A Stronger Effect of Body Mass Index and Waist Circumference on the Prevalence of Uncontrolled Hypertension among Caucasian Men than Women

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Keywords

Gender-related differences · Blood pressure control · Obesity · Visceral obesity · Hypertension · Real-life data

Abstract

Background: Gender-related differences in fat distribution may affect blood pressure (BP) control in hypertensive subjects. The aim of the study was to assess how body mass (BM), BMI, and waist circumference (WC) influence the effectiveness of antihypertension therapy in hypertensive men and women in daily clinical practice. **Patients and Methods:** The observational study involved 12,289 adult hypertensive Caucasians (6,163 women) declaring regular use of antihypertensive drugs. BP control was scored based on the mean values of 2 attended office BP measurements. WC thresholds for visceral obesity were adopted from definitions of the International Diabetes Federation ($\geq 94/80$ cm for men/women) and National Cholesterol Education Program Adult

Treatment Panel III ($\geq 102/88$ cm for men/women). Stepwise backward multivariable logistic regression was used to analyse correlates of the effectiveness of hypertension therapy. **Results:** The predictive value of BMI ≥ 30 (for uncontrolled hypertension) was stronger than that of visceral obesity, regardless of the criteria used. In men, BP control rapidly deteriorated with BMI (odds ratio [OR] up to 8.58 [95% CI: 5.74–12.83]) and WC (OR up to 5.09 [3.84–6.74]), while in women, the association was more flattened (OR up to 3.63 [2.78–4.74] and 1.93 [1.59–2.35], respectively). However, the highest risk of uncontrolled BP occurred in women with BM ≥ 110 kg (OR = 10.47 [5.05–21.71]) and men with BM ≥ 125 kg (OR = 9.66 [5.86–15.94]). **Conclusions:** (1) Obesity and visceral obesity limit the effectiveness of antihypertension therapy more in men than in women. (2) This phenomenon should be taken into account in the prescription of adequate doses of antihypertensive drugs.

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Introduction

High blood pressure (BP), tobacco smoking, including second-hand smoke, and alcohol abuse were identified as the 3 leading risk factors for global disease burden, explaining 7.0, 6.3, and 5.5% of global estimated deaths and 173.6, 156.8, and 136.1×10^6 disability-adjusted life years, worldwide, respectively [1]. Despite the substantial improvements in the efficacy of hypertension therapy, half of the treated patients did not reach the recommended BP targets in the USA [2] and Europe [3]. In Poland, the control of hypertension among treated patients in most recent population-based studies (NATPOL 2011 [4], PolSenior 1 [5]), not exceeding one-third of the patients, is shown to be worse among men.

Uncontrolled hypertension leads to remodelling of the arterial wall, acceleration of atherosclerosis (inter alia coronary artery disease [CAD]), left ventricular hypertrophy causing heart failure (HF), and arrhythmias [6, 7]. Therefore, effective, long-term treatment of hypertension with low BP variability seems necessary for the prevention of stroke and cognitive decline, and successful ageing [8].

It is well known that obesity is a significant risk factor for the development of hypertension [9, 10] and limiting the effectiveness of antihypertensive therapy [11, 12]. Pathogenesis of obesity-related hypertension is complex, involving activation of the sympathetic nervous system (stimulated by hyperleptinaemia and hyperinsulinaemia secondary to insulin resistance) and the renin-angiotensin-aldosterone system, endothelial dysfunction (induced by free fatty acids and adipokines), and impaired renal-pressure natriuresis (related to hyperinsulinaemia, renin-angiotensin-aldosterone system overactivity, and resistance to atrial natriuretic peptides) with hypervolaemia and increased venous return [9, 10]. The abdominal fat depot is hormonally active and strongly related to insulin resistance and low-grade systemic inflammation [13, 14].

Gender-specific mathematical models indicated that BMI is a stronger risk factor for the development of hypertension in men, while waist circumference (WC) in women [15]. Overweight and especially obesity and visceral obesity were shown to deteriorate BP control in a few large, real-life studies performed in Europe [11, 12]. However, the gender-related differences were not analysed. Having in mind the gender-based variability in fat distribution and distinct effect of BMI and WC on the prevalence of hypertension among men and women, we explored a large real-life database from a recent survey (2017–2018) performed by 570 physicians, analysing the

efficacy of hypertension therapy in 12,289 unselected outpatients [16]. The aim of the study was to assess how body mass (BM), BMI, and WC) influence the effectiveness of antihypertension therapy in hypertensive men and women in daily clinical practice.

Materials and Methods

Our survey was performed from February to December 2017 by physicians and medical trainees, who were recruited by Europharma via the Internet. Among 14,200 hypertensive participants, 12,289 were treated pharmacologically, declared regular use of antihypertensive drugs, and have filled in all of the questionnaires anonymously.

