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Review Article

Limited Long-Term Efficacy of Lifestyle-Mediated Weight Loss on Blood Pressure Control and the Biology of Weight Regain

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Abstract

Hypocaloric weight reduction, with or without increased physical activity, lowers blood pressure (BP). Heart rate, sympathetic nervous system, and renin-angiotensin-aldosterone system activity also decline. However, with time, substantial weight is typically regained in most individuals who lose weight, and the beneficial effects of weight loss on BP decline or are reversed. The initial decline in BP with weight loss is likely enhanced by negative caloric balance. Thus, even with isocaloric weight loss maintenance, the magnitude of the initial BP reduction appears to decline with time. Of further concern, the complex physiological (counterregulatory) adaptations to weight loss foster weight regain as more calories are desired than required and energy expenditure falls. Sustained weight loss generally requires a substantial long-term time commitment to physical activity and a high level of vigilance. High protein, low glycemic, high fiber, and reduced energy density diets may also be beneficial in reducing hunger and increasing satiety. Individuals who are counseled to lose weight should be aware of the challenges in maintaining weight loss, receive education on the lifestyle changes required to sustain weight loss, and commit to an evidence-based plan designed to foster long-term success. Future research directed at blocking or ameliorating the disproportionately large reductions of anorexigenic hormones and decreases in energy expenditure that accompany weight loss would help sustain the beneficial effects of weight loss on BP.

Key words: Lifestyle, weight loss, weight regain, hypertension, blood pressure

In 1923, William E. Preble stated that being overweight by 15 pounds or more is an increasingly serious condition with advancing years, conducive to heart, arterial and kidney diseases, diabetes, and hypertension.[1] Preble stated that obesity and its complications reflected an eating disorder. Along that line, in 1948, Brozek, Chapman, and Keys reported that various dietary limitations were recurring themes for the cure or amelioration of hypertension.[2] They summarized a "natural experiment" on prevalent hypertension before, during, and after the German siege of Leningrad in World War II.

The siege intentionally interrupted the food supply to Leningrad from October 1941, through March 1942.[3] The combination of harsh weather, multiple theaters of warfare, long supply lines, and local resistance kept German troops from occupying Leningrad, although some residents died from starvation. The percentage of admissions for hypertension to the First Medical Institute in Leningrad declined from 10% to 15% pre-siege to 2% during the siege [Figure 1].[1] Hypertension-related admissions rose to 24.5% with refeeding of the population over the next 8 months, then peaked at 50% in 1943 before declining to 35% in early 1944. The percentage of patients with hemorrhages and/or exudates on funduscopic examination also increased from ≤25% before to 70% after the siege, suggesting more severe hypertension with refeeding. In fact, prevalent hypertension rose 2–4-fold across age groups after as compared to before the siege [Figure 2] and coincided with hospital admissions for hypertension.[2]

Keys and colleagues subsequently conducted the "Minnesota experiment" of calorie deprivation and refeeding in 34 healthy young men.[2] After consuming a diet of <1500 kcal/d for 6 months, mean body weight fell 23.9%. Mean blood pressure (BP) for the group declined ~11.8/4.3 mmHg from 106.5/69.9 to 94.7/64.5 mmHg

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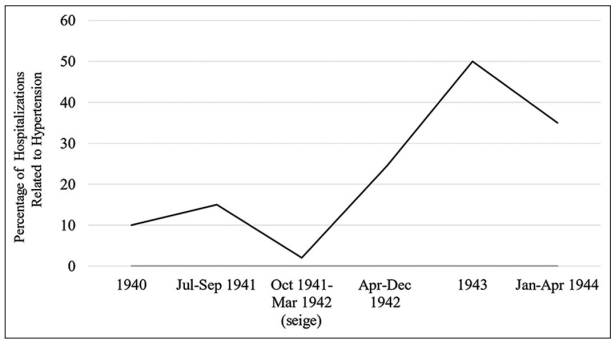

Figure 1: The percentage of hospital admissions at the First Pavlov Medical Institute was assessed at various time periods before, during, and following the German siege of Leningrad during World War II. As shown, hypertension-related hospital admission declined dramatically during the siege then rapidly increased above the pre-siege baseline with refeeding of the population post-siege

