Hypertension

AHA SCIENTIFIC STATEMENT

Weight-Loss Strategies for Prevention and Treatment of Hypertension

A Scientific Statement From the American Heart Association

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ABSTRACT: Hypertension is a major risk factor for cardiovascular and renal diseases in the United States and worldwide. Obesity accounts for much of the risk for primary hypertension through several mechanisms, including neurohormonal activation, inflammation, and kidney dysfunction. As the prevalence of obesity continues to increase, hypertension and associated cardiorenal diseases will also increase unless more effective strategies to prevent and treat obesity are developed. Lifestyle modification, including diet, reduced sedentariness, and increased physical activity, is usually recommended for patients with obesity; however, the long-term success of these strategies for reducing adiposity, maintaining weight loss, and reducing blood pressure has been limited. Effective pharmacotherapeutic and procedural strategies, including metabolic surgeries, are additional options to treat obesity and prevent or attenuate obesity hypertension, target organ damage, and subsequent disease. Medications can be useful for short- and long-term obesity treatment; however, prescription of these drugs is limited. Metabolic surgery is effective for producing sustained weight loss and for treating hypertension and metabolic disorders in many patients with severe obesity. Unanswered questions remain related to the mechanisms of obesity-related diseases, long-term efficacy of different treatment and prevention strategies, and timing of these interventions to prevent obesity and hypertension-mediated target organ damage. Further investigation, including randomized controlled trials, is essential to addressing these questions, and emphasis should be placed on the prevention of obesity to reduce the burden of hypertensive cardiovascular and kidney diseases and subsequent mortality.

Key Words: AHA Scientific Statements ■ blood pressure ■ metabolic surgery ■ obesity

Hypertension is a major risk factor for cardiovascular and renal diseases in the United States and worldwide. Obesity accounts for much of the risk for primary hypertension through several mechanisms, including neurohormonal activation, inflammation, and kidney dysfunction. As the prevalence of obesity continues to increase, hypertension and associated cardiorenal diseases will also increase unless more effective strategies to prevent and treat obesity are developed.

EPIDEMIOLOGY OF OBESITY HYPERTENSION AND CARDIOMETABOLIC RISK

According to recently published estimates, nearly half (45%) of adults in the United States have hypertension, defined as systolic blood pressure (SBP) ≥130 mm Hg, diastolic blood pressure (DBP) ≥80 mm Hg, or taking antihypertensive medications.[1,2] Hypertension is a major cause of increased mortality, chronic kidney disease, and cardiovascular disease (CVD), including myocardial infarction, heart failure, and stroke. Increased body weight and obesity are major risk factors for and often occur with hypertension; thus, intentional weight-loss strategies represent ideal targets to reduce risk for chronic diseases and mortality in individuals with overweight/obesity and hypertension.

Increased visceral adiposity, rather than subcutaneous adiposity, is robustly associated with incident hypertension.[3] The prevalence of hypertension is expected to

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increase with the growing prevalence of obesity worldwide. According to estimates from the World Health Organization, >1.0 billion adults were overweight and >650 million of these individuals had obesity in 2016.[4] The prevalence of severe obesity among US adults was 9.2% from 2017 to 2018, a 38% increase from just 10 years earlier.[5] Furthermore, the prevalence of obesity and overweight is dramatically increasing in children and adolescents, affecting >18% worldwide.[4] Thus, hypertension related to excess weight represents a growing problem that will markedly affect health care systems worldwide.

Intentional weight loss with dietary intervention or increased physical activity (PA) can produce clinically important reductions in blood pressure (BP) if the weight loss can be sustained. However, these weight-loss strategies can be challenging long term. When combined with lifestyle modifications, antiobesity pharmacotherapy and metabolic surgery (MS) can be effective long-term solutions for weight loss and BP control in appropriate patients with obesity. Evidence-based guidelines and scientific statements for obesity treatment have previously been published.[6–8]

IMPACT OF OBESITY HYPERTENSION: TARGET ORGAN DAMAGE

Obesity and hypertension are both strongly associated with target organ damage in the vasculature, heart, kidneys, and brain. Evidence from large-scale cohort studies demonstrates a clear dose-response relationship between greater adiposity and higher risk of incident heart failure, coronary heart disease, and stroke.[9,10] In addition, in a patient-level meta-analysis of participants of 39 cohort studies, Chang et al[11] found that a body mass index (BMI) of 40 kg/m^2 compared with 25 kg/m^2 was associated with a 2-fold higher risk of developing a 40% reduction in kidney function or end-stage kidney disease. Significant weight loss attributable to MS compared with usual care has been associated with a reduction in kidney hyperfiltration, proteinuria, and risk of major adverse CVD events and end-stage kidney disease.[12,13]

The relationship between obesity and risk of target organ damage dissipates after adjustment for hypertension, suggesting that hypertension is a key explanatory factor for target organ damage in obesity.[10] In a post hoc analysis of the Systolic Blood Pressure Intervention Trial, higher BMI was not associated with a differential effect of intensive BP control on CVD events.[14] Nonetheless, appropriate management of hypertension remains critical to reducing the adverse effects of obesity on target organs.

