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TITLE: Predictors of hypertension remission and recurrence after bariatric surgery

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ABSTRACT

Background: Few data exist on factors associated with hypertension remission post-bariatric surgery. No information on factors that may predict hypertension relapse is available. The aims were to assess the hypertension remission and relapse rates at 1 and 3 years, respectively, post-bariatric surgery, and determine predictive factors.

Methods: A non-randomized prospective cohort study on severely obese patients undergoing laparoscopic Roux-en-Y gastric bypass or laparoscopic sleeve gastrectomy with a follow-up of 36 months was conducted between 2005 and 2011. Criteria for hypertension diagnosis were current treatment with antihypertensive agents and/or systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg. Hypertension remission was defined as normalization of blood pressure maintained after discontinuation of medical treatment.

Results: 197 patients were included in the study. Hypertension was present in 47.7%; 68.1% of hypertensive patients showed hypertension remission 1 year after the surgical procedure, 21.9% of whom had relapsed at 3 years. The number of antihypertensive drugs prior to surgery was associated with a lower remission rate at the first year and a higher recurrence at 3 years. However, a smaller weight loss during the first year was associated with increased hypertension recurrence at 3 years.

Conclusion: Hypertension relapses in one of 5 hypertensives who have achieved remission at the first year of follow-up. Weight loss during the first postoperative year should be encouraged to avoid hypertension relapse at 3 years.

INTRODUCTION

Obesity is associated with an increase in cardiovascular risk factors, including hypertension (HTN)[1]. Epidemiological studies in the non-obese population estimated that each 1 kg/m^2 increase in body mass index (BMI) is associated with a 1-mm Hg rise in systolic blood pressure (BP)[2]. Inversely, a 1% weight loss achieved with conventional therapy leads to a 1-mm Hg and 2-mm Hg drop in systolic and diastolic BP, respectively[3-4]. Bariatric surgery is the most effective treatment for severe obesity, achieving not only significant weight loss but also remission of associated comorbidities such as HTN[5-6].

Recent studies on the effects of bariatric surgery focused on its impact on type 2 diabetes mellitus (T2DM). In this respect, short-term remission predictors and long-term remission rates have also been described as possible mechanisms involved in carbohydrate metabolism improvement[7-9]. Arterburn et al[10] reported that one third of patients achieving T2DM remission after bariatric surgery relapse in the following 5 years. Factors associated with T2DM relapse were older age, poorer preoperative glycemic control, previous insulin therapy and longer T2DM duration. With regard to HTN, few data on remission predictors after bariatric surgery are available, with variable results[11-15]. Although a decline over time in the beneficial effects on blood pressure has been suggested[16], little is known on the long-term effects and no studies have evaluated factors associated with HTN relapse. The aims of the present study were to assess HTN remission and relapse rates at 1 and 3 years, respectively, post-bariatric surgery, and determine predictive factors.

METHODS

Study protocol

A non-randomized prospective cohort study was conducted on severely obese patients undergoing bariatric surgery at the Hospital del Mar, Barcelona, since January 2005. Patients were aged between 18 and 55 years and met the 1991 bariatric surgery criteria of the National

Institutes of Health[17]. Indication for the type of surgical procedure [laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB)] was based on clinical criteria and the consensus of the Bariatric Surgery Unit. In accordance with the study protocol, all patients were evaluated preoperatively and at 3, 6, 12, 18, 24 and 36 months post-surgery. Protocol visits included measurements of weight, waist and hip circumferences, blood pressure and laboratory testing for glucose, insulin, glycated hemoglobin (HbA_{1c}), total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride levels. All patients signed their informed consent for the procedure and for the study. The Ethics Committee of our Institution in accordance with the ethical guidelines of the 1975 Declaration of Helsinki approved the protocol. All patients gave written informed consent before entering the study.