Survey Procedures

The physicians involved in this study were obliged to complete a questionnaire with data obtained during the interviews with the patients and their medical history. These data, among others, included the patients' age, sex, smoking/alcohol drinking habits, level of physical activity, BM, height, WC (with accuracy of 0.1 kg, 0.5, and 0.5 cm, respectively), 2 attended office BP measurements (performed with a validated BP monitor with adjustment to the arm circumference cuff in a seated position, on the right upper arm, after at least 5 min of rest and at 2-min intervals), duration of treated hypertension, current antihypertensive therapy (mono-/polytherapy) and groups of prescribed drugs for hypertension (β -adrenolytics, calcium channel blockers – CCBs, angiotensin-converting enzyme inhibitors – ACEIs, diuretics, and angiotensin receptor blockers – ARBs), and comorbidities.

Data Analysis

Nutritional status was defined based on BMI, according to the WHO criteria as underweight ($<18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}24.9$), overweight ($25.0\text{--}29.9$), and obesity (≥ 30.0) [17]. The BMI range was divided into 2.5 kg/m^2 intervals, and the $20.0\text{--}22.4 \text{ kg/m}^2$ interval within the normal weight category was adopted as the reference.

The WC thresholds for abdominal obesity in Caucasians were adopted from the International Diabetes Federation (IDF; $\geq 94 \text{ cm}$ in men and $\geq 80 \text{ cm}$ in women) and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III; $\geq 102 \text{ cm}$ in men and $\geq 88 \text{ cm}$ in women) definitions [18]. The WC range was divided into 8-cm intervals (based on the difference between IDF and NCEP ATP III cut-offs), and the $86\text{--}93.5 \text{ cm}$ for men and $72\text{--}79.5 \text{ cm}$ for women interval, first below the IDF threshold was adopted as the reference. The BM range was divided into 15-kg intervals, and the $<80 \text{ kg}$ for men and $<65 \text{ kg}$ for women interval was adopted as the reference.

In our study, the BP control was established on the basis of the mean of 2 attended office BP measurements. In line with the recommendations of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC), values which were below $140/90 \text{ mm Hg}$ were considered controlled BP [19].

Diagnoses of diabetes and dyslipidaemia were based on the medical history and antidiabetic/lipid-lowering therapy. CAD was defined as a history of acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, or the

Table 1. Comparison of men and women on antihypertensive pharmacotherapy

	Men (N = 6,126)	Women (N = 6,163)
Age, years	58±13	62±12 [^]
Age ≥65 yr, %	32.4	40.2 [^]
Active or passed smokers, %	45.5	25.4 [^]
Pack-years, N	23±14	16±11 [^]
Alcohol consumers, %	48.1	17.7 [^]
Sedentary lifestyle, %	72.4	79.6 [^]
BM, kg	92.3±14.3	78.3±13.5 [^]
BMI, kg/m ²	29.9±4.7	29.0±5.1 [^]
Underweight (BMI <18.5)	0.3	0.3
Normal weight (BMI 18.5–24.9)	10.3	20.5 [^]
Overweight (BMI 25.0–29.9)	45.6	39.4 [^]
Obesity (BMI ≥30)	43.8	39.9 [^]
WC, cm	96±13	89±14 [^]
WC ≥80 (W) 94 (M)	59.9	72.8 [^]
WC ≥88 (W) 102 (M)	32.2	53.4 [^]
Period of HA treatment, %		
≤5 yr	56.3	52.8 [^]
>5 yr	43.7	47.2 [^]
Systolic BP, mm Hg	145±15	143±16 [^]
Diastolic BP, mm Hg	87±10	86±10 [^]
Controlled BP (<140/90 mm Hg), %	32.9	36.1 [^]
Comorbidities, %		
Diabetes	22.4	26.0 [^]
Dyslipidaemia	53.0	46.0 [^]
CAD	31.6	27.4 [^]
PAD	10.0	7.6 [^]
HF	12.7	9.8 [^]
Severe CKD	9.1	5.1 [^]
Treatment of HA, %		
Monotherapy	23.0	23.4
Polytherapy	77.0	76.6
Antihypertensive drugs in polytherapy, N	2.6±0.8	2.6±0.7
Antihypertensive drugs, %		
β-adrenolytics	52.7	47.9 [^]
CCBs	43.6	47.7 [^]
ACEIs	59.6	58.5
Diuretics	46.5	45.1
ARBs	22.2	17.9 [^]

ACEI, angiotensin converting enzyme inhibitor; BP, blood pressure; BM, body mass, WC, waist circumference; CCB, calcium channel blocker; ARB, angiotensin receptor blocker; CAD, coronary artery disease; HF, heart failure; PAD, peripheral artery disease. [^] $p < 0.001$ statistical significance of the men-women difference.

occurrence of symptoms of angina pectoris. The clinical diagnosis of peripheral artery disease (PAD) was based on patients' symptoms (intermittent claudication), revascularization procedures, and imaging, if performed and available. The diagnosis of HF was based on clinical symptoms, regardless of the ejection fraction (restricted/preserved) of the left ventricle, if measured. Severe CKD was defined as the occurrence of estimated glomerular filtration rate below 30 mL/min/1.73 m² and/or proteinuria over 300 mg/24 h.