PATHOPHYSIOLOGY OF OBESITY HYPERTENSION

The pathophysiology of obesity hypertension is multifactorial and highly time dependent (Figure 1). Overfeeding humans and experimental animals rapidly activates the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), even before large increases in body weight occur.[15–18] Conversely, decreased caloric intake resulting from voluntary food restriction or MS rapidly reduces BP and attenuates metabolic disorders in most patients with obesity, including those with type 2 diabetes.[15,19] Although increases in BP that accompany excess weight gain are initially mild, with chronic obesity, there is gradual injury to target organs that exacerbates hypertension. The long-term impact of obesity on BP also depends on where excess fat is stored, with visceral fat conveying a greater risk for hypertension than subcutaneous fat.[20,21]

Mechanisms That Initiate Obesity Hypertension

Obesity results in extracellular fluid volume expansion and increased blood flow in many tissues, leading to increases in venous return and cardiac output.[16,22] Volume expansion is mediated by increased renal tubular sodium reabsorption because renal blood flow and glomerular filtration rate are initially elevated during obesity development, before kidney injury. At least 3 major factors contribute to increased sodium reabsorption: (1) RAAS activation, including mineralocorticoid receptor stimulation; (2) SNS activation, especially increased renal sympathetic nerve activity; and (3) kidney compression by visceral, retroperitoneal, and renal sinus fat. Several other factors have been reviewed as potential mediators of obesity hypertension, including insulin resistance, inflammation, natriuretic hormone deficiency, altered gut microbiota, and increased perivascular adipose tissue.[23,24] However, the importance of these mechanisms in initiating obesity hypertension is still unclear.

SNS Activation

Obesity causes SNS activation that is differentially controlled in various tissues and associated mainly with increased visceral adiposity.[25–27] Increased SNS activity is usually mild and does not reduce tissue blood flow, but it is sufficient to increase renal sodium reabsorption and renin release. Renal denervation markedly attenuates hypertension in experimental obesity, as well as in treatment-resistant patients with obesity.[15,25]

Multiple factors contribute to sympathetic activation in obesity, including baroreflex dysfunction, hypoxia, and chemoreceptor activation, especially in patients with sleep apnea.

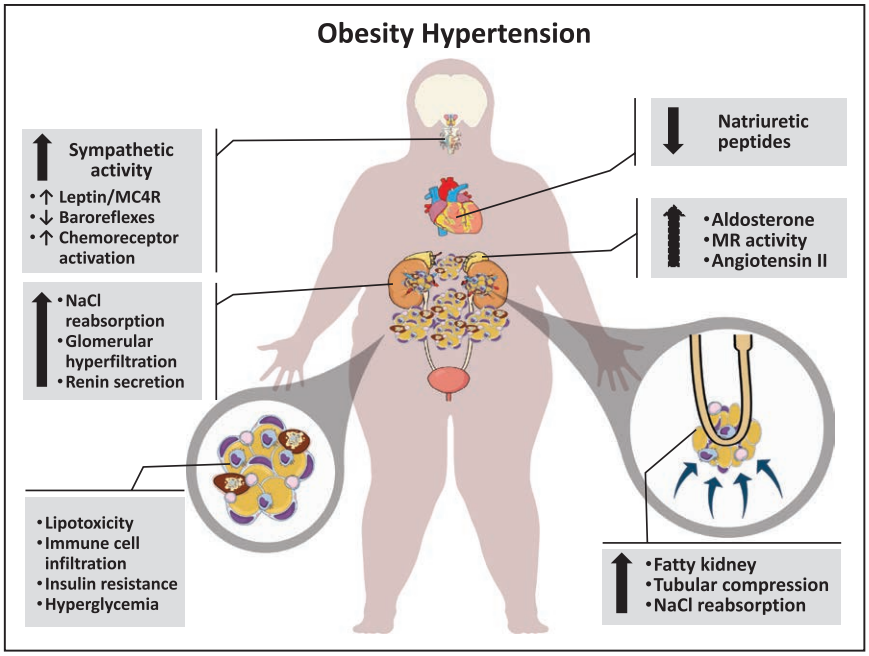

Figure 1. Effects of obesity to increase blood pressure are multifactorial and involve neurohormonal alterations, physical compression of the kidneys by fat, increased renal sodium chloride (NaCl) reabsorption, and inflammation. Metabolic abnormalities and inflammation interact with hypertension to cause kidney injury and exacerbate increases in blood pressure. MC4R indicates melanocortin 4 receptor; and MR, mineralocorticoid receptor.

Leptin, an adipokine secreted in proportion to the degree of adiposity, also stimulates SNS activity in obesity hypertension, mainly by activating proopiomelanocortin neurons, which, in turn, activate brain melanocortin 4 receptors.[15,28]

RAAS Activation

Multiple mechanisms associated with visceral obesity activate the RAAS, including kidney compression and increased SNS activation.[15,20] Experimental and clinical studies indicate that RAAS blockers are effective in reducing BP in subjects with obesity, although angiotensin II is only modestly elevated, suggesting increased sensitivity to angiotensin II. Antagonism of mineralocorticoid receptors also lowers BP and attenuates target organ injury in obesity hypertension even when plasma aldosterone is normal or subnormal, indicating that mineralocorticoid receptor activation is at least partly independent of aldosterone.[29,30]

Kidney Compression

As visceral, perirenal, and renal sinus fat accumulate and intra-abdominal pressure increases, the kidneys become compressed, further activating the RAAS, increasing sodium reabsorption, and contributing to the rise in BP initiated by the SNS.[15,31]

Inflammation, Metabolic Disorders, and Progressive Cardiorenal Injury Exacerbate Obesity Hypertension

Visceral obesity initiates inflammatory responses in adipose tissue and organs throughout the body, including the kidneys, as a result of activation of resident macrophages, infiltration of macrophages, and secretion of proinflammatory cytokines that act locally and in a paracrine/endocrine fashion.[32,33] Ectopic lipid accumulation in the liver, skeletal muscle, kidneys, blood vessels, and other organs leads to "lipotoxicity, inflammation, and a cascade of metabolic disorders including dyslipidemia, insulin resistance, glucose intolerance and type 2 diabetes over time."[15,32,33] These chronic inflammatory and metabolic disorders interact with elevated BP to cause oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction in the blood vessels, heart, and kidneys.