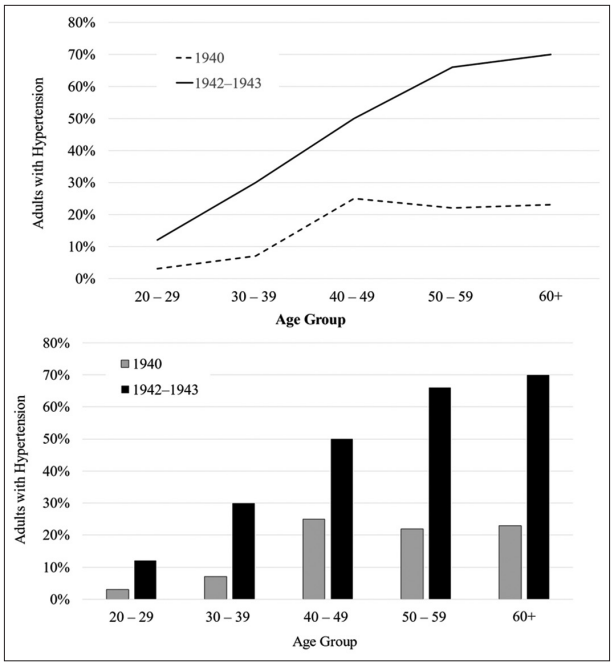

Figure 2: The prevalence of hypertension by age group in Leningrad is depicted in the calendar year before the siege (1940) and the year following the siege (1942–1943). As shown, the prevalence of hypertension was greater after than before the siege of Leningrad during World War II

as mean heart rate fell from ~56 to 37 beats/min. In a subset of 12 men, BP after 6 months of underfeeding was 92.7/63.2 mmHg and rose to 104.9/68.8 mmHg after 20 weeks of refeeding, an increase of ~12.2/4.5 mmHg. However, BP with refeeding did not exceed the original baseline of 105.3/79.1 mmHg, although mean body weight of 70.8 kg after 20 weeks refeeding was 3.1 kg higher than 67.7 kg at baseline. The fall in BP with calorie deprivation in normal volunteers was consistent with the decline in prevalent hypertension during the siege of Leningrad. The failure of BP to overshoot with refeeding in normal volunteers was inconsistent with the prominent rise in prevalence and severity of hypertension in Leningrad with refeeding after the siege.

Several subsequent studies addressed the BP effects of weight loss in response to lifestyle, primarily diet, and exercise, and BP responses to weight regain. The potential adverse health effects of weight cycling, that is, repeated episodes of weight loss and regain, and the biological mechanisms underlying recidivism after weight loss will be discussed.

Lifestyle Change, Weight Loss, and Hypertension

The medical literature

While this paper is not a systematic review or meta-analysis, this topic appears frequently in the medical literature. An Ovid Medline literature search using "weight loss and hypertension" identified 4277 original papers and 1306 review articles from 1946 to May 2020; 3441 original papers and 1074 review articles were identified since 2000. A search using "weight loss and BP" identified a moderately larger number of papers. Despite the relatively large number of papers, three systematic reviews found very few original studies of sufficient duration and quality to assess the long-term effects of weight loss on BP.[4-6]

Systematic reviews of long-term lifestyle interventions, weight loss, and BP

Horvath *et al*. identified a 6.3 mmHg reduction in mean systolic BP in two dietary interventions of limited duration, that is, one of 6 months and the other of 56 weeks [Table 1].[4] Body weight fell an average of 4.1 kg in five studies.

Aucott *et al*. included eight clinical trials and eight cohort studies of at least 2 years duration between 1990 and 2008. All studies assessed the effect of lifestyle interventions on weight loss and BP.[5] The 16 studies combined showed 2.8 kg weight loss (95% confidence interval [CI] −13.2, 7.5) and BP reduction of 2.9/1.9 mmHg (95% CI −9.2, 3.3/−9.5, 5.6). The changes of body weight and BP were not statistically significant given wide CI. In meta-regression analysis, systolic BP declined ~1 mmHg/kg weight loss for 2–3 years. BP appeared to revert to higher levels over longer time periods.

