primate model of insulin resistance, metabolic syndrome, and type 2 diabetes. Clin Transl Sci 2011;4:243-51.

28. Browse Dj, Mathie RT, Benjamin AS, Alexander B. The role of ATP and adenosine in the control of hepatic blood flow in the rabbit in vivo. Comp Hepatol 2003;2:9.

29. Brundin T, Wahren J. Influence of protein ingestion on human splanchnic and whole-body oxygen consumption, blood flow and blood temperature. Metabolism 1994;43:626-32.

30. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric Surgery: A systematic review and meta-analysis. JAMA 2004;292:1724-37.

31. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, et al. Weight and type 2 diabetes after bariatric surgery: Systematic review and meta-analysis. Am J Med 2009;122:248-56.

32. Buchwald H, Oien DM. Metabolic/bariatric surgery worldwide 2011. Obes Surgery 2012;22:427-36.

33. Carlyle M, Jones OB, Kuo JJ, Hall JE. Chronic cardiovascular and renal actions of leptin: Role of adrenergic activity. Hypertension 2002;39 (2 Pt 2):496-501.

34. Carnethon MR, Jacobs DR Jr, Sidney S, Liu K. Influence of autonomic nervous system dysfunction on the development of type 2 diabetes: The CARDIA study. Diabetes Care 2003;26:3035-41.

35. Catena C, Giacchetti G, Novello M, Colussi G, Cavarape A, Sechi LA. Cellular and metabolic changes in hepatic and splanchnic circulation: A noninvasive Doppler study in normal humans. Eur J Appl Physiol 1994;68:373-80.

36. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The clinical effect of chronic and progressive hepatic outflow blockade on renal function and sympathetic nervous system. Eurointervention 2013;(Suppl R):R42-7.

37. Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with obesity with hypertension in white vs black Americans. Curr Hypertens Rep 2012;14:973-8.

38. Cheung LY, Moody FG, Larson K, Lowry SF. Oxygen consumption during cimetidine and prostaglandin E2 inhibition of acid secretion. Am J Physiol 1978;234:E445-50.

39. Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. Am J Med 2007;120:442-7.

40. Christou NV, Sampalis JS, Liberman M, Look D, Auger S, McLean AP, et al. Surgery decreases long-term mortality, morbidity and health care use in morbidly obese patients. Ann Surg 2004;240:416-24.

41. Ciurla C, Struglia M, Giorgini P, Serrili R, Necozione S, Properzi G, et al. Serum uric acid levels and metabolic syndrome. Clin Sci 1995;89:145-54.

42. Cortez-Pinto H, Chatham J, Jackow VP, Arnold C, Rashid A, Diehl AM. Alterations in liver ATP homeostasis in human nonalcoholic steatohepatitis: A pilot study. JAMA 1999;282:1659-64.

43. Cox HS, Kaye DM, Thompson JM, Turner AG, Jennings GL, Istitiopoulos C, et al. Regional sympathetic nervous activation after a large meal in humans. Clin Sci 1995;89:145-54.

44. Cunninean SA. Review of meta-analytic comparisons of bariatric surgery with a focus on laparoscopic adjustable gastric banding. Surg Obes Relat Dis 2008;4 (3 Suppl):S47-55.

45. Dai S, McNeill JH. Fructose induced hypertension in rats is concentration and duration dependent. J Pharmocol Toxicol Methods 1995;33:101-7.

46. Daly PA, Landsberg L. Hyperpertension and obesity in nondiabetic rats. Diabetes Care 1991;14:240-8.

47. Davis MJ, Filion KB, Zhang D, Eisenberg MJ, Afilalo J, Schiffrin EL, et al. Effectiveness of renal denervation therapy for resistant hypertension: A systematic review and meta-analysis. J Am Coll Cardiol 2013;62:231-41.

48. Davly KP, Orr JS. Metabolic/bariatric surgery worldwide 2011. Obes Surgery 2012;22:427-36.

49. de Angelis K, Senator DD, Mostarda C, Irigoyen MC, Morris M. Metabolic surgery decreases long-term mortality, morbidity and health care use in morbidly obese patients. Ann Surg 2004;240:416-24.

50. de Jonge C, Rensen SS, Verdon F, Vincent RP, Bloom SR, Buurman WA, et al. Endoscopic duodenal jejunal bypass liner rapidly improves type 2 diabetes. Obes Surg 2013;23:1354-60.