Anthropometric and biochemical measurements

Blood pressure was taken using an Omron M6 AC (HEM-7322) automatic digital monitor (Omron Healthcare). Three blood pressure readings were taken at 1-minute intervals and the mean value of the second and third readings was used for study analysis. BP was measured in the seated position for ≥ 5 minutes in a quiet room, bladder empty and arm at heart level. Criteria for HTN diagnosis were current treatment with antihypertensive agents and/or systolic BP > 140 mm Hg and/or diastolic BP > 90 mm Hg[18]. HTN remission was defined as normal BP levels without antihypertensive therapy at 12 months (systolic BP < 140 mm Hg and diastolic BP < 90 mm Hg) and HTN improvement was considered when a decrease in dosage or number of antihypertensive medications was required or when a decrease in systolic or diastolic blood pressure levels was observed with the same medication[19] . Finally, HTN recurrence was considered when HTN diagnostic criteria reappeared after remission. T2DM was defined as two fasting plasma glucose values > 125 mg/dl or $HbA_{1c} \geq 6.5\%$, treatment with oral hypoglycemic agents or insulin[20]. Dyslipidemia was defined as a total

cholesterol concentration > 200 mg/dl and/or HDL cholesterol < 40 mg/dl in men or < 50 mg/dl in women and/or triglycerides > 200 mg/dl and/or use of lipid-lowering therapy[19].

The BMI was calculated as the weight in kilograms divided by the height in square meters. Percentage of BMI (%BMI) loss was referred to weight loss with respect to baseline. The percentage of excess weight loss (%EWL) was based on the weight in excess of that corresponding to a BMI of 25 kg/m^2 for each patient.

Total cholesterol and triglycerides were determined using enzymatic methods in a Cobas Mira automatic analyzer (Baxter Diagnostics AG, Düdingen, Switzerland). HDL cholesterol was measured using separation by precipitation with phosphotungstic acid and magnesium chloride. Glucose was determined by the oxidase method. HbA_{1c} was quantified by chromatography (Biosystem, Barcelona, Spain).

Surgical techniques

The LRYGB technique involved a 150-cm antecolic Roux limb with 25-mm circular pouch-jejunostomy and exclusion of 50 cm of the proximal jejunum. In LSG, a longitudinal resection of the stomach from the angle of His to approximately 5 cm proximal to the pylorus was performed using a 35 French bougie inserted along the lesser curvature. All operations were performed by the same team of surgeons.

Statistical analysis

Data were expressed as mean ± standard deviation for continuous variables and as percentages and frequencies for categorical variables. Student's t-test was performed to assess differences between two means. Chi-square or Fisher exact tests were used to evaluate the degree of association between categorical variables. Assuming that blood pressure and weight changes over time are not linear we used a linear mixed-effect model to analyze differences between groups at each time point from baseline (interaction effect). Logistic regression analysis including variables with a p value < 0.1 in univariate analysis was applied

to evaluate factors independently associated with HTN remission at the first year and recurrence at the third year post-surgery. A two-sided p value < 0.05 was considered statistically significant. Statistical analysis was calculated with SPSS (version 19.0 for Windows; SPSS, Chicago, IL).

RESULTS

Two hundred and forty-four Caucasian patients underwent surgery between 2005 and 2011 ; of these, 45 were lost during follow-up and two died, one from a myocardial infarction three months after surgery and one from acute leukemia at 11 months of follow-up. One hundred and seventeen (59.4%) of the 197 patients who completed follow-up underwent LRYGB and 80 (40.6%) LSG; 194 attended the visit at 3 months, 195 at 6 months, 196 at 12 months, 180 at 18 months, 188 at 2 years and 190 at 3 years. Women comprised 82.4% of patients, with a mean age of 46.0 ± 8.4 years, baseline BMI 44.8 ± 4.7 Kg/m^2 and baseline systolic and diastolic BP 138.7 ± 20.8 mm Hg and 86.0 ± 12.2 mm Hg, respectively. T2DM was present in 26.4% of the study cohort, dyslipidemia in 27.4% and HTN in 47.7%. Eighty-three (88.3%) hypertensive patients were on antihypertensive drug therapy (43.6% monotherapy, 29.8% bitherapy, and 14.9% three or more drugs). At baseline, hypertensive subjects were older, with a higher proportion of males and a higher prevalence of T2DM and dyslipidemia (Table 1). The evolution of BP and weight loss expressed as %EWL and %BMI loss in subjects with and without HTN is shown in Figure 1. Weight loss was progressive in both groups until 12 months, stabilizing at the end of follow-up. %BMI loss was higher in normotensive patients after 12 months of follow-up compared with hypertensive patients. %EWL was also higher in the normotensive group from the first year of follow-up, but only showed significant differences at 2 years. At 3 months of follow-up, systolic and diastolic BP levels had significantly decreased in both hypertensive and normotensive patients, with no differences between groups. In hypertensive patients, a continuous fall in systolic BP was

