Body weight variation and control of cardiovascular risk factors in essential hypertension

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Abstract
Objective: The objective was to assess the impact of weight changes on blood pressure (BP), lipids and glucose goals in a cohort of hypertensive subjects. Design. Prospective follow-up. Setting. Hypertension clinic. Patients. 326 hypertensive non-diabetic subjects, 46% with metabolic syndrome (MS). Interventions. Usual care treatment, which included diet, physical exercise and drugs prescribed when indicated. All patients were observed for up to 1 year. Main outcome measures. BP and low-density lipoprotein-cholesterol (LDL-C) goal were those in ESH/ESC and ATP III recommendations, respectively. The glucose goal was to delay progression to type 2 diabetes mellitus, or to achieve blood glucose <100 mg/dl for non-diabetics. According to body weight changes, patients were categorized using adjusted ROC curves models. Results. Overall, there was a significant weight increment of 0.5 kg (95% CI 0.1–0.9 kg); 28 patients (8.6%) lost more than 5 kg, and only four (1.2%) lost more than 10 kg. BP, LDL-C and glucose goals were achieved in 56%, 78% and 61% of patients, respectively. To lose or not gain weight was an independent prognostic factor to achieve the BP goal in all the patients and the LDL goal in the presence of MS. For glucose control, being treated with beta-blockers and/or diuretics was a negative factor. Conclusions. In hypertensive subjects, even small changes in weight may have an important impact on achieving cardiovascular goals, mainly in those with MS.

Key Words: Blood pressure control, metabolic syndrome, therapeutic goals, weight variation

Introduction
Antihypertensive treatment intends to reduce hypertension-induced morbidity and mortality. This requires individual assessment of global cardiovascular risk, and control of not only high blood pressure (BP) values but also other frequently associated cardiovascular risk factors (1–4). Among hypertensives, four out of five have one or more additional risk factors, including dyslipidemia, glucose metabolism abnormalities or obesity. A clustering of two or more of these metabolic abnormalities associated with high BP, the so-called metabolic syndrome (MS), has been described in as much as one-third of hypertensives. Overweight, obesity and mainly abdominal fat accumulation are key components for the clustering of cardiovascular risk factors and appears as one of the leading preventable causes of death in developed countries (3–9). Moreover, obesity is one of the main factors with the poorest rates of control among the cardiovascular risk factors (10).

The importance of weight reduction in achieving BP control has been emphasized in all the released guidelines on hypertension management (1,2), but the poor success in reducing body weight has been a constant in a large number of studies. The impact of body weight changes on the success of simultaneous
control not only of high BP but also of other cardiovascular risk factors has not been fully addressed in a usual care setting. This is the aim of the present study carried out in a cohort of previously untreated subjects with high BP referred to a hypertension clinic. The impact of weight changes on achieving recommended BP, lipid and glucose goals was analyzed.

**Patients and methods**

**Patient selection**

Between January 1, 2003, and December 31, 2005, all untreated patients >18 years old with primary hypertension attending the outpatient clinic of the Hospital de Sagunto, Spain, were invited to participate. All of them gave informed written consent to participate in the study, which was approved by the Ethical Committee of the Sagunto Hospital. Exclusion criteria were the presence of diabetes, secondary hypertension, neoplasia, hepatic and/or renal disease, chronic heart failure (NYHA class III and IV), and coronary heart disease.

Secondary causes of hypertension were ruled out after clinical examination and routine biochemical analyses. Further investigation was performed only when symptoms, signs or laboratory abnormalities suggesting secondary hypertension were present.

**Procedures**

In all subjects, clinical history and physical examination were performed. Family history, lifestyle habits and other possible cardiovascular risk factors were also assessed by using a standard questionnaire. Body weight, height, and waist circumference were measured and body mass index (BMI) was calculated. BP was measured using a mercury sphygmomanometer following the recommendations of the British Hypertension Society (11). The BP categories of the ESH/ESC 2003 guidelines were considered (1).