51. de Koning L, Merchant AT, Pogue J, Anand SS. Waist circumference and waist to hip ratio as predictors of cardiovascular events: Meta-regression analysis of prospective studies. Eur Heart J 2007;28:850-6.

52. de Moura EG, Martins BC, Lopes GS, Orso IR, de Oliveira SL, Galvão Neto MP, et al. Metabolic improvements in obese type 2 diabetes subjects implanted for 1 year with an endoscopically deployed duodenal-jejunal bypass liner. Diab Tech Ther 2012;14:183-9.

53. DiBona GF. Nervous kidney. Interaction between renal sympathetic nerves and the renin-angiotensin system in the control of renal function. Hypertension 2000;36:1083-8.

54. Dong M, Ren J. What fans the fire: Insights into mechanisms of leptin in metabolic syndrome associated heart diseases. Curr Pharm Des 2010;16:652-8.

55. Edfeldt H, Lundvall J. Sympathetic baroreflex control of vascular resistance in comfortably warm man. Analyses of neurogenic constrictor responses in the resting forearm and in its separate skeletal muscle and skin tissue compartments. Acta Physiol Scand 1993;147:437-47.

56. Egan BM. Insulin resistance and the sympathetic nervous system. Curr Hypertens Rep 2003;5:247-54.

57. Eipel C, Abshagen K, Voillmar B. Regulation of hepatic blood flow; the hepatic arterial buffer response revisited. World J Gastroenterol 2010;16:6046-57.

58. Erdogmus B, Tamer A, Buyukkaya R, Yazi B, Buyukkaya A, Korkut E, et al. Portal vein hemodynamics in patients with non-alcoholic fatty liver disease. Tohoku J Exp Med 2008;215:89-93.

59. Escalon A, Pimentel F, Sharp A, Becerra P, Slako M, Turiol D, et al. Weight loss and metabolic improvement in morbidly obese subjects implanted for 12 years with an endoscopically deployed duodenal-jejunal bypass liner. Ann Surg 2012;255:1080-5.

60. Escalon A, Yañez R, Pimentel F, Galvao M, Ramos AC, Turiol D, et al. Initial human experience with restrictive duodenal-jejunal bypass liner for treatment of morbid obesity. Surg Obes Relat Dis 2010;6:126-31.

61. Elami P, Tuck M. The role of the sympathetic nervous system in linking obesity with hypertension in white vs black Americans. Curr Hypertens Rep 2003;5:269-72.

62. Elser M, Rumantr M, Wiesner G, Kaye D, Hastings J, Lambert G. Sympathetic nervous system and insulin resistance: From obesity to diabetes. Am J Hypertens 2001;14:3045-9.

63. Ezzat W, Lautt WW. Hepatic arterial pressure flow autoregulation is not exist? Curr Atheroscler Rep 2014;16:441-6.

64. Farah V, Elased KM, Chen Y, Key MP, Cunha TS, Irigoyen MC, et al. Nocturnal hypertension in mice consuming a high fructose diet. Auton Neurosci 2006;130:41-50.

65. Farrell GC, Teoh NC, McCuskey RS. Hepatic microcirculation in fatty liver disease. Anat Record 2008;291:684-92.

66. Floras JS, Legault L, Morali GA, Hara K, Blendis LM. Increased sympathetic nervous system activity precedes metabolic dysfunction in a fructose model of glucose intolerance in mice. Am J Physiol Regul Integr Comp Physiol 2012;302:R950-7.

67. Frank NM, Deitrich AL. Uric acid, the metabolic syndrome and renal disease. J Am Soc Nephrol 2014;120:119-22.
of sympathetic overdrive in obesity involves purinergic

Grassi G. Sympathetic overdrive and cardiovascular risk in the metabolic

Grassi G, Quarti-Trevano F, Seravalle G, Dell’Oro R, Mancia G.

Grassini RH Jr, Chou CC, Kvyetsy PR, Sip ST. Regional blood flow during
digestion in the conscious dog. Am J Physiol 1980;238:H248-48.

Garrido-Sanchez L, Murri M, Rivas-Becerra J, Ocaña-Wilhelmi L, Cohen RV,

Garcia-Fuentes E, et al. Bypass of the duodenum improves insulin resistance
much more rapidly than sleeve gastrectomy. Surg Obes Rel Dis 2012;8:45-50.

Garzia P, Ferri GM, Ilardi M, Messina FR, Amoroso A. Pathophysiology,
clinical features and management of hepatoportal syndrome. Eur Rev Med Pharmacol Sci 1998;2:181-4.

