Original Paper

Intentional Weight Loss and Dose Reductions of Antihypertensive Medications: A Retrospective Cohort Study

Ghanshyam Palamaner Subash Shantha^{a, g} Anita Ashok Kumar^a
Scott Kahan^{b, f} Sang Yun Cheah^d Lawrence J. Cheskin^{c–e}

Departments of ^aEpidemiology, ^bHealth Policy and Management and ^cHealth, Behavior and Society, and ^dDepartment of International Health, Center for Human Nutrition, Johns Hopkins Bloomberg School of Public Health, and ^eJohns Hopkins Weight Management Center, Johns Hopkins University, Baltimore, Md., ^fDepartment of Health Policy, George Washington University School of Public Health and Health Services, Washington, D.C., and ^gThe Wright Center for Graduate Medical Education, Scranton, Pa., USA

Key Words

Weight loss · Obesity · Hypertension · Blood pressure · Antihypertensive agents

Abstract

Background: Though it is well known that weight loss tends to decrease blood pressure, the quantitative association between the magnitude of weight loss and the effect on the need for antihypertensive medications is not well studied. We analyzed this association among overweight and obese attendees at two outpatient weight management centers. **Methods:** Case records of patients with a body mass index >25 at baseline were analyzed. The weight loss intervention consisted of a calorie-restricted diet (~1,000 kcal/day deficit), a behavior modification plan, and a plan for increasing physical activity. **Results:** The study cohort consisted of 100 participants, and the mean follow-up period was 15 ± 3.5 months. Significant weight loss (12.2 ± 3.4 kg) and systolic/diastolic blood pressure reductions (9.1/6.3 mm Hg) were observed by study exit. For 5, 10, and 15% weight loss, respectively, 3, 39, and 39% of the patients achieved at least 1 discontinuation of any antihypertensive medication, and 8, 42, and 21 dose reductions were achieved. Dose reductions or discontinuations occurred in all classes of antihypertensive medications with similar magnitudes of weight loss. **Conclusions:** Intentional weight loss can potentially result in dose reductions/discontinuations of antihypertensive medications. Our results should be validated with data from larger randomized controlled studies and may help to inform the conduct of a systematic review of prior randomized controlled trials that contain data on medication changes accompanying weight loss.

Copyright © 2013 S. Karger AG, Basel

Lawrence J. Cheskin, MD, FACP
Director, Johns Hopkins Weight Management Center
550 North Broadway, Suite 1001
Baltimore, MD 21205 (USA)
E-Mail lcheskin@jhsph.edu

Introduction

The National Health and Nutrition Examination Survey (NHANES) has shown that, in the last decade, 35% of adult Americans were obese [body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) ≥ 30], and that the prevalence is expected to increase in the years to come [1]. Hypertension is common in obese individuals [2]. For every 10-kg increase in body weight, mean systolic and diastolic blood pressures (SPB and DBP) have been found to be increased by 3 and 2 mm Hg, respectively [3]. Furthermore, adults who are +20% overweight have an eight-fold greater incidence of hypertension [4]. Antihypertensive medications, though known to significantly decrease morbidity and mortality among individuals with hypertension [5–7], are costly and often accompanied by side effects.

The good news is that intentional weight loss significantly decreases both SPB and DBP [8–10]. A modest weight loss of 5–10% of body weight typically decreases both SBP and DBP by approximately 5 mm Hg [10], while a 15% weight loss will frequently decrease SBP by 10 mm Hg [8].

Though it is axiomatic that the reduction in blood pressure typically accompanying intentional weight loss could result in decreased requirements for antihypertensive medications, the quantitative association between the magnitude of weight loss and the expected dose reductions or discontinuations of antihypertensive medications is not well studied. Establishing this quantitative association would be clinically useful in treating, counseling, and motivating hypertensive, obese patients considering or attempting weight loss.

Thus, in this study of overweight and obese patients who achieved weight loss of variable degrees, we attempted to establish the association between the magnitude of weight loss and the expected dose reductions or discontinuations of antihypertensive medications.