detected until 6 months after surgery (-24.4 ± 26.2 mm Hg, p< 0.01) followed by a slight progressive increase (6.0 ± 17.6 mm Hg, p= 0.028) until the third year of follow-up. In contrast, systolic BP in normotensive patients decreased during the first year post-surgery (-20.2 ± 15.3 mm Hg, p< 0.001) and remained stable until the second year, ending in a slight increase at the third year of follow-up (4.3 ± 15.0 mm Hg, p= 0.011). Similarly, diastolic BP decreased in the first 6 months post-surgery in hypertensive patients (-13.8 ± 12.2 mm Hg, p< 0.001) and over 12 months in normotensive subjects (11.6 ± 12.5 mm Hg, p< 0.001), with no significant changes during the rest of the 3-year follow-up in either group (-2.2 ± 10.9, p= 0.171 and -0.9 ± 9.8 mm Hg, p= 0.389) (Figure 3).

The HTN remission rate 1-year post-bariatric surgery was 68.1% (64 of the 94 hypertensive patients). Furthermore, 21 (22.3%) patients showed HTN improvement and only 9 (9.6%) failed to improve. Patients with HTN remission showed a higher %EWL and %BMI loss from 12 months after surgery (Figure 2). Baseline characteristics of patients with HTN remission were comparable, except for the number of antihypertensive drugs used (Table 2). In the multivariate analysis, the number of antihypertensive drugs prior to surgery was the only factor independently associated with HTN remission at 1 year (Table 3).

HTN relapse at 3 years was observed in 21.9% of patients (14 of the 64 patients with HTN remission at 1 year). Patients with HTN recurrence were older, with higher baseline diastolic BP and had received a higher number of antihypertensive drugs than those without recurrence (Table 4). From the first year post-bariatric surgery to the final follow-up, patients with HTN recurrence had a lower %EWL and %BMI loss compared with those without recurrence (Figure 3). No differences were detected in %EWL regain between the first and third year after surgery among patients with HTN recurrence (6.3% ± 10.8%) and no HTN recurrence (6.2% ± 10.8, p= 0.868). Independent variables in the multivariate model were the %EWL 1 year after surgery and the number of antihypertensive drugs prior to surgery (Table 3). Only

one of the 103 normotensive patients developed HTN during follow-up (HTN incidence of 1.0%).

DISCUSSION

In the present study, two of three hypertensive patients undergoing bariatric surgery achieved HTN remission in the first year, but one in 5 had relapsed at 3 years. The number of anti-hypertensive drugs prior to surgery was independently associated with lower remission and higher relapse rates. Furthermore, weight loss at the first year post-surgery was inversely related to the relapse rate.

The 68% HTN remission rate at 1 year post-bariatric surgery found in the present study is consistent with previous studies, varying between 50 and 70% at 1-2 years[5,11-13,20-21]. Controversy exists as to remission predictors that may be useful for selecting individuals who will benefit more from the surgical procedure[11-15]. In agreement with Flores et al[11], the only independent predictor of HTN remission found in the present study was the number of antihypertensive drugs used preoperatively. This finding suggests that patients with greater disease severity are those who benefit less from bariatric surgery in terms of HTN remission. Other factors associated with greater HTN severity, such as disease duration, have also been related to a lower relapse rate[11,15]. The association between younger age and HTN remission reported in other studies[12,13], but not in our cohort, could reflect the fact that factors associated with HTN severity were not included in the analysis, since older subjects have more time from HTN diagnosis and an increased treatment burden.

We found that systolic and diastolic BP levels in hypertensive subjects dropped in the first 6 months after surgery. Thereafter, systolic BP increased slightly but progressively during follow-up whereas diastolic BP remained stable. These changes were responsible for the 21.9% detected HTN recurrence rate at 3 years. Although scant data on the medium-long-term effects of bariatric surgery on HTN have been reported, the Swedish Obese Study[16],

with an 8-year-follow-up of morbidly-obese patients undergoing bariatric surgery, offered significant information on the long-term effects of bariatric surgery on blood pressure. The results of that study were similar to those observed in the present cohort: an initial decrease in both systolic (11.4 ± 19.0 mm Hg) and diastolic BP (11.0 ± 7.0 mm Hg) during the first 12 months followed by a gradual increase in systolic and diastolic BP during the rest of follow-up and hypertension incidence of 26.4%. Likewise, in a recent study with medium term results after different bariatric techniques, Courcoulas et al found 38.2% HTN remission at 3 years after LRYGB and, thus, 50-70% lower than reported by others with 1-2 years of follow-up[21].