Blood samples were obtained in the morning after a minimum of 8 h fasting. Serum biochemical profiles were measured using a multiple-channel auto analyzer. Plasma glucose was assayed by the glucose oxidase method (Beckman Glucose Analyzer, Beckman Instruments, Fullerton, CA, USA). Total cholesterol (TC) and triglycerides (TG) were measured by enzymatic methods and high-density lipoprotein-cholesterol (HDL-C) was directly measured by an enzymatic in vitro assay (Roche Diagnostics). Low-density lipoprotein-cholesterol (LDL-C) was calculated using Friedewald equation.

The glomerular filtration rate was estimated (eGFR) by the MDRD abbreviated formula (12).

Urinary albumin excretion (UAE) was measured in two separate 24-h urine collections, using a nephelometric immunoassay (Behring Institute, Marburg, Germany). Proteinuria was measured using the sulfosalicylic acid method. For each patient, the UAE was considered as the mean value obtained in the two separate 24-h urine collections. Microalbuminuria was considered when UAE ≥ 30 mg/24 h.

In order to assess the individual level of risk, all individuals were categorized according the absolute 10-year Framingham risk scoring system (6) into three risk categories: (i) high-risk (10-year risk > 20%) and patients with any clinical form of atherosclerotic cardiovascular disease or with diabetes; (ii) moderately high-risk (10-year risk 10–20%), and (iii) lower to moderate risk (10-year risk < 10%).

Patients were considered as having MS on the basis of the AHA-NHLBI (13) when they fulfilled three out of five criteria: (i) abdominal obesity (waist circumference ≥ 102 cm for men and ≥ 88 cm for women); (ii) TG ≥ 150 mg/dl; (iii) HDL-C < 40 mg/dl for men and < 50 mg/dl for women; (iv) BP > 130/85 mmHg; and (v) fasting blood glucose ≥ 100 mg/dl. All of the subjects have at least one criterion, high BP.

**Table I. General characteristics of the study population.**

| Parameter                          | Number | Sex female, n (%) | Age (years) | Waist circumference (cm) | Weight (kg) | BMI (kg/height²) | SBP (mmHg) | DBP (mmHg) | Heart rate (beats/min) | Fasting glucose (mg/dl) | Creatinine (mg/dl) | Glomerular filtration rate (ml/min/1.73 m²) | Uric acid (mg/dl) | Total cholesterol (mg/dl) | HDL-cholesterol (mg/dl) | LDL-cholesterol (mg/dl) | Triglycerides (mg/dl) | Urinary albumin excretion (μg/min) | Microalbuminuria, n (%) | C-reactive protein (mg/l) | Smokers, n (%) | Metabolic syndrome, n (%) | Abdominal obesity (waist circumference ≥ 102 cm for men and ≥ 88 cm for women) | Triglycerides ≥ 150 mg/dl | HDL-cholesterol (< 40 mg/dl for men and < 50 mg/dl for women) | Blood pressure > 135/85 mmHg | Fasting glucose > 100 mg/dl | Coronary risk (Framingham-ATP-III), n (%) |
|-----------------------------------|--------|-------------------|-------------|--------------------------|-------------|-----------------|------------|------------|-----------------------|------------------------|------------------|-------------------------------|----------------|---------------------------|------------------------|--------------------------|-----------------|------------------------|---------------------------------|---------------------------|-----------------------------|------------------------|--------------------------|------------------------|
|                                  | 326    | 179 (54.9)        | 46.7 (13.8) | 91 (12)                  | 75.4 (14.6) | 27.9 (4.4)     | 146.4 (15.3) | 87.5 (10.9) | 77.8 (13.0)          | 97.2 (10.1)            | 1.0 (0.9–1.1)    | 78 (68–87)                     | 5.3 (1.4)        | 210 (40)                  | 45 (40–59)            | 133 (38)                 | 106 (79–151)   | 11 (6–22)               | 57 (17.5)                           | 1.3 (0.7–2.7)   | 68 (20.9)                  | 149 (45.7)                      | 117 (35.9)                | ≥ 102 cm for men and ≥ 88 cm for women |
|                                  |        |                   |             |                          |             |                 |            |            |                       |                        |                 |                              |                |                          |                        |                         |                 |                        |                                |                          |                             |                        |                          |                        |

Values are average (standard deviation). *Values are median (interquartile range). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Prospective assessment and goals

For 1 year, visits at 3-month intervals were scheduled. In each of the visits usual clinical assessments were performed. A complete clinical assessment and analytical procedures were performed at the end of the study period.