Materials and Methods

Study Setting and Design

This retrospective cohort study was conducted in two university-based specialty outpatient weight management clinics, the Johns Hopkins Weight Management Center in Baltimore, Md., and the George Washington Weight Management program in Washington, D.C. Institutional review board approval was obtained for conducting the study. Informed consent was not obtained from the participants as the data were analyzed anonymously per institutional review board guidelines.

Case records of patients with a BMI >25 at the time of enrollment into the two weight management programs during the period from March 2008 to October 2011 were assessed for eligibility. Both were convenience samples. Patients were sampled if they had a diagnosis of essential hypertension at the time of enrollment into the programs, reported taking antihypertensive medications at the time of enrollment, and had at least 1 documented dose reduction or discontinuation of at least 1 of the antihypertensive medications before the study concluded in October 2011. Patients thus sampled formed the study cohort. The following exclusion criteria were applied: no diagnosis of hypertension at the time of enrollment into the programs or no documented dose reductions of antihypertensive medications (control group). Patients receiving treatment with 4 antihypertensive medications were excluded both from the study cohort and the control group as they present a more severe form of hypertension and are less likely to respond to weight loss. All excluded patients formed the excluded cohort.

Baseline Data Collection

Demographic data (age, gender, and race/ethnicity), cardiovascular risk factors (smoking, diabetes, and hypertension), medication history (antidiabetic medications, antihypertensive medications, and lipid-lowering drugs), clinical parameters (height, weight, SBP, and DBP), and laboratory parameters (fasting glucose, HbA1C, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides) were collected for the total cohort. BMI was calculated as per standard guidelines [11].

Metabolic syndrome was determined using the National Cholesterol Education program (NCEP ATP III) guidelines [12]. Hypertension was identified by physician diagnosis. All patients in our study had essential hypertension. There were none with secondary forms of hypertension. The severity of hypertension was classified using the Joint National Committee (JNC)-7 criteria [13].

Patient Follow-Up and Weight Management Intervention Details

The weight loss intervention protocols followed at the two participating clinics were similar and consisted of team-based, comprehensive evaluation and treatment for weight loss. The study participants had physician visits and evaluations on average twice a month. The baseline visit consisted of a physician-conducted medical history and physical examination, blood tests (as described above), and detailed dietary, behavioral, and exercise evaluations. Treatment was individualized but typically consisted of an approximately 1,000-kcal/day energy deficit diet, a behavior modification plan, and a plan for increasing physical activity utilizing both aerobic exercise and strength training. The diet composition was individualized but was generally low fat and initially mildly carbohydrate restricted as well. Meal replacements were often utilized as part of the diet prescription to improve adherence and increase weight loss. Depending on treatment response, the intervention was further tailored to address individual patient needs. The decision to alter the dose of or discontinue antihypertensive medications was based on the clinical judgment of the treating physicians. Factors considered in deciding dose reductions included symptoms and signs suggestive of orthostatic hypotension, magnitude of weight loss, blood pressure control, and the patient's compliance to the weight management protocol.

Outcomes

The outcomes that were determined included the number (%) of patients achieving 5, 10, and 15% weight loss, time taken to reach those goals, mean SBP/DBP, mean SBP/DBP reduction, number of discontinuations, and number of dose reductions of antihypertensive medications associated with 5, 10, and 15% weight loss, and weight and blood pressure at study exit.

Patients exited the cohort if they required an increase in dose or restarting of an antihypertensive medication after the initial dose reduction or discontinuation (defined as relapse) or were administratively censored at study conclusion. The decision to restart or increase the dose of antihypertensive medications was individualized by the treating physicians, taking into account blood pressure as monitored over 2–3 consecutive visits. The time between the visit when the last documented medication dose reduction occurred until the visit when the patients relapsed was defined as time to relapse.

Statistical Analysis

Data were expressed as number (%) for categorical variables and as mean $\pm$ standard deviation for continuous variables. Two-group comparisons were performed using Student's *t* test and χ^2 test, as appropriate.