On the other hand, the present study describes for the first time factors associated with HTN recurrence at 3 years post-bariatric surgery. The number of antihypertensive drugs used before surgery independently correlated with HTN recurrence, as occurred with HTN remission. Interestingly, greater weight loss during the first year after bariatric surgery was also associated with lower HTN recurrence. Some authors reported that BP levels significantly improved within days of bariatric surgery when significant weight loss had not yet been achieved. This finding suggests that hormonal mechanisms could be involved in blood pressure profile improvement[22]. The lack of association between HTN remission and weight loss at one year and the fact that in HTN patients BP began to worsen after 6 months when maximum weight loss had not yet been achieved may indicate that weight loss during the early months is not a decisive factor in the fall in BP levels post-bariatric surgery. In contrast, the association between HTN relapse at 3 years and weight loss suggests that, from 6-12 months after surgery, the effect of these hormonal mechanisms is lost or mitigated and weight loss becomes a determining factor in the evolution of BP control.

The type of surgical technique (LRYGB or LSG) was not a determining factor for HTN remission or recurrence in the present study. Similarly, the meta-analysis of Buchwald et al[5]

did not detect differences in short-term HTN remission between LRYGB (75.4%) and a restrictive technique such as adjustable gastric band (72.5%). The results contrast with those of the Swedish Obese Subjects study, where LRYGB achieved better long-term results than restrictive techniques in terms of BP reduction[16]. Nevertheless, in that study, restrictive techniques did not include LSG, a relatively new technique[23], which yields better beneficial effects than other restrictive techniques in terms of weight loss, T2DM remission and HTN and comparable to those achieved with LRYGB[24-26]. Additional benefits of LSG have been attributed to a reduction in ghrelin-producing fundus cells[27].

In a previous study on morbidly-obese but metabolically-healthy patients, blood glucose, HbA_{1c}, lipids and BP levels significantly improved after bariatric surgery[28]. In the present study, unlike in hypertensive subjects, the reduction in systolic and diastolic BP levels continued up to 12 months after surgery and only one new case of HTN was diagnosed during follow-up. This very low incidence of HTN during follow-up among normotensive individuals suggests a protective effect of bariatric surgery in this population.

The present study has some limitations. Certain factors such as HTN duration after diagnosis, vitamin D status, salt inake, renal function, serum uric acid, metabolic syndrome, post-surgery diet and exercise, education and income were not analyzed as predictors of remission or recurrence. Twenty-four-hour ambulatory blood pressure monitoring, which would have permitted greater diagnostic and evolution accuracy, could not be performed. Neither were parameters of cardiac structure and function considered. In this respect, a meta-analysis of Cuspidi et al recently showed beneficial effects of bariatric surgery on these factors in which improvement in BP can play an important pathophysiologic role[29]. A further constraint of this study was the 19% loss rate; however, this is similar to studies conducted in other countries with a National Health Care Service such as ours[11] and lower than other countries with a non-public system that has been linked to the lack of insurance coverage[30]. On the other hand, a

longer follow-up period would be required to allow conclusions to be drawn on the long-term effects of LSG on HTN.

CONCLUSIONS

In hypertensive severely-obese patients, bariatric surgery is associated with an initial drop in systolic BP levels followed by a progressive increase during follow-up. These changes account for the 20% relapse rates after three years in those who initially achieve remission. Since weight loss during the first postoperative year is a marker for HTN recurrence at 3 years, it should be encouraged to prevent HTN relapse.

DISCLOSURE

The authors declare no conflict of interest.

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Figure Legends

Figure 1: Changes in systolic (A) and diastolic blood pressure (mm Hg) (B), percentage of excess weight loss (C) and percentage of body mass index loss (D) during follow-up after the bariatric surgical procedure in hypertensive and non hypertensive patients.

LEGEND: %EWL: percentage of excess weight loss; %BMI: percentage of body mass index. Data are expressed as means. Significance at $p < 0.05$ was determined using linear mixed-effect models. P-values are for the differences between groups during follow-up at each time point from baseline (interaction effect).