Gebrhardt R, Matz-Soja M. Liver zonation; novel aspects of its regulation
and its impact on homeostasis. World J Gastroenterol 2014;20:8491-504.

Gelber RP, Gaziano JM, Otway RJ, Manson JE, Buring JE, Kurth T. Measures of
obesity and cardiovascular risk among men and women. J Am Coll Cardiol
2008;52:605-15.

Gill RS, Birch DW, Shi X, Sharma AM, Karmali S. Sleeve gastrectomy and
complicated by obstructive sleep apnea. J Hypertens 2010;28:1313-20.

Gelber RP, Gaziano JM, Otway RJ, Manson JE, Buring JE, Kurth T. Measures of
obesity and cardiovascular risk among men and women. J Am Coll Cardiol
2008;52:605-15.

Gill RS, Birch DW, Shi X, Sharma AM, Karmali S. Sleeve gastrectomy and
type 2 diabetes: A systematic review. Surg Obes Relat Dis 2010;6:707-13.

Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, et al.
Bariatric surgery versus non-surgical treatment for obesity: A systematic
review and meta-analysis of randomized controlled trials. BMJ 2013;347:f5934.

Goyal RK. Hyperinsulinemia and insulin resistance in hypertension: Differential
sympathetic activation in muscle and skin neural districts in the
diabetic rat. Diabetes Care 2005;28:391-7.

Granger DN, Holm L, Kvietys P. The gastrointestinal circulation; physiology
and pathophysiology. Comp Physiol 2015;5:1541-83.

Granger DN, Holm L, Kvietys P. The gastrointestinal circulation; physiology
and pathophysiology. Comp Physiol 2015;5:1541-83.

Granger DN, Holm L, Kvietys P. The gastrointestinal circulation; physiology
and pathophysiology. Comp Physiol 2015;5:1541-83.

Granger DN, Holm L, Kvietys P. The gastrointestinal circulation; physiology
and pathophysiology. Comp Physiol 2015;5:1541-83.

Granger DN, Holm L, Kvietys P. The gastrointestinal circulation; physiology
and pathophysiology. Comp Physiol 2015;5:1541-83.

Granger DN, Holm L, Kvietys P. The gastrointestinal circulation; physiology
and pathophysiology. Comp Physiol 2015;5:1541-83.

Granger DN, Holm L, Kvietys P. The gastrointestinal circulation; physiology
and pathophysiology. Comp Physiol 2015;5:1541-83.
of the clinically used low-dose pressor, norepinephrine. Diabetes Metab Res Rev 2011;27:604-8.

123. Kissler HJ, Ssetmacher U. Bariatric surgery to treat obesity. Semin Nephrol 2013;33:75-89.

124. Kohli R, Stelfater MA, Inge TH. Molecular insights from bariatric surgery. Rev Endocr Metab Disord 2011;12:211-7.

125. Kolaki C, Roden M. Hepatic energy metabolism in human diabetes mellitus, obesity and non-alcoholic fatty liver disease. Mol Cellular Endocrinol 2013;379:35-42.

126. Koppel MH, Coburn JW, Mims MM, Goldstein H, Boyle JD, Rubini ME. Transplantation of cadaveric kidneys from patients with hepatoportal syndrome. Evidence functional nature of renal failure. N Engl J Med 1969;280:1367-71.

127. Kostrevs DR, Catanier A, Kamping JP. Reflex effects of hepatic baroreceptors on renal and cardiac sympathetic nerve activity. Am J Physiol 1980;238:R390-4.

128. Kowalowski K, Kolodaj A. Relation between hydrogen ion secretion and oxygen consumption by ex vivo isolated canine stomach, perfused with homologous blood. Can J Physiol Pharmacol 1972;50:955-61.

129. Koyama S, Kanai K, Aibiki M, Fujita T Reflex increases in renal nerve activity during acutely altered portal venous pressure. J Auton Nerv Syst 1998;23:55-62.

130. Lambert E, Straznicky N, Schlaich M, Dawood T, Hotchkin E, et al. Differences in pattern of sympathoexcitation in normal-weight and obesity-related hypertension. Hypertension 2007;50:862-8.

131. Lautt WW. Relationship between hepatic blood flow and overall metabolism; consequences and therapeutic implications. Pharmacol Ther 2010;126:159-72.