Baseline characteristics, weight changes, blood pressure changes, and the outcome variables described above were compared between the study cohort and excluded cohort participants who failed to achieve dose reductions despite success with weight loss (control group). Then, multiple linear regression and multiple logistic regression analyses were performed to identify the association between percent weight loss (centered at 5%) and the mean percent dose reductions of antihypertensive medications (for multiple linear regression) and discontinuation of any antihypertensive medications (coded as dichotomous variable for logistic regression) for the study cohort [adjusted for age, gender, JNC class, baseline BMI, number of antihypertensive medications, and type 2 diabetes mellitus (DM) diagnosis]. Multiple logistic regression analyses were also performed to identify factors associated with relapse using the study cohort (adjusted for age, gender, JNC class, baseline BMI, number of antihypertensive medications, and type 2 DM diagnosis). For all these analyses, individuals treated with 4 antihypertensive medications (2 patients) were excluded as they present a more severe form of hypertension and hence were less likely to respond to weight loss. Akaike's information criteria and Hosmer-Lemeshow goodness-of-fit were used as needed while determining the variables to be included in the model [14]. A *p* value <0.05 was considered statistically significant. All analyses were performed using Stata 11.0 statistical software (StataCorp, College Station, Tex., USA).

Table 1. Baseline characteristics of the study cohort and the control group

Variables	Study cohort (n = 100)	Control group (n = 37)	p value
Age, years	51.6±8.9	55.7±10.4	0.221
Males	54 (54)	22 (59)	0.055
Caucasians	72 (72)	27 (73)	0.173
African-Americans	28 (28)	10 (27)	0.220
Current smoking	20 (20)	8 (22)	0.091
Mean BMI	36.1±5.5	35.7±4.4	0.337
BMI 25–30	25 (25)	8 (22)	0.069
BMI 31–40	53 (53)	25 (68)	0.024
BMI ≥41	22 (22)	4 (11)	0.045
DM diagnosis	57 (58)	16 (43)	0.041
HbA1C, %	8.2±1.6	8.1±1.8	0.115
HTN diagnosis	102 (100)	37 (100)	1.000
Mean duration of hypertension, years	9±3.5	9±4.5	0.368
Mean SBP, mm Hg	144±8.9	140±14.1	0.319
Mean DBP, mm Hg	94±4.2	93±2.9	0.263
Pre-HTN	25 (25)	3 (8)	0.022
JNC stage I HTN	70 (70)	15 (41)	0.017
JNC stage II HTN	5 (5)	19 (51)	0.011
Mean TC, mmol/l	5.2±1.4	5.2±1.1	0.226
Mean LDL-C, mmol/l	4.2±1.2	4.1±1.7	0.317
Mean HDL-C, mmol/l	1.2±0.4	1.0±0.4	0.071
Mean TGL, mmol/l	1.7±0.5	1.7±0.4	0.118
Metabolic syndrome	55 (55)	29 (78)	0.014
Anti-DM drugs	57 (57)	16 (43)	0.046
Lipid-lowering drugs	75 (75)	30 (81)	0.069
Antihypertensive drugs	100 (100)	37 (100)	1.000
ACE-I	49 (49)	8 (22)	0.028
ARB	68 (68)	6 (16)	0.013
BB	23 (23)	3 (8)	0.025
CCB	22 (22)	3 (8)	0.012
Diuretics	38 (38)	10 (27)	0.043
Treated with 1 antihypertensive drug	23 (23)	4 (11)	0.047
Treated with 2 antihypertensive drugs	64 (64)	10 (27)	<0.001
Treated with 3 antihypertensive drugs	13 (13)	23 (62)	0.010

Values represent n (%) or mean ± SD.

TC = Total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TGL = triglycerides; ACE-I = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta-blockers; CCB = calcium channel blockers.

Control group: hypertensive patients with no documented dose reductions of antihypertensive medications despite success in weight loss.