Statistical Analysis

The analysis involved 12,289 of 14,200 hypertensive patients, declaring regular use of antihypertensive medicines. Interval data were expressed as mean ± standard deviation, while qualitative data were shown as numbers with percentage. Interval data in 2 groups were compared with the Student t test for independent data. There was no data imputation. The homogeneity of variances was assessed by the Fisher-Snedecor test. Qualitative data were compared with the χ^2 test. Odds ratio (OR) in the risk of uncon-

trolled BP against BMI, WC, and BM categories was calculated based on the 2 by 2 table with the χ^2 test. Correlates of the effectiveness of hypertension therapy were analysed with a univariable and a stepwise backward multivariable logistic regression. Results were presented as odds ratio (OR) with 95% confidence interval (CI) and corresponding p value. Factors significant in univariate analysis were included in the initial multivariable model (age ≥ 65 years, gender, active or passed smokers, sedentary lifestyle, HA treatment > 5 years, diabetes, dyslipidaemia, CAD or PAD, HF, CKD, polytherapy, β -adrenolytics, CCBs, ACEIs, diuretics, and ARBs). The relationship between BMI and WC with the number of antihypertensive drugs and the frequency of diuretic use was assessed with the interval regression. The power of the tests ($1 - \beta$) not less than 70% was assured. Statistical analysis was performed using STATISTICA 13.0 PL (Tibco Software Inc., Palo Alto, CA, USA) and R software (R Core Team [2013]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <http://www.R-project.org/>). Statistical significance was set at a p value below 0.05. All tests were 2-tailed.

Results

Analysed Group Characteristics

The analysis included 6,126 men and 6,163 women on antihypertensive therapy (Table 1). Smoking and frequent alcohol consumption were more frequently declared by men. In contrast, a sedentary lifestyle was more often declared by women (Table 1).

There were more obese men than women (43.8 vs. 39.9%; $p < 0.001$), but the proportion of viscerally obese was inverse, regardless of the criteria used: IDF (59.9 vs. 72.8%; $p < 0.001$) or NCEP ATP III (32.2 vs. 53.4%; $p < 0.001$). The prevalence of diabetes was greater among women, while of dyslipidaemia, CAD, PAD, HF, and severe CKD among men (Table 1).

Prescribed treatment of hypertension was similar in men and women in respect of frequency of polytherapy (77.0 vs. 76.6%; $p = 0.62$) and the number of antihypertensive drugs used in polytherapy (2.6 ± 0.8 vs. 2.6 ± 0.7 ; $p = 0.10$). However, men were more often treated with β -adrenolytics and ARBs, while women were treated with CCBs. There were small, but significant, differences in systolic (143 ± 16 mm Hg in women and 145 ± 15 mm Hg in men; $p < 0.001$) and diastolic BP (86 ± 10 mm Hg in women and 87 ± 10 mm Hg in men; $p < 0.01$), and in parallel, more female patients had controlled hypertension (36.1 vs. 32.9%; $p < 0.001$).

Uncontrolled Hypertension and Its Predictors

The cohort with uncontrolled hypertension was 2 years older, comprising of more men, smokers, individuals with a sedentary lifestyle, obese, viscerally obese (re-

gardless of the definition used), longer treated for hypertension, those diagnosed with diabetes, dyslipidaemia, CAD, PAD, HF, and CKD (Table 2). The predictive value of obesity for uncontrolled hypertension was stronger than that of visceral obesity, regardless of the criteria used (for obesity – OR = 3.01 [95% CI: 2.70–3.36], for IDF criteria – OR = 2.11 [1.95–2.28], and for NCEP ATP III criteria OR = 2.31 [2.12–2.52]); Table 3.

There was a small, but significant difference in the prevalence of polytherapy – it was greater in the group with controlled hypertension. The number of medications used in antihypertensive polytherapy was slightly greater in the group with uncontrolled hypertension. In addition, those with uncontrolled hypertension were less frequently treated with CCBs and ARBs but more often treated with β -adrenolytics. More than half of the patients with uncontrolled hypertension were not receiving diuretics (Table 2). In the univariate logistic regression analysis polytherapy, the use of CCBs and ACEIs decreased risk for uncontrolled hypertension (Table 3).