132. Landsberg L, Tschernko E, Schulze E, Ottl I, Ritter M, Völkl H, et al. Obesity, metabolism, and the sympathetic nervous system. Am J Hypertens 1989;2:125S-32.

133. Lambert EA, Straznicky NE, Schlaich M, Esler M, Dawood T, Hotchkin E, et al. Antagonist of adenosine and an inhibitor of the intrinsic regulatory mechanism of replenishing: Comparison between obese and nonobese normal individuals. J Clin Endocrinol Metab 2013;98:2484-93.

134. Liew PL, Lee WJ, Lee YC, Wang HH, Wang W, Lin YC. Hepatic histopathology of morbid obesity; concurrence of other forms of chronic liver disease. Obes Surg 2006;16:1584-93.

135. Lintenberg G, Blankestein Pj, Oey PL, Klein IH, Dijkhorst-Oei LT, et al. Reduction of sympathetic hyperactivity by enalapril in patients with chronic renal failure. N Engl J Med 1999;340:1321-8.

136. Lutz J, Henrich H, Baurerien E. Oxygen supply and uptake in the liver and the intestine. Pflogers Arch 1975;360:7-15.

137. Lautt WW. Control of hepatic and intestinal blood flow: Effect of isovolemic haemodilution on blood flow and oxygen uptake in the intact liver and intestines. J Physiol 1977;265:313-26.

138. Lautt WW. Mechanism and role of intrinsic regulation of hepatic arterial blood flow; hepatic arterial buffer response. Am J Physiol 1985;249:G549-56.

139. Lautt WW. Relationship between hepatic blood flow and overall metabolism; the hepatic arterial buffer. Fed Proc 1983;42:1662-6.

140. Lembo G, Capaldo B, Rendina V, Iaccarino G, Napoli R, Guida R, et al. Acute noradrenergic activation induces insulin resistance in human skeletal muscle. Am J Physiol 1994;266:E242-7.

141. Licht CM, de Gusse EJ, Penninx BW. Dysregulation of the autonomic nervous system predicts the development of the metabolic syndrome. J Clin Endocrinol Metab 2013;98:2484-93.

142. Lichtenberg G, Blankestein Pj, Oey PL, Klein IH, Dijkhorst-Oei LT, et al. Reduction of sympathetic hyperactivity by enalapril in patients with chronic renal failure. N Engl J Med 1999;340:1321-8.

143. Lietz J, Henrich H, Baurerien E. Oxygen supply and uptake in the liver and the intestine. Pflogers Arch 1975;360:7-15.

144. Madsen JL, Sondergaard SB, Moller S. Meal induced changes in splanchnic blood flow and oxygen uptake in middle aged healthy humans. Scand J Gastroenterol 2006;41:87-92.

145. Majumber S, Birk J. A review of the current status of endoluminal therapy as a primary approach to obesity management. Surg Endosc 2013;27:2305-11.

146. Mancy G, Bouquet P, Elggozi JJ, Esler M, Grassi G, Julius S, et al. The sympathetic nervous system and the metabolic syndrome. J Hypertens 2007;25:909-20.

147. Mason EE, Munns JR, Kealey GP, Wangler R, Clarke WR, Cheng HF, et al. Effect of gastric bypass on gastric secretion. Surg Obes Relat Dis 2005;1:155-60.

148. Mayer MA, Höcht C, Gironacci M, Opezzo JA, Taira CA, Fernández BE, et al. Hypothalamic angiotensinergic-noradrenergic systems in fructose induced hypertension. Regul Pept 2008;146:38-45.

149. McCarty MF. Elevated sympathetic activity may promote insulin resistance syndrome by activating α1-adrenergic receptors on adipocytes. Med Hypotheses 2004;62:830-8.

150. Meijer RI, van Wagensveld BA, Siegert CE, Eringa EC, Serné EH, Smulders YM. Bariatric surgery as a novel treatment for type 2 diabetes mellitus: A systematic review. Arch Surg 2011;146:744-50.

151. Michalakis K, le Roux C. Gut hormones and leptin: Impact on energy control and changes after bariatric surgery—What the future holds. Obes Surg 2012;22:1648-57.

152. Ming Z, Fan YJ, Yang X, Lautt WW. Blockade of intrahepatic adenosine receptors improves urine excretion in cirrhotic rats induced by thioacetamide. J Hepatol 2005;42:680-6.