Results

In total, 179 patient records (107 from Johns Hopkins and 72 from George Washington) were identified and reviewed. Of these, 77 (43%) were excluded (excluded cohort) because of the following exclusion criteria: no diagnosis of hypertension (30, 17%) or no documented dose reductions of antihypertensive medications despite success at weight loss (control group; n = 47, 26%). The remaining 102 (57%) patients formed the study cohort. Further, 2 patients from the study cohort and 10 patients from the control group were excluded as they

Fig. 1. SBP and DBP drop with % weight loss (study cohort). The x-axis represents % weight loss the study cohort participants achieved during the follow-up period, and the y-axis represents changes in SBP and DBP.

were receiving treatment with 4 antihypertensive medications. Hence, the final analytical sample size for the study cohort was 100 (56%) patients, and the control group consisted of 37 (21%) patients. The mean duration of hypertension among the study cohort was 9 ± 3.5 years. Demographic characteristics, medication details, and patient follow-up information are shown in table 1 and in online supplementary tables S1 and S2 (for all online suppl. material, see www.karger.com/doi/10.1159/000347048).

The study cohort showed a significant weight loss (12.2 ± 3.4 kg) and significant SBP/DBP reductions ($9.1/6.3$ mm Hg), with 91 (89%), 46 (46%), and 18 (18%) of the patients achieving 5, 10, and 15% weight loss, respectively, by the time of study exit (table 2). In comparison, the 37 participants from the excluded cohort who did not achieve dose reductions despite some weight loss (control group) presented nonsignificant weight losses (3.9 ± 3.1 kg) and nonsignificant SBP/DBP reductions ($2.5/2$ mm Hg), with only 6 (22%) achieving 5% weight loss and none achieving 10 or 15% weight loss.

In the study cohort, for 5, 10, and 15% weight loss, 3, 39, and 39% in the respective groups achieved at least 1 discontinuation of any antihypertensive medication (table 2). Also, for 5, 10, and 15% weight loss, 8, 42, and 21 dose reductions were observed in the respective groups (table 2). Dose reductions or discontinuations occurred in all classes of antihypertensive medications with similar magnitudes of weight loss (online suppl. table S3). Figures 1 and 2 detail blood pressure and medication changes of the study cohort with weight loss.

Additionally, 38 (38%) of the patients in the study cohort relapsed, with a weight regain of 8.3 ± 3.9 kg and an increase in SBP/DBP of $6.5 \pm 2.5/3.5 \pm 2$ mm Hg. Though the blood pressure increases of relapsing patients were significantly higher, the weight regains were not significantly different from their weight at their last dose reduction.

For every 5% weight loss, the patients in the study cohort achieved 36% reductions in their antihypertensive medication dose and had a 29% higher probability of stopping one of their antihypertensive medications (table 3). Factors such as age, gender, JNC class, baseline BMI, number of antihypertensive medications, and DM diagnosis were not associated with relapse (online suppl. table S4).

Fig. 2. Probability of dose reduction of antihypertensive medication with weight loss. The x-axis represents % weight loss, and the y-axis represents the probability for dose reductions of antihypertensive medications. Diamonds represent each dose reduction that was observed, and the vertical bars represent the distribution density of dose reductions with weight loss.

Table 2. Weight loss and antihypertensive drug dose reduction/discontinuation (study cohort n = 100)

	5% weight loss	10% weight loss	15% weight loss
Patients, n (%)	91 (91)	46 (46)	18 (18)
Time taken, weeks	5±2.5	7±2	9±2
SBP, mm Hg	136±8	135±4.6	130±4.5
SBP reduction, mm Hg	4.5±2	8.1±3.0	12.7±5
DBP, mm Hg	91±4	89±3.0	87±5.1
DBP reduction, mm Hg	2.4±0.9	4.5±2.2	7.4±2.7
Discontinuations, n (%)	3 (3)	18 (39)	7 (39)
Dose reductions, n	8	42	21

Table 3. Association between percentage weight loss (every 5%) and dose reductions/discontinuation of antihypertensive medications

	Mean % dose reduction ¹			Discontinuation of antihypertensive drugs ²		
	mean %	95% CI	p value	odds ratio	95% CI	p value
Study cohort*	36	11–79	0.036	1.29	1.04 – 1.85	0.037

* Adjusted for age, gender, type 2 DM diagnosis, BMI, JNC class, and number of antihypertensive drugs.
¹ Linear regression analysis. ² Logistic regression analysis.