Figure 2: Changes in percentage of excess weight loss (A) and percentage of BMI loss (B) during follow-up after the bariatric surgery in hypertensive patients with and without hypertension remission at one year.

LEGEND: %EWL: percentage of excess weight loss; %BMI: percentage of body mass index; HTN: hypertension. Data are expressed as means. Significance at $p < 0.05$ was determined using linear mixed-effect models. P-values are for the differences between groups at each time point from baseline (interaction effect).

Figure 3: Changes in percentage of excess weight loss (A) and percentage of BMI loss (B) during follow-up after the bariatric surgery in patients with hypertension remission at one year with and without hypertension recurrence at 3 years.

LEGEND: %EWL: percentage of excess weight loss; %BMI: percentage of body mass index; HTN: hypertension. Data are expressed as means. Significance at $p < 0.05$ was determined using linear mixed-effect models. P-values are for the differences between groups at each time point from baseline (interaction effect).

Table 1. Clinical characteristics of patients with and without hypertension

	Normotensive patients (n=103)	Hypertensive patients (n= 94)	p value
Age (years)	42.9 ± 9.1	49.2 ± 6.2	<0.001
Women (%)	92 (89.3)	73 (77.7)	0.021
BMI (kg/m²)	45.0 ± 4.4	44.5 ± 5.0	0.442
Systolic BP (mm Hg)	134 ± 18	144 ± 23	0.001
Diastolic BP (mm Hg)	84 ± 12	89 ± 12	0.005
Fasting glucose (mg/dL)	103.7 ± 19.5	123.7 ± 37.9	<0.001
Basal insulin (mU/ml)	14.7 ± 8.6	18.7 ± 13.8	0.016
HOMA-IR	3.9 ± 2.8	5.7 ± 4.1	0.001
HbA_{1C} (%)	5.4 ± 0.6	6.1 ± 1.0	0.001
Total cholesterol (mg/dL)	194 ± 39	197 ± 34	0.596
HDL cholesterol (mg/dL)	52 ± 18	49 ± 12	0.197
Triglycerides (mg/dL)	127 ± 69	145 ± 68	0.069
Type 2 diabetes mellitus	13 (12.6)	39 (41.5)	<0.001
Dyslipidemia (%)	15 (14.6)	39 (41.5)	<0.001
Current smokers (%)	26 (25.2)	25 (26.6)	0.478
Type of surgery (% LRYGB)	61 (59.2)	56 (59.6)	0.538

Data are given as mean ± standard deviation or percentage (%).

BMI: body mass index; BP: blood pressure; HbA_{1C}: glycated hemoglobin; HDL: high-density lipoprotein; HOMA-IR: homeostatic model assessment-insulin resistance; LRYGB: laparoscopic Roux-en-Y gastric bypass.

Table 2. Baseline clinical characteristics of patients with and without hypertension remission 12 months after bariatric surgery

	HTN remission (n=64)	No HTN remission (n= 30)	p value
Age (years)	48.7 ± 6.2	50.4 ± 6.0	0.218
Women (%)	50 (78.1)	23 (76.7)	0.535
BMI (kg/m²)	44.2 ± 4.5	45.2 ± 6.1	0.362
Systolic BP (mm Hg)	144 ± 22	144 ± 25	0.991
Diastolic BP (mm Hg)	89 ± 11	87 ± 15	0.403
Antihypertensive drugs used	1.3 ± 0.9	2.0 ± 0.9	0.001
Type 2 diabetes mellitus (%)	27 (42.2)	12 (30)	0.841
Dyslipidemia (%)	28 (43.8)	11 (36.7)	0.337
Current smokers (%)	19 (29.7)	6 (20)	0.232
Type of surgery (% LRYGB)	23 (35.9)	15 (50)	0.143

Data are given as mean ± standard deviation or percentage (%).

HTN: hypertension; BMI: body mass index; BP: blood pressure; LRYGB: laparoscopic Roux-en-Y gastric bypass.

Table 3. Multivariate analysis of predictor factors for 1-year hypertension remission and 3-year hypertension recurrence after bariatric surgery.

	Odds ratio	95% CI	P value
1-year HTN remission			
Gender (female)	1.2	0.3 -4.1	0.782
Age (years)	1.1	0.9-1.2	0.147
Number of antihypertensive drugs	2.5	1.4 – 4.3	0.002
12 months %EWL (10% change)	0.7	0.5 – 1.0	0.087
3-year HTN recurrence			
Number of antihypertensive drugs	2.4	1.1 – 5.2	0.024
12 months %EWL (10% change)	0.5	0.3 – 0.9	0.043

HTN: hypertension; BP: blood pressure; CI: confidence interval; % EWL: percentage of excess weight loss.