153. Ming Z, Fan YJ, Yang X, Lautt WW. Contribution of hepatic adenosine A1 receptors to renal dysfunction associated with acute liver injury in rats. Hepatology 2006;44:813-22.

154. Ming Z, Lautt WW. Intrahepatic adenosine-mediated activation of hepatorenal reflex is via A1 receptors in rats. Can J Physiol Pharmacol 2006;84:177-84.

155. Ming Z, Smyth DD, Lautt WW. Decreases in portal flow trigger a hepatorenal reflex to inhibit renal sodium and water excretion in rats: Role of adenosine. Hepatology 2002;35:167-75.

156. Ming Z, Smyth DD, Lautt WW. Intrahepatic adenosine triggers a hepatorenal reflex to regulate renal sodium and water excretion. Auton Neurosci 2001;93:1-7.

157. Mingrone G, Castagneto-Gissey L. Mechanisms of early improvement/ resolution of type 2 diabetes after bariatric surgery. Diabetes Metab 2009;35:318-23.

158. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Leccesi L, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med 2012;366:577-85.

159. Moceri A, Rissanger T, Eide I, Kjeldsen SE. The effect of the angiotensin II receptor blocker on insulin sensitivity and sympathetic nervous activity in primary hypertension. Blood Press 1994;3:185-8.

160. Moneta GL, Taylor DC, Helton WS, Mulholland MW, Strandness DE Jr. Duplex ultrasound measurement of postprandial intestinal blood flow; effect of meal composition. Gastroenterology 1988;95:1294-301.

161. Moody FG. Oxygen consumption during thiocyanate inhibition of gastric acid secretion in dogs. Am J Physiol 1969;215:127-31.

162. Moant G, Bousquet P, Eihozhi JJ, Esler M, Grassi G, Julius S, et al. The sympathetic nervous system and the metabolic syndrome. J Clin Endocrinol Metab 2013;98:2484-93.

163. Nascimento FP, Macedo-Júnior SJ, Pamplona FA, Luiz-Cerutti M, et al. Acute antinociception induced by inosine in mice; pharmacological, genetic and biochemical aspects. Mol Neurobiol 2015;51:1368-78.

164. Nair S, Chacko V, Arnold C, Diehl AM. Hepatic ATP reserve and efficiency of replenishing: Comparison between obese and nonobese normal individuals. Am J Gastroenterol 2003;98:466-70.

165. Nascimento FP, Macedo-Júnior SJ, Pamplona FA, Luiz-Cerutti M, Córdova MM, Constantino L, et al. Adenosine A1 receptor dependent antinociception induced by inosine in mice; pharmacological, genetic and biochemical aspects. Mol Neurobiol 2015;51:1368-78.

166. Nelson DW, Blair KS, Martin MJ. Analysis of obesity-related outcomes and...
bariatric surgery and the effect of gastric bypass on morbidity and mortality in morbid obesity. Arch Surg 2012;147:847-54.

172. Neovius M, Linne Y, Rossner S. BMI, waist circumference and waist-to-hip ratio as diagnostic test for fatness in adolescents. Int J Obes 2005;29:163-9.

173. Nora M, Guimaraes M, Almeida R, Martins P, Goncalves G, Freire MJ, et al. Metabolic laparoscopic gastric bypass for obese patients with type 2 diabetes. Obes Surg 2011;21:1643-9.

174. Noria SF, Grantcharov T. Biologic effects of bariatric surgery on obesity-related comorbidities. Can J Surg 2013;56:46-57.

175. Norgard C, Denker H, Lunderquist A, Olin T, Tylejan U. Superior mesenteric blood flow during digestion in man. Acta Chir Scand 1975;141:197-202.

176. Oberbach A, Neuhaus J, Inge T, Kirsch K, Schlichting N, Bliher S, et al. Bariatric surgery in severely obese adolescents improves major comorbidities including hyperuricemia. Metabolism 2014;63:242-9.

177. O'Brien PE, MacDonald L, Anderson M, Brennan L, Brown WA. Long-term outcomes after bariatric surgery: Fifteen year follow up of adjustable gastric banding and a systematic review of the bariatric surgery literature. Ann Surg 2013;257:87-94.

178. Palomar R, Fernandez-Fresnedo G, Dominguez-Diez A, Lopez-Deogracias M, Olmedo F, Martin de Francisco AL, et al. Effects of weight loss after BPD on metabolism and cardiovascular profile. Obesity Surg 2005;15:794-8.