Discussion

In this sample of overweight and obese adults, we observed that, with intentional weight loss of 5, 10, and 15% of starting body weight, 3, 38, and 39% of the patients, respectively, could achieve at least 1 discontinuation of an antihypertensive medication, and 8, 42 and 78 dose reductions of at least 1 antihypertensive medication were achieved.

The independent association between intentional weight loss and blood pressure reduction is well established [8–10]. The mechanism for this effect likely stems from the fact that obesity is typically a high-catecholamine and high-renin state [15–17]. Weight loss, by decreasing catecholamine, renin, and aldosterone levels, lowers blood pressure by decreasing vascular tone, reducing myocardial contractility, ameliorating the high-output state, reducing the intravascular fluid volume, and promoting natriuresis [15–17]. Of note, weight loss can thus potentially substitute for the mechanisms of action of all existing classes of antihypertensive medications. True to this hypothesis, with weight loss of similar magnitudes, we observed that it was possible to reduce the doses of antihypertensive medications of any class.

Most of the hormonal changes involved in obesity-associated hypertension correlate with the level of adiposity, and the degree of mitigation of these hormonal changes correlates with the magnitude of weight loss [18, 19]. This may be why participants in the excluded cohort with nonsignificant weight loss had poorer blood pressure reduction and thus could not achieve reductions in dosage of their antihypertensive medications (control group).

It is noteworthy that over a third (37%) of the patients in the study cohort relapsed from their reductions in and/or discontinuations of antihypertensive medications. Hypertension, being a chronic, progressive disease, usually relapses when medication discontinuation is attempted [18, 19]. Our analysis of patient factors associated with relapse revealed no significant associations. However, among patients who relapsed, though on average they had experienced some weight regain, the weight at the time of relapse was not significantly different from the weight at their last dose reduction. Thus, it is possible that the natural history of hypertension progression was being observed, resulting in relapse, or that even the modest, not statistically significant level of weight regain experienced may have partly reinstated the hormonal milieu, discussed earlier, that fosters hypertension among obese individuals.

Limitations

We observed significantly greater magnitudes of weight loss (12.2 kg by 15 months of follow-up) and blood pressure reductions (SBP/DBP: 9.1/6.3 mm Hg at 15 months) compared to typical randomized controlled weight loss trials (weight loss: 4–6 kg within 12–15 months of follow-up, SBP/DBP: 3–4/2–3 mm Hg) [20, 21]. It is thus possible that confounding due to unknown factors may have played a role. Or else, surveillance bias is possible due to the intensity of weight loss intervention being individualized and the decision to reduce the dose being subjective and at the discretion of the treating physicians. Additionally, the small sample size limited us from analyzing associations specific to individual medications and BMI categories. Finally, the study's retrospective cohort design limited our data to whatever was recorded in the patient records.

Conclusions

We found that intentional weight loss was frequently an effective intervention for achieving discontinuations and dose reductions of all classes of antihypertensive medications. Validation of the results of our study with data from larger randomized controlled trials is needed. Since a report of the association between the magnitude of weight loss and dose reductions of antihypertensive medications is novel, these findings can help to inform the conduct of a systematic review using data from prior randomized controlled trials that have

evaluated interventions for weight loss. Such information, if confirmed, can add a quantitative aspect to the oft-cited advice health-care providers give to obese, hypertensive patients: ‘lose weight, and you will reduce your blood pressure and need for medications’.

Acknowledgments

We thank Mr. Rohit Joshua Samson and Mr. Nelson David Boddu for their help with the chart review. Dr. Ghanshyam Palamaner Subash Shantha, MD, MPH, is supported in part by a NIH/NHLBI T32HL007024 Cardiovascular Epidemiology Training Grant for his research training at the Johns Hopkins Bloomberg School of Public Health.