After enrollment, patients were placed on usual care treatment, which included: (i) dietary advice on moderate salt restriction and low saturated-fat diet, rich in fresh fruits and vegetables; (ii) individualized 500–600 kcal/day [2092–2510M] deficit diet if overweight or obese; (iii) physical exercise of up to at least 3 h/walking; (iv) antihypertensive drugs, lipid-lowering agents and/or oral anti-hyperglycemic agents drugs when necessary according to guidelines (1,2,6,11).

The BP goal was to achieve BP of <140/90 mmHg or <130/80 mmHg if diabetes was developed during the study period. Elevated LDL-C was the primary target of lipid-lowering therapy. The goal was <100 mg/dl for high-risk patients, <130 mg/dl for moderately high-risk, and <160 mg/dl for lower-risk patients. According to NCEP ATP III guidelines (6), non-HDL-C goals are secondary goals for patients who have TG levels ≥200 mg/dl. Because non-HDL-C goals are likely to be especially important for patients with MS, we also calculated the percentage of patients whose TG levels were ≥200 mg/dl who met NCEP ATP III non-HDL-C goals. Non-HDL-C was calculated by subtracting HDL-C from TC levels; it represents the atherogenic or apolipoprotein (apo) B-containing blood lipid components. Non-HDL-C goal was 30 mg/dl higher than LDL-C goals, therefore, non-HDL-C goals were <130 mg/dl for high-risk <160 mg/dl for moderately high-risk or <190 mg/dl for lower-risk patients. Glucose goal was to delay progression to type 2 diabetes mellitus, mainly for patients with impaired fasting glucose. For those patients who became diabetic during the follow-up, the goal was hemoglobin A1C <7.0%, or for those non-diabetics to achieve blood glucose <100 mg/dl. Finally, the weight reduction goal for overweight individuals (BMI>25 kg/m²) was to achieve a reduction of about 5–10% of total body weight.

Statistical analysis

The results are expressed as mean ± SD for continuous variables and as percentages for categorical variables. Variables with skewed distribution are expressed as the median and interquartile interval (IQI). Variables found to deviate from normality were log-transformed (Log). Differences in parameters of interest between patients during follow-up were sought by paired sample t-test or Wilcoxon test. Comparison of proportion among groups was performed using the chi-square test. Logistic regression analysis was used to assess the factors related to achieve BP, lipid and glucose goals. Adjusted area under receiver operating characteristic (ROC) curve was used to evaluate the accuracy of the models with different weight variation cut-off. Adjusted relative risk was calculated and expressed along with the 95% confidence interval. Statistical significance was assumed if p < 0.05 (two-tailed). Stata 8.0 was used to perform the analysis.

Results

Eight hundred and forty-five new subjects with high BP were evaluated in the study period. Among them, 292 patients with previous cardiovascular disease or being treated with cardiovascular drugs, 182 with diabetes and 45 with secondary hypertension were excluded from the study.