179. Pan H, Guo J, Xu Z. Advances in understanding the interrelations between leptin resistance and obesity. Physiol and Behav 2014;130:57-69.

180. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: Prevalence and associated risk factor findings in the US population from the third National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med 2003;163:427-36.

181. Penesova A, Radikova Z, Cizmarova E, Kvetnansky R, Blazicek P, Vicek M, et al. The role of norepinephrine and insulin resistance in an early stage of hypertension. Annals Y N Acad Sci 2008;1148:490-4.

182. Perin PC, Maule S, Quadri R. Sympathetic nervous system, diabetes and lifestyle factors. PLoS One 2013;8:e76188.

183. Perry CD, Hutter MM, Smith DB, Newhouse JP, McNeil BJ. Survival and 2 year outcomes. Ann Surg 2010;252:966-71.

184. Perin PC, Maule S, Quadri R. Sympathetic nervous system, diabetes and lifestyle factors. PLoS One 2013;8:e76188.

185. Pories WJ. Gastric bypass and banding. J Med Sci 2014;348:244-8.

186. Pories WJ, Albrecht RJ. Etiology of type II diabetes mellitus: Role of the liver. Surg Clin North Am 1995;75:239-52.

187. Plourde CÉ, Grenier-Larouche T, Caron-Dorval D, Biron S, Marceau S, et al. Type 2 diabetes after gastric bypass and banding: Mechanisms and 2 year outcomes. Ann Surg 2010;252:966-71.

188. Porte D, Robertson RP. Control of insulin by catecholamines, stress and substrate metabolism. Diabetes 2010;59:2747-54.

189. Porte D, Robertson RP. Control of insulin by catecholamines, stress and the sympathetic nervous system. Fed Proc 1973;32:1792-6.

190. Pories WJ, Macdonald L, Anderson M, Brennan L, Brown WA. Long term outcomes after bariatric surgery: Fifteen year follow up of adjustable gastric banding and a systematic review of the bariatric surgery literature. Ann Surg 2013;257:87-94.

191. Pories WJ, Robertson RP. Control of insulin by catecholamines, stress and substrate metabolism. Diabetes 2010;59:2747-54.

192. Pories WJ, Robertson RP. Control of insulin by catecholamines, stress and substrate metabolism. Diabetes 2010;59:2747-54.

193. Pories WJ, Robertson RP. Control of insulin by catecholamines, stress and substrate metabolism. Diabetes 2010;59:2747-54.

194. Pories WJ, Robertson RP. Control of insulin by catecholamines, stress and substrate metabolism. Diabetes 2010;59:2747-54.

195. Pories WJ, Robertson RP. Control of insulin by catecholamines, stress and substrate metabolism. Diabetes 2010;59:2747-54.

196. Pories WJ, Robertson RP. Control of insulin by catecholamines, stress and substrate metabolism. Diabetes 2010;59:2747-54.

197. Pories WJ, Robertson RP. Control of insulin by catecholamines, stress and substrate metabolism. Diabetes 2010;59:2747-54.
HOPE Study Investigators. Ramipril and the development of diabetes. JAMA 2001;286:1882-5.

272. Zacho HD, Henriksen JH, Abrahamsen J. Chronic intestinal and splanchnic blood flow; reference values and correlation with body-composition. World J Gastroenterol 2013;19:882-8.

273. Zhang C, Yuan Y, Qiu C, Zhang W. A meta-analysis of 2-year effect after surgery: Laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy for morbid obesity and diabetes mellitus. Obes Surg 2014;24:1528-35.

274. Zhang H, Pu Y, Chen J, Tong W, Cui Y, Sun F, et al. Gastrointestinal intervention ameliorates high blood pressure through antagonizing overdrive of the sympathetic nerve in hypertensive patients and rats. J Am Heart Assoc 2014;3:e000929.

275. Zhang N, Maffei A, Cerabona T, Pahuja A, Omana J, Kaul A. Reduction in obesity related comorbidities; is gastric bypass better than sleeve gastrectomy. Surg Endosc 2013;27:1273-80.

276. Zhu S, Wang Z, Heshka S, Heo M, Faith MS, Heymsfield SB. Waist circumference and obesity associated risk factors among whites. Am J Clin Nutr 2002;76:743-9.

277. Zimmerman MA, Kam I, Eltzschig H, Grenz A. Biological implications of extracellular adenosine in hepatic ischemia and reperfusion injury. Am J Transplant 2013;13:2524-9.