Early in obesity, there is mild to moderate kidney fibrosis, microalbuminuria, expansion of mesangial matrix, glomerulomegaly, focal segmental glomerular sclerosis, and podocyte injury associated with elevated glomerular filtration rate (glomerular hyperfiltration).[34,35] As obesity, hypertension, metabolic, and inflammatory disorders are sustained over many years, glomerular hyperfiltration subsides and is replaced by declining glomerular filtration rate and increasing BP salt sensitivity associated with nephron loss. Obesity also aggravates the deleterious effects of other primary kidney insults such as unilateral nephrectomy, kidney transplantation, and immunoglobulin A nephropathy.[31] As renal function declines, hypertension becomes more severe, adequate BP control becomes more challenging, and injury to the heart and blood vessels throughout the body progresses.

IMPACT OF DIET ON SUSTAINED WEIGHT LOSS AND HYPERTENSION CONTROL

Several national guidelines recommended a heart-healthy diet alone or as part of a holistic healthy lifestyle

for hypertension control, weight management, and CVD risk reduction.[2,6,36,37] Current dietary guidelines emphasize dietary pattern–based approaches over individual foods and nutrients for CVD prevention and control.[38] The most well-established healthy dietary patterns are the Mediterranean diet and Dietary Approaches to Stop Hypertension (DASH). These 2 dietary patterns are similarly rich in fruits, vegetables, legumes, nuts, and seeds, with moderate intakes of fish, seafood, poultry, and dairy and low intakes of red and processed meats and sweets. The Mediterranean diet also promotes plentiful use of olive oil and regular but moderate consumption of wine (especially red wine).

The Mediterranean Diet

A 2019 Cochrane review of randomized controlled trials (RCTs) found that the Mediterranean diet had a significant beneficial effect on SBP (−3.0 mm Hg [95% CI, −3.5 to −2.5]) and DBP (−2.0 mm Hg [95% CI, −2.3 to −1.7]).[39] A meta-analysis of 16 RCTs found that Mediterranean diet interventions also reduced body weight (−1.8 kg [95% CI, −2.9 to −0.6]) and BMI (−0.6 kg/m^2 [95% CI, −0.9 to −0.2]).[40]

The DASH Diet

Compared with the Mediterranean diet, the DASH diet seems to provide more robust BP-lowering effects. In a meta-analysis of 24 RCTs of dietary pattern interventions, the DASH diet had a strong effect to reduce SBP (−7.6 mm Hg [95% CI, −10.0 to −5.3]) and DBP (−4.2 mm Hg [95% CI, −5.9 to −2.6]).[41] When combined with a weight-loss and exercise intervention, the DASH diet led to significantly greater BP reductions (−16.1/9.9 mm Hg) than DASH alone (−11.2/7.5 mm Hg).[42] The BP-lowering effect of the DASH diet also seems to be stronger when combined with low sodium intake, especially in individuals who are hypertensive. In the DASH-Sodium trial, compared with the DASH diet with high sodium intake (3450 mg/d), the DASH diet with low sodium intake (1150 mg/d) reduced SBP by 0.9 mm Hg (95% CI, −2.1 to 0.3), 3.3 mm Hg (95% CI, −4.7 to −1.9), 4.9 mm Hg (95% CI, −7.3 to −2.6), and 10.4 mm Hg (95% CI, −15.5 to −5.3) in adults with baseline SBP <130, 130 to 139, 140 to 149, and ≥150 mm Hg, respectively.[43]

Independently of dietary pattern, low-sodium consumption has also been shown to benefit BP control. In a meta-regression analysis of 133 RCTs, a 2300-mg/d reduction in sodium intake was associated with a decrease of 7.7 mm Hg (95% CI, −10.4 to −5.0) in SBP and 3.0 mm Hg (95% CI, −4.6 to −1.4) in DBP among people with BP >131/78 mm Hg.[44] In addition, meta-analysis results showed that each 50-mmol reduction in 24-hour urinary sodium (an objective measure of sodium intake) was associated with a 1.10–mm Hg (95% CI, 0.7–1.5) decrease in SBP.[45] The effects of sodium reduction on BP appear to be particularly evident in individuals who are older, hypertensive, and Black.[45–47] Increased potassium consumption is also associated with a reduction in BP, although excessive potassium intake has been associated with adverse outcomes.[48,49]

Intermittent Fasting

Besides these widely recommended approaches to improve diet composition and quality, some studies have investigated the timing of eating for weight loss and BP control. Small clinical studies in patients with metabolic syndrome suggest that intermittent fasting may produce modest reductions in SBP and DBP,[50] similar to reductions achieved by weight loss through other interventions. A systematic review of 4 RCTs showed that although intermittent fasting was effective for short-term weight loss, its effects on BP reduction were weak.[51] Another systematic review and meta-analysis of 6 RCTs showed that intermittent fasting was more effective than no treatment for weight loss (−4.1 kg [95% CI, −2.0 to −6.3]) but not significantly different from continuous energy restriction (−1.0 kg [95% CI, −2.5 to 0.4]).[52] The effect of intermittent fasting on BP control needs further research.