General characteristics at baseline

The general characteristics of the 326 patients included are shown in Table I. The prevalence of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>End of follow-up</th>
<th>Variation average (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>91.0 (12.4)</td>
<td>91.9 (12.2)</td>
<td>0.9 (0.2/1.6)</td>
<td>0.01 (a)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.4 (14.6)</td>
<td>75.9 (15.1)</td>
<td>0.5 (0.1/0.9)</td>
<td>0.02 (a)</td>
</tr>
<tr>
<td>BMI (kg/height²)</td>
<td>27.9 (4.4)</td>
<td>28.1 (4.6)</td>
<td>0.19 (0.04/0.34)</td>
<td>0.01 (a)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>146.4 (15.3)</td>
<td>136.6 (16.7)</td>
<td>9.7 (-11.7/-7.7)</td>
<td>&lt;0.001 (a)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>85.7 (10.9)</td>
<td>82.0 (10.4)</td>
<td>3.5 (-6.8/-4.2)</td>
<td>&lt;0.001 (a)</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>97.2 (10.1)</td>
<td>98.8 (12.1)</td>
<td>1.6 (0.4/2.8)</td>
<td>0.009 (a)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.0 (0.9–1.1)</td>
<td>1.0 (0.9–1.1)</td>
<td>–</td>
<td>0.21 (b)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>78.0 (68–87)</td>
<td>76.7 (66–88)</td>
<td>–</td>
<td>0.009 (b)</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.4 (1.4)</td>
<td>5.6 (1.4)</td>
<td>0.2 (0.1/0.4)</td>
<td>&lt;0.001 (a)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>210 (40)</td>
<td>206 (40)</td>
<td>4.0 (-6.4/0.4)</td>
<td>0.09 (a)</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>45 (40–59)</td>
<td>50 (40–64)</td>
<td>–</td>
<td>&lt;0.001 (b)</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>133 (38)</td>
<td>128.3 (38.0)</td>
<td>4.8 (-8.1/-1.5)</td>
<td>0.005 (a)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>106 (79–151)</td>
<td>104 (73–147)</td>
<td>–</td>
<td>0.02 (b)</td>
</tr>
<tr>
<td>UAE (mg/24h)</td>
<td>11 (6–22)</td>
<td>8 (6–16)</td>
<td>–</td>
<td>0.007 (b)</td>
</tr>
</tbody>
</table>

Values are average (standard deviation). *Values are median (interquartile interval). (a) Paired-samples t-test. (b) Wilcoxon test. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
microalbuminuria was 17.5% and 21% of patients were smokers. The prevalence of the various components of MS was as follows: BP level 100%, HDL-C 42%, glycemia 38%, abdominal obesity 36% and triglycerides 27%. A total of 58% of the subjects had only one of the clinical traits of MS other than high BP, and 29%, 15% and 2% had, two, three, or four additional traits, respectively. One hundred and forty-nine subjects (46%) fulfilled the criteria for MS.

During the follow-up, 130 of the patients (40%) were on non-pharmacological treatment only, and 196 (60%) also received antihypertensive drugs. The average number of antihypertensive drugs was 1.4 ± 0.3. Seventy-five patients (38% of them) were receiving beta-blockers and/or thiazide diuretics and 121 (62%) other antihypertensive drugs (calcium-channel blockers and/or angiotensin-converting enzyme inhibitors or angiotensin receptor blockers). In addition, 25 (7.9%) were receiving statins or fibrates. No patients received anti-obesity drugs during the study period. Similarly, they did not receive oral antidiabetic drugs before developing diabetes.

Changes during the follow-up

The changes in the most important clinical parameters after 1 year of treatment are shown in Table II. Overall, there was a significant weight increment of 0.5 kg (95% CI 0.1–0.9 kg), waist circumference of 0.9 cm (95% CI 0.2–1.6 cm) and BMI of 0.19 kg/height^2 (95% CI 0.04–0.34 kg/height^2). One hundred and fifteen patients (35.3%) lost more than 0.5 kg, 28 (8.6%) lost more than 5 kg and only four (1.2%) lost more than 10 kg. A significant reduction in SBP of 9.7 mmHg (95% CI −11.7/−7.7 mmHg) and in DBP of −5.5 mmHg (95% CI −6.8/−4.2 mmHg) was observed at the end of the study.

Although there was a significant decrease in LDL-C and an increase in uric acid, HDL-C, and fasting glucose, their biological impact is meaningful. Ten patients (3.1%), six men, had become diabetics by the end of follow-up; all received only diet and four metformin. Urinary albumin excretion was reduced, but 51% of patients with UAE ≥30 mg/24 h remained microalbuminics at the end of the study. A small but significant reduction in eGFR was also observed.