Table 4. Baseline clinical characteristics of patients with and without hypertension recurrence three years after bariatric surgery

	HTN recurrence (n=14)	No HTN recurrence (n= 50)	p value
Age (years)	51.1 ± 4.4	48.0 ± 6.5	0.049
Women (%)	12 (85.7)	38 (76.0)	0.354
BMI (kg/m²)	45.1 ± 5.0	43.9 ± 4.4	0.391
Systolic BP (mm Hg)	140 ± 19	145 ± 22	0.416
Diastolic BP (mm Hg)	84 ± 13	91 ± 10	0.060
Antihypertensive drugs used	1.8 ± 1.0	1.1 ± 0.8	0.014
Type 2 diabetes mellitus (%)	7 (50.0)	20 (40.0)	0.503
Dyslipidemia (%)	4 (28.6)	24 (48.0)	0.161
Current smokers (%)	3 (21.4)	16 (32.0)	0.341
Type of surgery (% LRYGB)	5 (35.7)	18 (36.0)	0.622

Data are given as mean ± standard deviation or percentage (%).

HTN: hypertension; BMI: body mass index; BP: blood pressure; LRYGB: laparoscopic-Roux-en Y gastric bypass.

Figure 1

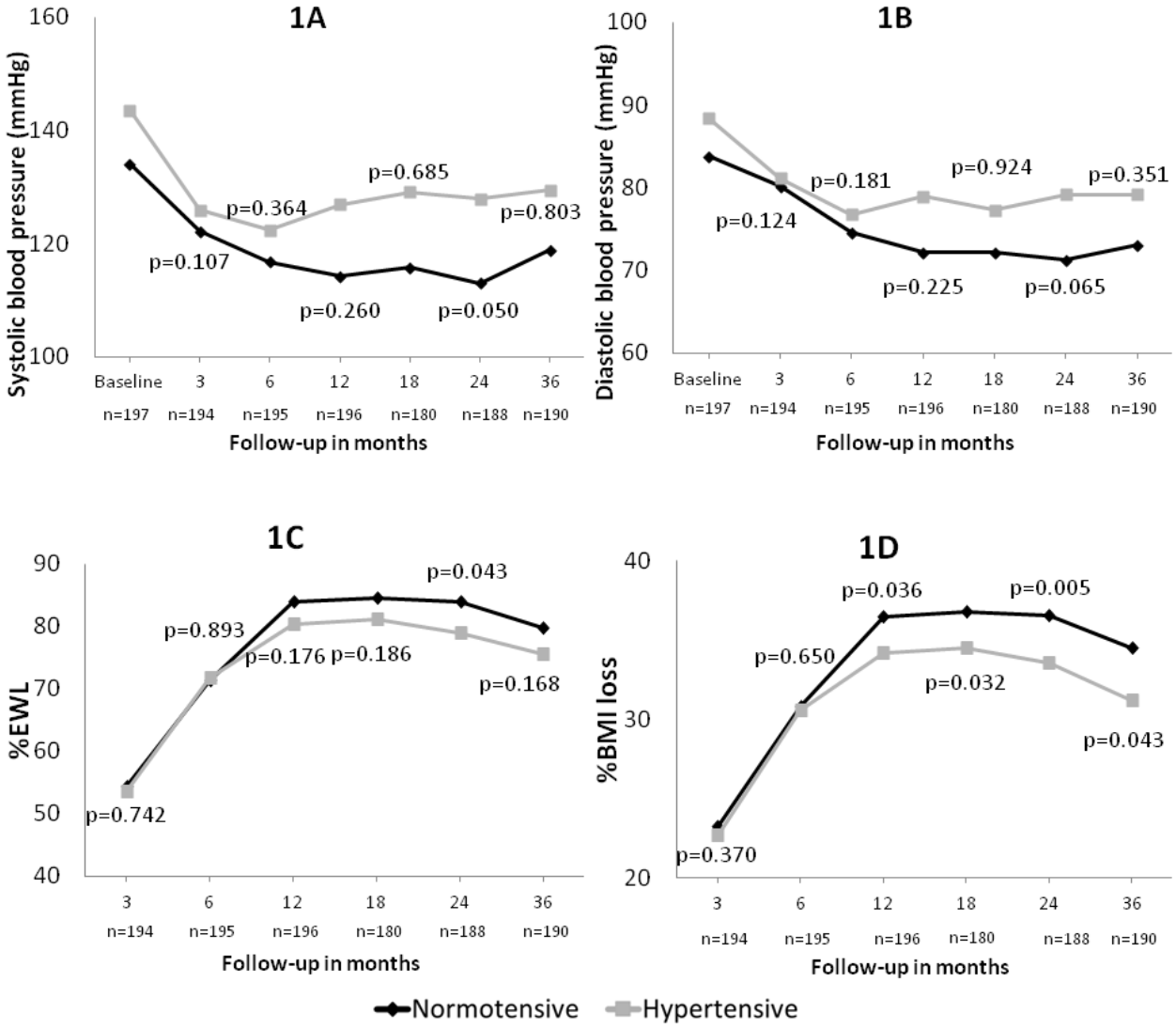
1A
Systolic blood pressure (mmHg)
160
140
120
100
p=0.685
p=0.364
p=0.803
p=0.107
p=0.260
p=0.050
Baseline 3 6 12 18 24 36
n=197 n=194 n=195 n=196 n=180 n=188 n=190
Follow-up in months
1B
Diastolic blood pressure (mmHg)
100
90
80
70
60
p=0.181
p=0.924
p=0.351
p=0.124
p=0.225
p=0.065
Baseline 3 6 12 18 24 36
n=197 n=194 n=195 n=196 n=180 n=188 n=190
Follow-up in months
1C
%EWL
90
80
70
60
50
40
p=0.043
p=0.893
p=0.176 p=0.186
p=0.168
p=0.742
3 6 12 18 24 36
n=194 n=195 n=196 n=180 n=188 n=190
Follow-up in months
1D
%BMI loss
40
30
20
p=0.036
p=0.005
p=0.650
p=0.032
p=0.043
p=0.370
3 6 12 18 24 36
n=194 n=195 n=196 n=180 n=188 n=190
Follow-up in months
Normotensive
Hypertensive