Semlitsch *et al*. conducted a systematic review of randomized dietary weight loss interventions at least 24 weeks in duration on patients with hypertension.[6] In three studies with 371 patients in the dietary intervention and 360 controls, systolic BP declined 4.5 mmHg on evidence deemed low quality. Body weight fell 4.0 kg in five studies with 435 participants assigned to the intervention and 445 to control. Weight loss data were of moderate quality. The authors concluded that weight loss diets reduced body weight and BP. The magnitude of effects was uncertain given small numbers of subjects in studies of low-to-moderate quality. The systematic reviews are consistent with the conclusion that the long-term impact of weight loss on BP in adults with hypertension is uncertain but appeared limited.[7]

A recent review of weight loss and hypertension in obese subjects included 13 interventional or observational studies

Table 1: Summary of studies and systematic reviews on studies showing limited long-term impact of weight loss on BP

Author, Ref#	Study description	Study sample	N	BP results	Weight	Notes
Systematic reviews of long-term lifestyle interventions, weight loss, and BP						
Horvath[4]	2 diet interventions 6 months, 56 wks			SBP −6.3	−4.1 kg	
Aucott[5]	8 Trials+8 Cohort ≥2 years			−2.9/−1.9	−2.8 kg	SBP −1 mmHg/1 kg loss over 2–3 years, but BP reverted over longer time
Semlitsch[6]	Randomized trials >24 wks, 3 studies	Patients with Hypertension	371 diet 360 controls	SBP −4.5		Low quality
Semlitsch[6,7]	5 studies, randomized trials	Patients with hypertension	435 diet 445 controls		−4.0 kg	Moderate quality
Fantin[8]	13 studies (2010–2019)	Obese patients				Lack of evidence on long-term BP effects with weight loss
Selected studies of weight loss, weight regain, and BP						
Brozek,Leningrad WW II[2,3]	Ecological					Rates of HTN fell markedly with starvation during siege and exceeded baseline with refeeding after siege
Keys, Minnesota Experiment[2]	<1500 kcal/d×6 months	Healthy young men	34	106.5/69.9 94.7/64.5	69.4 kg 52.9 kg	BP decreased with weight loss
Keys, Minnesota Subset[2]	Baseline/6 mo underfeeding/20 wks refeeding	Healthy young men (subset)	12	105.3/79.1 92.7/63.2 104.9/68.8	67.7 kg --- 70.8 kg	Weight gain with refeeding but BP did not rise above baseline
Stevens, TOHP II[9]	Weight loss and usual care arms	Men, Women 30–54 years. BP <140/83–89, 110–165% IBW	595 weight loss; 596 usual care	−3.7/−2.7 −1.8/−1.3 −1.3/−0.9	−4.4 kg 6 mo −2 kg 18 mo −0.2 kg 36 mo	Risk ratio for HTN weight loss versus control 0.58 (0.36–0.94) at 6 mo., 0.78 (0.62–1.00) at 18 mo., and 0.81 (0.70–0.95) at 36 mo.

wks: Weeks; SBP: Systolic BP; kg: Kilogram; HTN: Hypertension; kcal: Kilocalories; mo: Months; vs: Versus; IBW: Ideal body weight

between 2010 and 2019.[8] A positive effect of weight loss on BP was found in each study, albeit with differences in the magnitude and durability of BP reduction overtime. The authors concluded that "there is still a lack of evidence about long-term effects of weight loss on hypertension," yet recommended that weight management should be pursued in patients with obesity and hypertension.

Selected studies of weight loss and BP

Systematic reviews provide a useful overview of the extant literature, yet further insights can be gained by evaluating details of individual interventional and observational studies. The Trials of Hypertension Prevention (TOHP), Phase II, included adults 35–54 years old with untreated BP <140/83–89 mmHg and body weight 110–165% of ideal [Table 1]. One TOHP II report focused on 595 overweight and obese adults randomized to weight loss (diet change, physical activity, and lifestyle support) and 596 to usual care.[9] Mean weight changes at 6, 18, and 36 months in the intervention and control groups, respectively, were −4.4 versus 0.1 kg, −2.0 versus 0.7, and −0.2 versus 1.8. The magnitude of weight loss and the difference in weight between the intervention and control groups declined with time.

In a *post hoc* analysis of the TOHP, subjects randomized to weight loss were divided into three subgroups: (i) Weight loss ≥4.5 kg at 6 and 36 months (successful maintenance [n = 73, 12.3%]), (ii) weight loss ≥4.5 kg at 6 months but <2.5 kg at 36 months (relapse [n = 129, 21.7%]), and (iii) weight loss ≤2.5 kg at 6 and 36 months (no loss [n = 198, 33.3%]) with 195 (32.8%) who did not fit these groups. Systolic BP fell approximately 9.5 and 5.8 mmHg at 6 and 36 months, respectively, in successful maintainers, ~9 and 0 in the relapse group, and ~2.8 and +1.8 in the no loss group. Successful maintainers had ~65% lower risk for hypertension than participants randomized to the control group. Thus, ~1 in 8 (12.3%) intervention participants attained significant reductions in BP and hypertension risk with modest sustained weight loss.