IMPACT OF PA ON SUSTAINED WEIGHT LOSS AND HYPERTENSION CONTROL MECHANISMS OF PA TO REDUCE BP

PA is defined as a bodily movement produced by contraction of skeletal muscles that increases energy expenditure above resting levels.[53] Exercise is moderate- to vigorous-intensive PA that is planned, structured, and repetitive with the intent of improving or maintaining health.[53] Sedentary behavior, characterized by an energy expenditure ≤1.5 metabolic equivalents while in a sitting or reclining posture, is considered to be a distinct construct from the time spent in moderate- or vigorous-intensity PA because both are independently associated with all-cause mortality.[54] Table 1 shows proposed mechanisms that may underlie the benefits of higher levels of PA on BP and cardiometabolic risk.

Impact of PA on Obesity Hypertension

There is evidence that PA and exercise training (ET) reduce obesity, BP, and obesity hypertension. Although improvements in CVD risk factors are noted with just 2% to 3% weight loss, the current recommendations are for at least 5% to 10% (clinically significant weight loss) within 6 months because of the more profound

Table 1. Proposed Mechanisms of BP Reductions Attributable to Higher Levels of PA

Weight loss and reduced adiposity
Increased insulin sensitivity and glucose handling
Decreased sympathetic activity and increased parasympathetic activity
Increased baroreflex sensitivity
Decreased vascular resistance
Increased vascular compliance
Improvements in nitric oxide–mediated endothelial function
Improvements in arterial stiffness
Reduced oxidative stress
Reduced inflammation
Reduced endothelin-1
Less fluid retention, which decreases the risk of obstructive sleep apnea

BP indicates blood pressure; and PA, physical activity.

improvements in the major CVD risk factors, including lipids, and other relevant cardiometabolic risk factors, including insulin sensitivity, arterial stiffness, and resting BP.[55] ET also has a significant impact on BP independently of weight. Recently, Noone et al[56] performed a meta-analysis of 93 RCTs, and both ET and medications lowered BP effectively. Although the point estimate favored medications more than ET, these were not statistically significant differences. Because of its low cost and lack of major adverse effects or medication interactions, in addition to the impact of ET on improving levels of cardiorespiratory fitness, perhaps one of the strongest CVD risk markers, ET should be part of all antihypertension and weight-loss efforts.

Achieving 5% to 10% of one's body weight loss can lead to >5– and 4–mm Hg reductions in SBP and DBP, respectively, and 10 kg of weight loss may lower SBP by 5 to 20 mm Hg.[55,57] Typically, <150 min/wk of PA produces no to minimal weight loss, 150 to 225 min/wk of PA produces 2- to 3-kg weight loss, 225 to 420 min/wk of PA produces 5- to 7.5-kg weight loss, and 200 to 300 min/wk of PA is needed for long-term weight maintenance.[55] Resistance training does not promote major clinically significant weight loss, although it does have mild effects on improving BP and promoting beneficial body composition changes,[55] and resistance training and muscle strength have effects on lowering CVD mortality independently of PA/cardiorespiratory fitness.[58]

Reducing Sedentariness to Reduce BP

There is strong evidence to indicate that PA interventions reduce BP. A systematic review of 26 studies showed that pedometers increased PA and reduced SBP and DBP among adult outpatients.[59] Increasing evidence from intervention studies suggests that reducing sedentariness (ie, reducing or interrupting sitting time with walking or standing breaks) leads to a reduction in SBP or DBP ranging from 1 to 16 mm Hg.[60–65] The magnitude of reductions on BP with interruptions in sitting time may be greater in individuals with hypertension compared with those without hypertension. Because of the complex relationship between PA and sedentariness, guidelines do not currently recommend a specific prescription for how much sitting time should be reduced for BP reductions to be observed.[66]

HIGH RECIDIVISM RATES AND REDUCED LONG-TERM EFFICACY OF DIET AND EXERCISE ON BP CONTROL

Although dietary modification, exercise, and associated weight loss are effective strategies for reducing BP, recidivism rates for hypertension are high among those receiving such lifestyle interventions. According to a review of prospective trials, the beneficial effects of weight loss on BP are significantly diminished or reversed over time.[67] Much of this recidivism is related to the common occurrence of weight regain. For example, the TOHP phase II study (Trials of Hypertension Prevention) demonstrated that in adults with modestly elevated BP, weight loss or sodium intake reduction reduced BP, although this effect was attenuated over time.[68] A post hoc analysis of TOHP-II among the weight-loss group showed that those who maintained weight loss had a 65% lower likelihood of developing hypertension than participants randomized to the usual care control group.[69] Several complex physiological adaptations to weight loss foster weight regain, including increased energy efficiency attributable to a lower resting metabolic rate and decreased energy expenditures, as well as decreased satiety resulting from hormonal changes.[70] Successful weight-loss maintenance over years therefore typically requires high levels of PA and limited sedentary time, frequent weight monitoring, and high levels of dietary restraint.[71]