Disclosure Statement

Lawrence Jay Cheskin serves as a consultant and stockholder for Medifast, Inc. and Vivus, Inc. All other authors have no conflicts of interest to declare.

References

- 1 Flegal KM, Carroll MD, Kit BK, Ogden CL: Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *JAMA* 2012;307:491–497.
- 2 Stamler R, Stamler J, Riedlinger WF, Algera G, Roberts RH: Weight and blood pressure. Findings in hypertension screening of 1 million Americans. *JAMA* 1978;240:1607–1610.
- 3 Boe J, Humerfelt S, Wedervang G: The blood pressure in a population: blood pressure readings and height and weight determinations in the adult population of the city of Bergen. *Acta Med Scand Suppl* 1957;321:1–336.
- 4 Kannel WB, Gordon T, Offutt D: Left ventricular hypertrophy by electrocardiogram. Prevalence, incidence, and mortality in the Framingham study. *Ann Intern Med* 1969;71:89–105.
- 5 Five-year findings of the hypertension detection and follow-up program: I. Reduction in mortality of persons with high blood pressure, including mild hypertension. Hypertension Detection and Follow-up Program Cooperative Group. *JAMA* 1979;242:2562–2571.
- 6 Five-year findings of the hypertension detection and follow-up program: II. Mortality by race-sex and age. Hypertension Detection and Follow-up Program Cooperative Group. *JAMA* 1979;242:2572–2577.
- 7 The Australian therapeutic trial in mild hypertension: Report by the Management Committee. *Lancet* 1980;1:1261–1267.
- 8 Salzano JV, Gunning RV, Mastopaulo TN, Tuttle WW: Effect of weight loss on blood pressure. *J Am Diet Assoc* 1958;34:1309–1312.
- 9 Reisin E, Abel R, Modan M, Silverberg DS, Eliahou HE, Modan B: Effect of weight loss without salt restriction on the reduction of blood pressure in overweight hypertensive patients. *N Engl J Med* 1978;298:1–6.
- 10 Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, et al: Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* 2011;34:1481–1486.
- 11 Jeffrey SF, Eleftheria MF: Obesity; in Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL (eds): *Harrison’s Principles of Internal Medicine*, ed 16. New York, McGraw Hill Inc, 2005, vol 1, pp 422–423.
- 12 Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–2497.
- 13 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al, National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560–2571.
- 14 Hosmer D, Lemeshow S: *Applied Logistic Regression Analysis*, ed 2. New York, John Wiley & Sons, 2000.
- 15 Landsberg L, Young JB: Fasting, feeding and regulation of the sympathetic nervous system. *N Engl J Med* 1978;298:1295–1301.
- 16 Jung RT, Shetty PS, Barrand M, Callingham BA, James WP: Role of catecholamines in hypotensive response to dieting. *Br Med J* 1979;1:12–13.

- 17 Messerli FH, Christie B, DeCarvalho JG, Aristimuno GG, Suarez DH, Dreslinski GR, et al: Obesity and essential hypertension. Hemodynamics, intravascular volume, sodium excretion, and plasma renin activity. Arch Intern Med 1981;141:81–85.
- 18 Dannenberg AL, Kannel WB: Remission of hypertension. The ‘natural’ history of blood pressure treatment in the Framingham Study. JAMA 1987;257:1477–1483.
- 19 Schmieder RE, Rockstroh JK, Messerli FH: Antihypertensive therapy. To stop or not to stop? JAMA 1991;265:1566.
- 20 Appel LJ, Clark JM, Yeh HC, Wang NY, Coughlin JW, Daumit G, et al: Comparative effectiveness of weight-loss interventions in clinical practice. N Engl J Med 2011;365:1959–1968.
- 21 Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. The Trials of Hypertension Prevention Collaborative Research Group. Arch Intern Med 1997;157:657–667.