Therapeutic goals

BP goals were achieved in 183 (56%) of the patients and LDL-C goal in 248 patients (78%). For those reaching the LDL-C goal, 33 had triglycerides ≥200 mg/dl and the non-HDL goal was achieved in 13 (39%) of them. The goal for glycemia was achieved in 61% of the patients. The changes in body weight during the follow-up were categorized in two groups.
Body weight changes and cardiovascular goals

using adjusted models of the area under ROC curves for each goal [for BP goal ≥1.5 kg (ROC=0.709, p=0.008); for LDL-C ≥0.5 kg (ROC=0.85, p=0.005); for glucose goal no significant cut-off was found].

**BP goal:** In a logistic regression analysis, initial SBP, absence of MS, to lose or not to increase weight ≥1.5 kg, and treatment with antihypertensive drugs were associated with higher success in achieving BP goal. Interaction between MS and gender (p=0.022) was observed in terms of the presence of MS reduced the rate of success in women but not in men. No interaction, however, between MS and weight variation was observed in women (p=0.29) or in men (p=0.61). Because of the different impact of gender, the OR for each of the factors was calculated separately for men and women and they are shown in Table III.

**LDL-C goal:** Initial LDL-C values were the most important factors related to achieving LDL-C control, the higher the levels the lower the control rates. Since interaction between MS and weight variation was observed (p=0.019) two different models were calculated (Table IV). In patients with MS, to lose or not to increase weight >0.5 kg was independently related to achieving the LDL-C goal. In patients without MS, changes in weight was not related to achieving LDL-C goal, with only the initial LDL-C values being the most important factor for the probability of achieving control. No interaction between MS and gender (p=0.77) or weight variation (p=0.17) was found.

**Glucose goal:** Higher values of fasting glucose at the beginning and being treated with beta-blockers and/or diuretics were the factors related to achieving the glucose goal (Table V). Weight variation during follow-up was not a significant factor (p=0.83), and no cut-off levels were calculated. No interaction between MS and gender (p=0.84) was found for the probability of getting the goal.

**Discussion**

In a cohort of essential untreated hypertensives in usual care, the factors associated with achieving recommended goals for the main cardiovascular risk factors have been analyzed during the first year after the initial evaluation. Overall, diet and exercise were not a success in weight control since only one patient out of three lost 0.5 kg or more. However, a modest variation in body weight may have an impact on achieving cardiovascular goals. Changes in body weight in men and women and MS in women were the main factors that influenced the possibility of achieving the BP goal. Changes in body weight also
influence the probability to achieve LDL-C goal in patients with MS. Then, changes in body weight are important in MS patients even when the extent of the changes is small. Moreover, less weight change seems to be needed to achieve the lipid goal than the BP goal. In contrast, the impact of both MS and changes in body weight in achieving glucose goals are negligible in this relatively short period. Initial low glucose level and not being treated with beta-blockers and/or diuretics were the most important factors in achieving the glucose goal.

Some characteristics of the study design should be highlighted. It was performed on a cohort of previously untreated subjects in the absence of diabetes or established cardiovascular or renal disease, with a large proportion of subjects receiving only non-pharmacological treatment. Moreover, a small number of patients were receiving medications other than antihypertensive drugs following the guidelines recommendations. The goals for each of the main cardiovascular risk factors were those recommended at the time of starting the follow-up of the patients. Consequently, non-pharmacological treatment, antihypertensive drugs and other additional drugs were introduced and have been modified throughout the study following the same prespecified criteria. These characteristics allowed us to evaluate not only the impact of the clinical conditions such as MS but also to explore the importance of changes in body weight and the possible influence of antihypertensive class of drugs. The selected subjects, however, may not be representative of the general population since selection and referral bias may have modified our estimate.