Figure 2

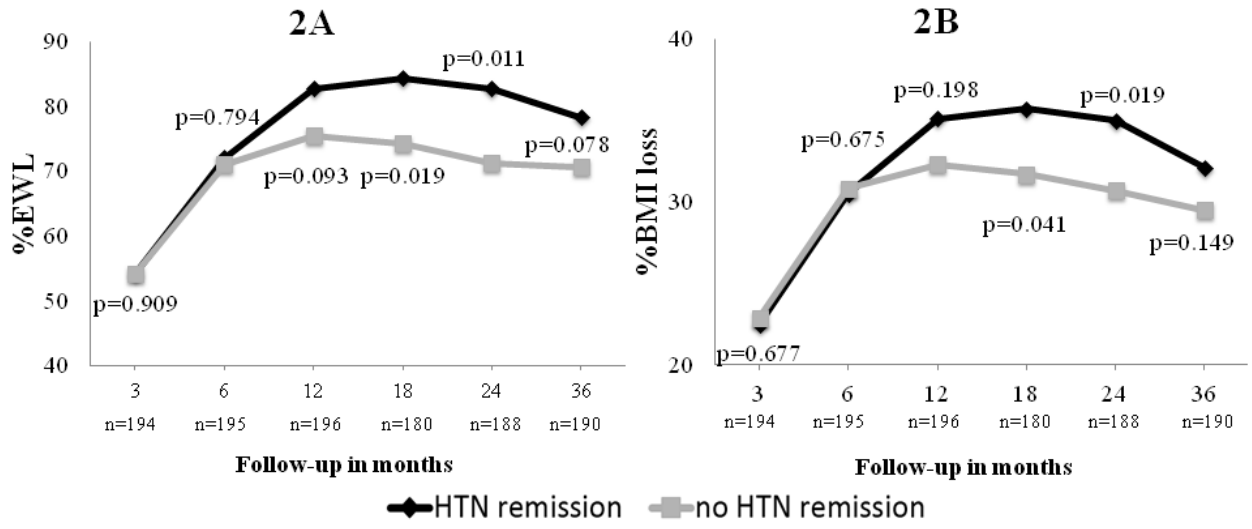

Figure 3