Among 14,306 adult participants who were ever overweight or obese (cross-sectional representative samples of the U.S. population repeated at 2-year intervals from 1999 to 2006), 82.3% had hypertension. For the entire group, 36.6% and 17.3% had maintained weight loss of ≥5% and ≥10%, respectively, for at least a year.[10] Lower income, less education, female sex, older age, poor health status, and diabetes, and non-Hispanic White race/ethnicity were among the independent predictors of ≥10% weight loss.

A trial of sodium reduction and weight loss in older persons provided support for the success of older adults in sustaining weight loss.[10,11] The study included a subset of 585 adults 60–80 years who were overweight or obese with BP <145/<85 mmHg on a single antihypertensive medication. Overweight and obese participants were randomized to

reduced sodium intake (goal 80 mmol/d), weight loss (goal ≥4.5 kg), both, or usual care. After 90 days intervention, the protocol required attempted withdrawal of antihypertensive therapy. Participants were then followed for the primary outcome of BP ≥150/≥90 mmHg, restarting antihypertensive medication, or a cardiovascular event. BP medications were successfully withdrawn in 93% of weight loss and 87% of control participants. Adults randomized to weight loss achieved a 5 kg weight reduction at 6 and 9 months and maintained weight loss of 4 kg at 21 and 24 months, 4.4 kg at 27 months, and 4.7 kg at 30 months (median follow-up 29 months). In addition to successful long-term weight loss, older adults randomized to weight loss had a lower relative hazard ratio for the primary outcome (0.64, 95% CI 0.49–0.84, p=.002) compared to the control group.

A systematic review and meta-analysis of long-term weight loss in adults ≥60 years identified nine studies from a literature search spanning 1966 through 2008.[12] A median weight loss of 3 kg at 1 year was identified from seven studies. No significant changes were seen in the lipid profile. Only one study in the meta-analysis included sufficient data to assess BP.[11] BP fell 4.0/1.1 mmHg after 90 days of the weight loss intervention and before withdrawal of antihypertensive medication compared to 0.8/0.8 mmHg in the control arm.

Biological and Behavioral Mechanisms Contributing to Weight Regain Following Weight Loss

On balance, studies of lifestyle and weight loss in overweight and obese adults with hypertension show a recurring pattern of initial success with reduction of weight and BP. Overtime weight and BP return toward baseline. In fact, a substantial proportion of normal weight, overweight, and obese individuals has repeated cycles of weight loss followed by weight regain, that is, weight cycling.[13] In fact, some evidence suggests that the adverse health effects of weight cycling may be greater among individuals of normal than excess weight.

Not surprisingly, obese individuals maintaining weight loss report a higher burden of effort than reported by normal weight individuals maintaining weight.[14] While both groups had similar levels of energy intake, the obese weight maintenance group reported significantly higher levels of physical activity. Moreover, the obese weight maintenance group reported both more restraint and greater disinhibition of eating behaviors, while normal weight individuals relied more on internal cues. The biology of weight regain may account for the greater effort including the need for greater restraint and higher levels of physical activity by previously obese individuals sustaining weight loss than the effort of normal weight individuals maintaining weight.

In their review, "Attenuating the biologic drive for weight regain following weight loss," Melby *et al.* summarized and integrated 150 research reports on the biology of weight loss and regain.[15] They describe an "energy gap" following weight loss in which more energy is desired than required. The experience of hunger in excess of needs is associated with and likely driven at least partially by elevation of ghrelin, an orexigenic hormone, and reduction of anorexigenic hormones, for example, cholecystokinin, peptide YY, amylin, pancreatic polypeptide, and glucagon-like peptide-1. Moreover, the decline in anorexigenic hormones exceeds that expected for the magnitude of weight loss. After weight loss in obese individuals, total daily energy expenditure, thermic effect of food, resting metabolic rate, and physical activity energy expenditure all decline, that is, energy efficiency rises. The authors succinctly summarized the multiple changes in energy regulation, which serve to powerfully promote weight regain [Figure 1].