Recurrent increases in BP among those receiving lifestyle interventions are also partially independent of weight regain. For example, in response to an 800-calorie-a-day diet for 9 weeks, body weight declined among 34 men and women from a mean of 101.7 to 87.3 kg (−14.4 kg) and 24-hour ambulatory SBP fell from 130.1 to 121.1 mm Hg (−9 mm Hg).[72] However, despite full maintenance of weight loss at 6 months, mean 24-hour SBP rose to 126.5 mm Hg (−3.6 mm Hg from baseline, 40% of initial response). Similarly, although ≈88% of initial weight loss was sustained at 1 year (−12.6 kg), SBP rose to 127.9 mm Hg (−2.2 mm Hg from baseline, ≈24% of initial BP response). Some of the physiological changes that promote BP reduction in the setting of weight loss, including decreases in SNS activity and plasma renin activity, are transient even in those with persistent weight loss.[73] This suggests that nonsustained neurohormonal responses to weight loss may further contribute to recidivism of

hypertension in subjects achieving weight loss through lifestyle modification.

PHARMACOTHERAPY

Drugs Approved by the US Food and Drug Administration for Weight Loss

Pharmacotherapy can be considered for weight management in patients who have limited treatment response to lifestyle modifications alone and have a BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 in the presence of weight-related comorbidities such as hypertension.[6] Antiobesity pharmacotherapy is intended for use as an adjunct to diet and exercise. Four drug therapies are approved by the US Food and Drug Administration (FDA) only for short-term use (up to 12 weeks) for obesity treatment: phentermine, diethylpropion, phendimetrazine, and benzphetamine. These drugs have a close structural and mechanistic relationship with amphetamine.[74] Currently, 5 drug therapies are approved by the FDA for long-term weight loss: orlistat, phentermine/topiramate extended release, naltrexone/bupropion, liraglutide 3.0 mg, and semaglutide 2.4 mg weekly subcutaneously. The primary mechanism of action of orlistat is a reduction in intestinal fat absorption.[74] Phentermine/topiramate, naltrexone/bupropion, and liraglutide are centrally acting drugs that enhance satiety and decrease hunger. In RCTs, the drugs approved for long-term use (along with lifestyle modifications) reduce weight by an average of 3% to 9% more than placebo (with lifestyle modifications) over 1 year.[75] Weight loss in the first 3 to 4 months after initiation of pharmacotherapy is the most consistent predictor of 1-year response to these drugs and can be used as a guide for continuation of pharmacotherapy versus changing to an alternative weight-loss strategy.[76] Patients with sustained weight loss and in whom these drugs are well tolerated may benefit from long-term use of antiobesity pharmacotherapy. Weight regain or additional weight gain is sometimes observed when these drugs are continued beyond 1 year or after they are discontinued.[74]

The long-term effects of antiobesity medication on BP are mixed as a result of various factors, including the differences in mechanisms of action, weight-loss efficacy, and study populations. RCTs demonstrate a slight decline in BP in patients randomized to orlistat, phentermine/topiramate, and liraglutide versus placebo at 1 year (mean, 1– to 3–mm Hg decline in SBP and 1–mm Hg decline in DBP; Table 2), which is thought to be mediated by weight loss.[75,76] Alternatively, RCTs demonstrate a slight increase in BP in patients randomized to naltrexone/bupropion versus placebo (mean, 2–mm Hg increase in SBP and 1–mm Hg increase in DBP).[76] Of note, only a subset of participants in RCTs of long-term use of antiobesity medications had hypertension at baseline. For antiobesity medications that have demonstrated a decline in BP, the decline is slightly greater (by an average of 1 mm Hg) among the subset of participants with an underlying diagnosis of hypertension.[75,76] Recently, once-weekly semaglutide 2.4 mg subcutaneous injection as an adjunct to lifestyle therapy resulted in a 14.9% reduction in mean body weight and a 6.2–mm Hg reduction in SBP from baseline to 68 weeks. This drug, originally developed for diabetes treatment, shows promise for larger mean reductions in body weight with potentially greater improvements in cardiometabolic risk, especially when used in combination with lifestyle intervention.[77]

Table 2. Effect of Antiobesity Pharmacotherapy Compared With Placebo on Weight and BP at 1 Year*

Drug	Percent change in weight	Mean change in SBP, mm Hg	Mean change in DBP, mm Hg
Orlistat	−3	−1	−1
Phentermine/topiramate	−9	−3	−1
Naltrexone/bupropion	−4	2	1
Liraglutide	−5	−3	−1
Semaglutide†	−15	−6	−3

BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

*For orlistat, weight and BP changes were estimated from various meta-analyses and systematic reviews.[75] For phentermine/topiramate, naltrexone/bupropion, and liraglutide, weight and BP changes were obtained from pooled data of phase 3 randomized controlled trials in patients with obesity and without diabetes. When >1 dose of a drug was studied, the estimates are based on the results from the most effective dose.