In the present study, the two most important factors at the time of reducing the cardiovascular risk associated with essential hypertension were the presence of MS and the changes in body weight, placing in first line the importance of the metabolic component at the time of starting antihypertensive treatment. This is not unexpected because of the relationship between hypertension and metabolic alterations being well recognized. Hypertension is highly prevalent in subjects with insulin resistance and MS (14), and in patients with HT the prevalence of MS is greater than in the general population (15–17). MS was defined according to the AHA-NHLBI (13) in the present study. The prevalence of MS in our study, 45.7%, was considerably greater than the prevalence reported in previous studies of hypertensives (18), since the patients were recruited in a referral clinic and the waist circumference threshold was lower than that applied in other studies.

MS significantly influences the outcome in two of the three main cardiovascular risk factors, BP and LDL-C. The lower BP achieved in patients with MS, as compared with those without it, can be related to the high prevalence of target organ damage, LVH or kidney dysfunction, highest established cardiovascular risk (19) and the poorest prognosis observed in these patients (16). Whether the low BP control is the culprit or it is the consequence of organ damage in MS is a matter of debate. Whatever the case, the clinical relevance of this finding is that patients with MS require more aggressive treatment in terms of using early antihypertensive drugs and frequent combination therapy.

Insulin resistance and hyperinsulinemia, a key element underlying MS, can also contribute not only to the poor BP control observed but also to the poor glucose control. That MS is a clinical condition prone to develop diabetes overtime has been demonstrated in several prospective studies. Nevertheless, the follow-up did not last long enough to prove it in the present cohort.

A large bulk of evidence exists about the relationship between weight and BP leading to an increase in the prevalence of hypertension in overweight and obese subjects (20,21). The influence of weight gain on BP changes or on the development of hypertension has also been observed in several studies. In a cohort of 82,473 female nurses aged 30–55 years followed up for 16 years, BMI at 18 years of age and during midlife was positively associated with its occurrence. Long-term weight gain dramatically increases the risk of hypertension and weight loss reduces the risk, regardless of the initial age or BMI (22). In the
Trial of Hypertension Prevention (23), in which only non-pharmacological treatment was used, changes in BP were directly related to changes in body weight.

Obesity is one of the main factors related to therapeutic failure to achieve BP goal during antihypertensive treatment. It has been demonstrated that obese subjects need a higher number of antihypertensive drugs than their sex- and age-matched lean counterparts (9). In the present study, an increment of more than 1.5 kg was associated with more risk of treatment failure as compared with those with less weight gain or weight loss. The cutoff selected to divide the potential impact of changes in weight differs from the cutoffs used in other studies (24,25) because it was derived from the best-fit of the ROC curve generated with the values of the present cohort. Reduction in body weight addresses the mechanism of MS that influences both hemodynamic and metabolic parameters (26).

The high rate of achieved LDL-C goal, about 78% of the patients as compared with 56% of BP control and 61% of glucose control, is probably related to the low-risk profile of our patients; 86% were of low Framingham coronary risk, requiring only a LDL-C target <160 mg/dl, moreover the efficacy of statins reaching those values is well established. It is worth commenting on the interaction of MS and weight variation in order to achieve the LDL-goal, only a modest variation of weight, 0.5 kg, may have an influence on lipid control of patients with MS.

Finally, the impact of the kind of antihypertensive treatment needs to be commented on. Only two out of three patients received pharmacological treatment. The kind of drugs had no influence on achieving the BP or the LDL-C goals, but for the glucose, those who received beta-blockers and/or diuretics were less likely to achieve the goal. The importance of metabolic abnormalities induced by the antihypertensive drugs has been recently emphasized (26).

The information derived from the present study recognizes the presence of MS as a marker of poor outcome in the control of cardiovascular risk factors. Furthermore, the observed impact of changes in body weight in the rates of cardiovascular risk factor control reinforces the necessity to be proactive in achieving weight reduction not only if overweight or obesity is present. Failure to control weight over time is a harbinger not only of poor BP control but also of the other main cardiovascular risk factors and as a consequence insufficient cardiovascular risk reduction.

**Declaration of interest:** The authors declare no conflict of interest.

**References**