A report from the Biggest Losers weight loss competition is consistent with the aforementioned adaptive changes to weight loss that foster weight regain.[16] This group achieved a mean weight loss of 58.3 kg after 30 weeks in the competition, which was accompanied by a reduction in resting metabolic rate averaging 610 kcal/day. After 6 years follow-up, they regained a mean of 41.0 kg (70% weight regain). Of note, resting metabolic rate remained 704 kcal/day below the pre-weight loss baseline and was similar to the change at 30 weeks, despite weight regain. The fall in resting metabolic rate with weight loss is termed metabolic adaptation or adaptive thermogenesis and emerges as a major contributor to weight regain.

Applying the Biology of Weight Regain to Approaches that Sustain Weight Loss

The counterregulatory responses to weight loss promote weight regain [Figure 3, right upper half]. On a positive note, the factors that promote weight regain can help inform an intervention to mitigate recidivism after successful weight loss [Figure 3, right lower half].[15] Of the various factors shown, high-protein diets and consistent time commitment to physical activity emerge as especially important factors in sustained weight loss. On a calorie basis, the thermic effect of protein is roughly 3 times greater than that of carbohydrates and fat. Protein also produces greater satiety than comparable calories from carbohydrate or fat. High levels of physical activity increase exercise energy expenditure during exercise and for several hours after physical activity ends. The effect of physical activity to raise resting metabolic rate essentially requires daily renewal. After successful weight loss, a high level of daily exercise raises physical activity energy expenditure and total daily energy expenditure, which support a higher isocaloric ceiling than lesser exercise. The greater isocaloric ceiling maintains a higher thermic effect of food, especially when protein comprises a relatively high percentage of total calories. Under these conditions, a more favorable equilibrium is maintained between calories desired and required, resulting in better weight loss maintenance.

Among 170 subjects on a reduced calorie diet for 18 months, weight loss was not significantly different at 18 months in those

randomized to supervised exercise for 300 min/week in months 0–6 versus 7–12 (−6.9 vs. −7.9 kg, P = NS).[17] Weight loss at 6 months was greater in the group that received supervised exercise in the first 6 months (−8.7 vs. −6.9, P = 0.047). Both groups had approximately 60 min daily of moderate physical activity at baseline, which rose to ~90 min/day during supervised exercise training. During months 12–18, when neither group received supervised exercise, both groups averaged ~75 min daily of moderate physical activity. This study is consistent with other reports indicating that a significant time commitment to physical activity is a component of successful long-term weight loss.

Individuals in the National Weight Control Registry have maintained a minimum 13.6 kg weight loss for a year or more with a mean 33 kg weight loss over 5 years.[15,18] These registrants provide additional confirmation on the importance of high levels of physical activity and limited sedentary time, frequent weight monitoring, and high levels of dietary restraint. Conversely, weight regain was associated with more depression, hunger, disinhibition, and binge eating as well as higher fat consumption than in those who successfully sustained weight loss.

Adverse Health Effects of Weight Regain and Cycling: Focus on BP

Several variables may impact the assessment of BP responses to weight loss and regain. One important concept to consider is that the BP response to the initial period of weight loss with negative caloric balance may be substantially greater than longer-term effects of isocaloric sustained weight reduction. For example, in response to an 800 calorie daily diet for 9 weeks, body weight declined among 34 men and women from a mean of 101.7 to 87.3 (−14.4 kg) and 24 h ambulatory systolic BP fell from 130.1 to 122.1 (−9 mmHg).[19] Despite full maintenance of weight loss at 6 months, mean 24 h systolic BP rose to 126.5 (−3.6 mmHg from baseline [40% of initial response]). Although ~88% of initial weight loss was sustained at 1 year (−12.6 kg), systolic BP rose to 127.9 (−2.2 mmHg from baseline [~24% of initial BP response]).

In a study of 18 non-diabetic adults with the metabolic syndrome, 9% weight loss over 12 weeks reduced total body norepinephrine spillover by 23%, muscle sympathetic nerve activity (MSNA) by ~40%, and plasma renin activity ~25% (all changes statistically significant).[20] Despite excellent maintenance of weight loss at 7 months, MSNA and plasma renin activity returned to baseline levels, although norepinephrine turnover remained lower. Unlike the preceding report, BP responses at 12 weeks were largely maintained at 7 months. Yet, these data suggest that even with sustained weight loss, key neurohormonal responses to initial weight loss are not fully retained over longer time periods. In other words, the biological responses to initial weight loss with negative caloric balance are often not as robust as the longer-term responses to successful, isocaloric weight loss maintenance.