†Semaglutide was recently approved by the US Food and Drug Administration for weight loss.[77]

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Safety and Complications

Patients should be advised of potential adverse effects of antiobesity pharmacotherapy before use. The most common side effects from sympathomimetic amines such as phentermine are constipation, dizziness, dry mouth, and insomnia.[74] There is also a potential risk for increased BP related to the mechanism of action, which includes increasing catecholamine levels. Although FDA labels warn about this risk in drugs approved for long-term weight loss (eg, combination phentermine/topiramate), clinically significant increases in BP have not been observed in RCTs of these drugs,[76] which may be attributable to concomitant weight loss. Orlistat has a generally favorable safety profile attributable to its peripheral mechanism of action. However, it is often poorly tolerated because of a high incidence of loose stools, fecal urgency, and flatus when patients do not strictly adhere to a low-fat diet. Patients prescribed orlistat should take a multivitamin because of reduced absorption of fat-soluble vitamins. Lorcaserin was previously approved by the FDA for long-term use for weight loss but was voluntarily withdrawn from the US market in February 2020

as a result of an elevated incidence of cancers (including pancreatic, colorectal, and lung cancer) observed among patients on lorcaserin compared with placebo during the 5-year follow-up of an RCT.[78] In an analysis of a national sample of electronic medical record data, Zhang et al[79] observed that <1% of almost 2 million eligible patients were prescribed pharmacotherapy for weight loss. Low prescribing rates may be attributable to greater perceived risk than benefit by many clinicians, considering the minimal effect on BP and a lack of data on the long-term effects of these drugs on target organ damage.

METABOLIC SURGERY

Bariatric Operations

A total of 216 000 MSs were performed in the United States in 2016.[80] Sleeve gastrectomy is the most common metabolic procedure (58%), followed by Roux-en-Y gastric bypass (RYGB; 19%), adjustable gastric band (3%), and biliopancreatic diversion with duodenal switch (0.6%). Currently, >98% of metabolic procedures are performed laparoscopically,[81] with a perioperative major morbidity of <5%, mortality of <0.2%, hospital stay of 1 to 2 days, and recovery of 2 to 4 weeks. In general terms, these operations involve some degree of gastric volume reduction or intestinal bypass. Weight loss and metabolic improvements are currently thought to be driven primarily by neuroendocrine mechanisms that reduce appetite and enhance satiety, as well as improve insulin sensitivity and secretion. In addition, intestinal bypass procedures lead to a reduction in intestinal absorption of calories, further reducing overall calorie intake.

Current Indications

Patients with a BMI ≥40 kg/m^2 or ≥35 kg/m^2 with comorbidity are candidates for MS if they are psychologically stable and have no active substance abuse.[82] Patients with type 2 diabetes and BMI ≥30 kg/m^2 (≥27.5 kg/m^2 for patients who are Asian) are candidates for MS if they are not in good glycemic control while on reasonable medical therapy.[83] MS should be performed in centers with a multidisciplinary team that includes a bariatric surgeon, endocrinologist/diabetologist, cardiologist, anesthesiologist, psychologist, and dietician with expertise in obesity and diabetes care.

Mechanisms by Which Metabolic Surgery Reduces BP

The mechanisms for improved BP control after MS appear to be multifactorial, complex, and not well understood at this time. BP reduction occurs as early as 1 week postoperatively, ie, before any significant weight loss, suggesting a role for neuroendocrine mechanisms. Increases in levels of the incretin glucagon-like peptide-1 have been observed after various types of MS. Glucagon-like peptide-1 stimulates postprandial insulin secretion, inhibits glucagon secretion, and has several central actions, including hypophagia.[84] The SNS might be implicated in the BP-lowering effects of MS given that the area postrema, one of the circumventricular organs in the fourth ventricle, contains glucagon-like peptide-1–responsive catecholaminergic neurons. Glucagon-like peptide-1 may be important for water and salt homeostasis, with high levels being associated with natriuresis. Natriuretic peptides also may play a role in MS-induced BP improvement; their circulating concentrations are low in patients with obesity and increase after MS.[85] Hypertension may also be affected by alterations in polypeptides secreted by white adipose tissue, that is, cytokines (adipokines), and systemic and renal inflammation.[86] Finally, individuals with central obesity have an increased activation of the RAAS that may normalize after surgery.

Review of Clinical Studies With MS as the Intervention

Systematic reviews of observational data have suggested that MS may improve hypertension. One example (136 studies, 22 094 patients) found an overall 63% resolution of hypertension, with procedure-specific percentages of 68%, 43%, and 83% for RYGB, adjustable gastric band, and biliopancreatic diversion with duodenal switch, respectively.[87] At a median 10-year follow-up, investigators from the SOS study (Swedish Obese Subject) observed a significantly greater reduction in both SBP and DBP in patients who underwent RYGB compared with nonsurgically treated control subjects (patients receiving RYGB, −5.1 and −5.6 mm Hg; control subjects, 1.2 and −3.8 mm Hg; $P<0.01$ for difference).[88] In addition, the percentage of patients on antihypertensive medication was significantly lower in the RYGB group compared with the control group (35% versus 53%; $P<0.001$). However, reductions in BP that correlated with reductions in BMI at 2 years were not present at 10 years. Adams et al[89] found that BP stabilized 12 years after RYGB, whereas significantly increasing BPs over time (adjusted >6–mm Hg increases SBP and DBP) were seen in the 2 nonoperated control groups ($P<0.05$ for all comparisons between the RYGB group and control subjects). On the other hand, RCTs comparing MS with medical treatment of diabetes did not find significant long-term benefits on BP with MS versus medical treatment. However, Schauer et al[90] noted a reduction in the use of antihypertensive agents after MS compared with medical management.

GATEWAY Trial

GATEWAY (Gastric Bypass to Treat Obese Patients With Steady Hypertension) is the only controlled trial

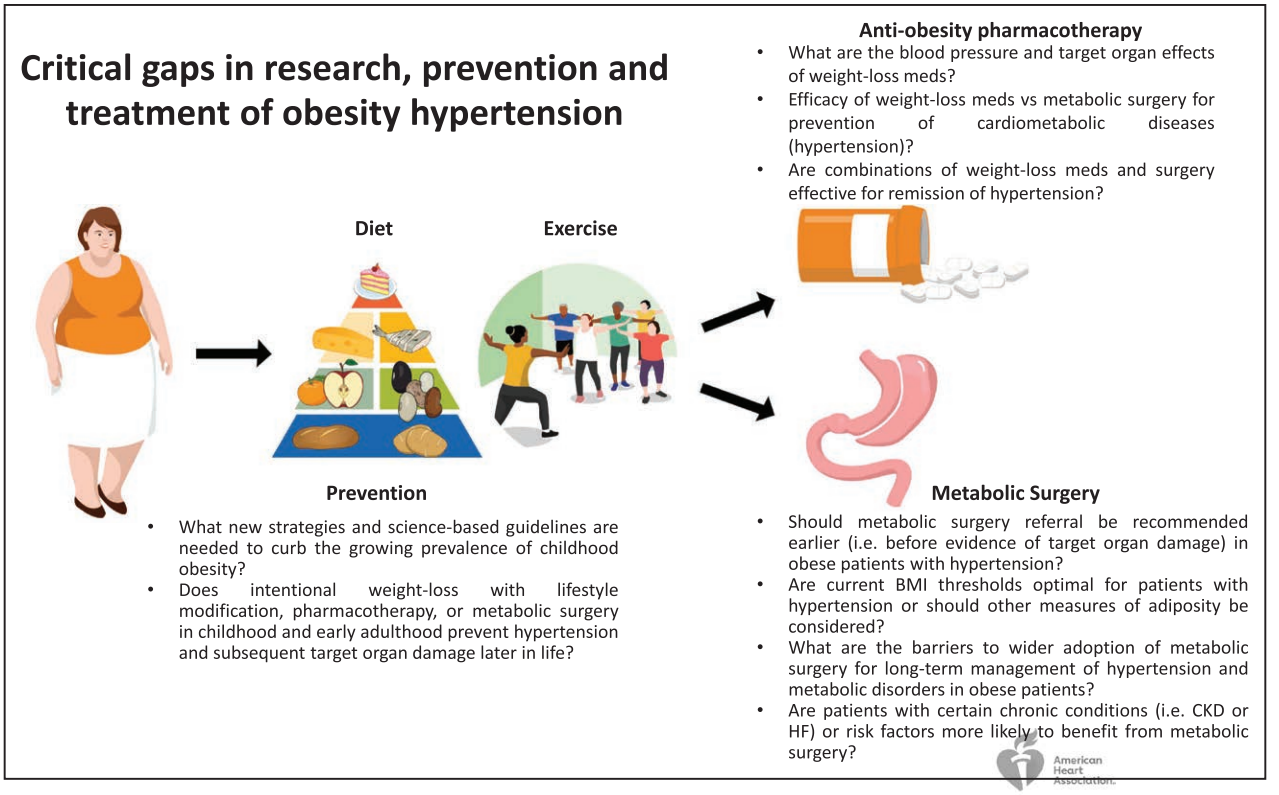

Figure 2. Critical gaps remain in research and implementation of appropriate therapies (diet, increased physical activity, reduced sedentariness, antiobesity pharmacotherapy, and metabolic surgery) in obesity hypertension.
BMI indicates body mass index; CKD, chronic kidney disease; and HF, heart failure.

involving MS to specifically evaluate BP as the primary end point.[91] In GATEWAY, 100 patients with a BMI of 30 to 39.9 kg/m^2 who were treated with ≥2 antihypertensive agents at maximum doses or >2 agents at moderate doses were randomized 1:1 to receive either RYGB plus medical therapy (n=50) or medical therapy alone (n=50). At 12 months, the primary outcome, a ≥30% reduction of the total number of BP medications while maintaining office BP <140/90 mm Hg, was more common in the RYGB group compared with the control group (83.7% versus 12.8%; rate ratio, 6.6 [95% CI, 3.1–14.0]; P<0.001). Remission of hypertension, defined as BP <140/90 mm Hg without medication use, was more common after RYGB (51% versus 0%). At 3 years follow-up of GATEWAY, the primary outcome occurred in 73% of patients from the RYGB group compared with 11% of patients from the medical therapy group (relative risk, 6.52 [95% CI, 2.50–17.03]; P<0.001).[92] Remission of hypertension (35% versus 2%) and medication use (median, 1 [interquartile range, 0–2] versus 3 [interquartile range, 2.8–4]) favored RYGB versus medical therapy, respectively (P<0.001). Total weight loss was 27.8% and −0.1% in the RYGB and medical therapy groups, respectively. In the RYGB group, 13 patients developed hypovitaminosis B_{12}, and 2 patients required reoperation.