The relationship of weight cycling to incident hypertension has not been consistent across studies.[13] Among 46,224 women in the Nurses Heath Study II who had non-hypertensive BP values, weight gain was associated with incident hypertension

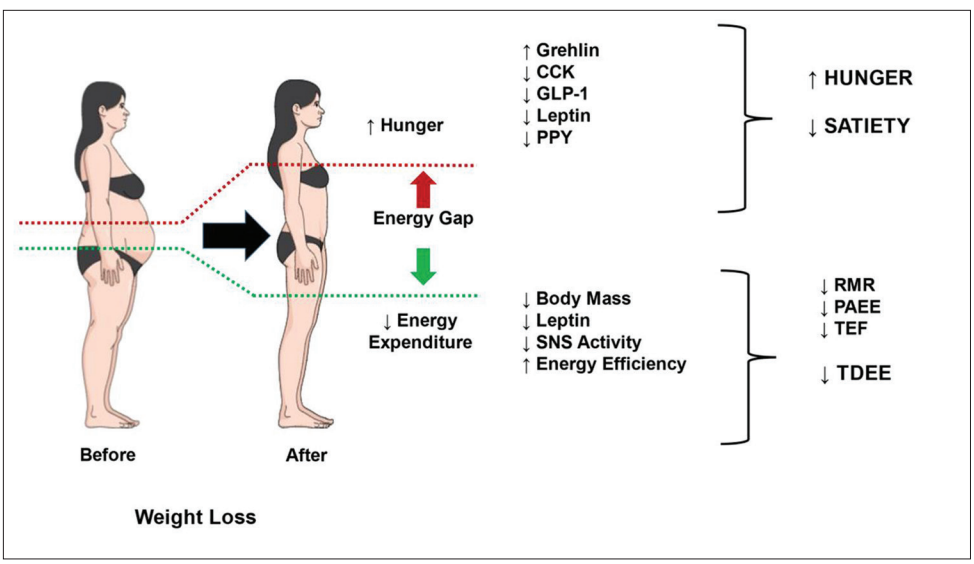

Figure 3: Successful weight loss activates pathways fostering weight regain (from reference 15). Energy intake and expenditure are balanced in weight stable obesity. Weight loss from decreased energy intake heightens hunger and lowers energy expenditure resulting in an "energy gap." The energy gap is linked to increased orexigenic and decreased anorexigenic peptides, which signal nutrient deprivation to the brain resulting in hunger, food cravings, and less satiety. Diet-induced weight loss also reduces total daily energy expenditure, physical activity energy expenditure as resting metabolic rate, and the thermic effect of food fall. Greater hunger and less energy expenditure promote weight regain

but mild or severe weight cycling was not.[21] In 12,362 middle-aged German men and women, weight cycling was positively associated with incident hypertension among individuals who were obese but not among those who were not obese.[22] Among 3965 men and women participating in a prospective primary prevention study of heart disease and cancer in France, weight fluctuations were not associated with incident hypertension after adjusting for relative weight change.[23] In a cross-sectional study of 664 Japanese men 40–49 years old, weight cycling was not significantly related to incident hypertension after adjusting for the slope of weight overtime and body mass index at the time of study and at age 20.[24] Similar findings were reported from a single clinical site in Italy that evaluated 459 obese men and women.[25] On balance, the effect of weight cycling on BP and incident hypertension appears minimal after accounting for the magnitude and rate of increase in weight and adiposity.

Summary and Clinical Implications

Hypocaloric weight reduction lowers BP, heart rate, sympathetic nervous system, and renin-angiotensin-aldosterone system activity. Yet, overtime weight is regained in most individuals who lose weight, and the beneficial effects of weight loss on BP are significantly diminished or reversed. Moreover, the initial BP responses to weight loss are likely enhanced by negative caloric balance with a diminished longer-term BP response, despite successful, isocaloric maintenance of weight loss. Moreover, the complex physiological adaptations to weight loss foster weight regain as more calories are desired than required and energy expenditure falls. Sustained weight loss generally requires a long-term commitment to physical activity and a high level of vigilance. High protein, low glycemic, high-fiber diets, reduced energy density diets may also be beneficial in reducing hunger and increasing satiety. Patients who are counseled to lose weight should be aware of the challenges in maintaining weight loss, understand the potential loss of some BP benefits with isocaloric weight maintenance or weight regain, and be committed to an evidence-based plan to foster long-term success. Future research directed at blocking or ameliorating the disproportionately large reductions of anorexigenic hormones and decreases in energy expenditure that accompany weight loss would help sustain the beneficial effects of weight loss on BP.

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