Safety and Complications

Since minimally invasive surgery was introduced in the 1990s, there has been a significant decrease in perioperative morbidity and mortality rates associated with MS. The US Nationwide Inpatient Sample database showed a total in-hospital morbidity rate of 9% and mortality risk of 0.1%.[93] A systematic review reported that the perioperative complication rate among patients undergoing MS ranged from 10% to 17%, and the 30-day mortality rate was 0.08%.[94] The perioperative complication rate of MS is approximately equivalent to that of laparoscopic cholecystectomy or laparoscopic appendectomy or hysterectomy.[95]

PREVENTION OF OBESITY HYPERTENSION

Prevention of weight gain and obesity is paramount to prevent cardiometabolic diseases, including hypertension and subsequent heart, kidney, and brain diseases. The prevalence of obesity in children and adolescents 2 to 19 years of age was 18.5% and affected ≈13.7 million individuals from 2015 to 2016.[96] In children and adolescents, increases in BMI are strongly correlated with increases in BP. Children with obesity have a 2-fold increased risk of incident hypertension and children with severe obesity have a >4-fold increased risk

Table 3. Unanswered Questions and Future Directions

What new strategies and science-based guidelines are needed to prevent childhood obesity and hypertension?
Does intentional weight loss with pharmacotherapy or MS in childhood and early adulthood prevent hypertension and subsequent target organ damage in later life?
What is the optimal amount of time that clinicians should allow before recommending more aggressive weight management strategies (ie, antiobesity medications or MS) beyond lifestyle changes?
What is the optimal amount of time that clinicians should allow before recommending more aggressive hypertension management strategies beyond lifestyle changes?
Is MS or antiobesity pharmacotherapy beneficial in patients with prevalent CVD, including HF (particularly HF with preserved ejection fraction)?
At what point or age are weight-loss therapies beyond diet and exercise potentially past the point of benefit? Is there harm associated with antiobesity pharmacotherapy or MS in older individuals?
What are opportunities to identify and stratify patients with obesity who may be at higher risk for target organ damage and subsequent cardiometabolic or kidney disease risk?
Should antiobesity pharmacotherapy or MS be more strongly considered for less severe obesity (ie, BMI <35 kg/m^2) or those who are overweight with early target organ damage (ie, left ventricular hypertrophy or CKD)?
Further studies are needed to examine how negative social determinants of health and inequities in health care access adversely affect obesity-related health outcomes among underrepresented racial and ethnic groups.
Do interventions targeting the large reductions of anorexigenic hormones and decreases in energy expenditure that accompany weight loss help sustain the beneficial effects of weight loss on BP?
RCTs evaluating MS vs pharmacotherapy to reduce risk for CKD, HF, and stroke are needed.
It is unclear whether the mechanisms that explain the beneficial effects of reducing sedentariness on BP are different from the mechanisms that underlie BP reductions with increasing PA.
What are the minimal and maximal tolerated doses for reducing sitting time to lower BP?
What are the mechanisms of maternal and paternal programming of early-onset obesity and hypertension in offspring?
Are weight management interventions during critical periods of pregnancy in expectant mothers and in postnatal life of their offspring effective in preventing childhood obesity and attendant cardiorenal and metabolic disorders?
What are the long-term consequences of MS in adolescents with obesity in preventing cardiorenal and metabolic diseases later in life? Do the benefits of MS in these adolescents outweigh the risks?
Why does MS cause rapid reductions in BP and metabolic disorders even before there is significant reduction in body weight or adiposity?

BMI indicates body mass index; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure; MS, metabolic surgery; PA, physical activity; and RCT, randomized controlled trial.

of developing hypertension compared with children who maintain healthy weight. Therefore, comprehensive and coordinated efforts, including multidisciplinary strategies across health care systems, research programs, advocacy, education, media, and consumer organizations, are necessary.[97] Other factors, including maternal and paternal obesity and hypertension, hypertensive diseases in pregnancy, and genetic causes of early-onset obesity, may play important roles in the development of obesity hypertension later in life and are areas that need further investigation.[98,99]

UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

Figure 2 and Table 3 address research gaps and unanswered questions, with suggestions for future directions.

CONCLUSIONS

Obesity is a major cause of hypertension and subsequent cardiovascular, kidney, and brain injury. The mechanisms for decreased BP after weight loss may be caused largely by reversal of the mechanisms that mediate increased BP with weight gain. Some of these mechanisms, however, such as reduced sympathetic activity appear to be rapidly reversed with reductions in caloric intake, even before there is significant weight loss. Intentional weight-loss strategies, including lifestyle changes such as diet, increased PA, and reduced sedentariness, are important ways to reduce BP in individuals with obesity that may attenuate risks of hypertension and related diseases. However, these lifestyle modifications are difficult for many patients to maintain, and rates of weight regain are high. Evidence-based treatments such as pharmacotherapy and MS can be used to treat obesity and, as a result, lower BP. Antiobesity medications are available for short- and long-term use; however, prescription rates for these drugs remain low, likely because of limited insurance coverage and low levels of clinician proficiency with treating obesity. When antiobesity pharmacotherapy is prescribed for individuals at risk for or with hypertension, it is important to consider the mechanism of action when identifying a treatment option. MS is an effective long-term way to reduce adiposity in individuals with severe obesity. Furthermore, MS has both short-term and important long-term effects on reduction of BP in patients with obesity. Additional RCTs to assess the effects of MS on downstream risk reduction for obesity-related diseases such as chronic kidney disease, stroke, and heart failure are warranted.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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