In the multiple regression analysis models (Table 3), obesity (OR = 2.57 [95% CI: 2.26–2.93]), much more than visceral obesity for IDF criteria (OR = 1.79 [1.64–1.94]) and for NCEP ATP III criteria (OR = 1.95 [1.77–2.15]), explained the variability in the prevalence of uncontrolled hypertension. In addition, in all models, smoking status, sedentary lifestyle, diabetes, dyslipidaemia, CAD or PAD, and CKD (with exception of BMI model) were independent predictors of uncontrolled hypertension.

Diverse Effect of BMI on the Occurrence of Uncontrolled Hypertension in Men and Women

As shown in Table 4, there was a marked increase in the risk of uncontrolled BP along with BMI, in both men and women. Taking the subgroup with BMI values between 20 and 22.4 kg/m² as a reference (0), there was a rapid increase in the risk from 1.78 in the subgroup with values 22.5–24.9 kg/m² to 8.58 in those ≥ 35 kg/m² for men, and from 1.37 in the subgroup with values 25–27.4 kg/m² to 3.63 in the subgroup ≥ 35 kg/m² for women. One may notice that the risk increase was more than twice smaller for women than for men. The increase in uncontrolled hypertension was also observed in underweight subgroups (Fig. 1). According to the interval regression analysis, for each 2.5 kg/m² increase in BMI, there was a 0.14 (both in men and women) mean increase in the number of antihypertensive drugs and 6.0/7.5% (in women and men, respectively) in the frequency of diuretic use.

Table 2. Comparison of patients with controlled and uncontrolled hypertension

	Controlled hypertension (N = 4,238)	Uncontrolled hypertension (N = 8,051)	p value (χ^2)
Systolic BP, mm Hg	128±8	152±12	<0.001
Diastolic BP, mm Hg	77±6	91±8	<0.001
Age, years	59±14	61±12	<0.001
Age ≥65 yr, N; %	1,446; 34.1	3,019; 37.5	<0.001
Sex			
Men, N; %	2,015; 47.5	4,111; 51.1	<0.001
Women, N; %	2,223; 52.5	3,940; 48.9	
Active or passed smokers, N; %	1,167; 27.5	3,188; 39.6	<0.001
Pack-years, N	20±12	20±15	0.60
Alcohol consumers, N; %	1,519; 35.8	2,520; 31.3	<0.001
Sedentary lifestyle, N; %	3,013; 71.1	6,324; 78.5	<0.001
BM, kg	80.9±13.8	87.6±15.9	<0.001
Men	87.4±12.4	94.7±14.5	<0.001
Women	75.1±12.3	80.1±13.8	<0.001
BMI, kg/m ²	28.0±4.5	30.2±5.0	<0.001
Underweight (BMI <18.5)	27; 0.6	9; 0.1	<0.001
Normal weight (BMI 18.5–24.9)	925; 21.8	968; 12.0	<0.001
Overweight (BMI 25.0–29.9)	2,048; 48.3	3,173; 39.4	<0.001
Obesity (BMI ≥30)	1,238; 29.2	3,901; 48.5	<0.001
WC, cm	89±13	95±14	<0.001
WC ≥80 (W) 94 (M)	2,341; 55.2	5,814; 72.2	<0.001
WC ≥88 (W) 102 (M)	1,415; 33.4	3,850; 47.8	<0.001
Period of HA treatment, N; %			
≤5 yr	2,449; 57.8	4,258; 52.9	<0.001
>5 yr	1,789; 42.2	3,793; 47.1	
Comorbidities, N; %			
Diabetes	746; 17.6	2,234; 27.7	<0.001
Dyslipidaemia	1,535; 36.2	4,547; 56.5	<0.001
CAD	927; 21.9	2,696; 33.5	<0.001
PAD	300; 7.1	779; 9.7	<0.001
HF	431; 10.2	951; 11.8	<0.05
Severe CKD	218; 5.1	655; 8.1	<0.001
Treatment of HA, N; %			
Monotherapy	894; 21.1	1,958; 24.3	<0.001
Polytherapy	3,344; 78.9	6,093; 75.7	
Antihypertensive drugs in polytherapy, N	2.5±0.7	2.6±0.8	<0.05
Antihypertensive drugs, N; %			
β-adrenolytics	1,860; 43.9	4,320; 53.7	<0.001
CCBs	2,159; 50.9	3,455; 42.9	<0.001
ACEIs	2,583; 60.9	4,672; 58.0	<0.01
Diuretics	1,902; 44.9	3,725; 46.3	0.14
ARBs	878; 20.7	1,580; 19.6	0.15

ACEI, angiotensin converting enzyme inhibitor; BP, blood pressure; BM, body mass; WC, waist circumference; CCB, calcium channel blocker; ARB, angiotensin receptor blocker; CAD, coronary artery disease; HF, heart failure; PAD, peripheral artery disease.

Diverse Effect of WC on the Occurrence of Uncontrolled Hypertension in Men and Women

In the analysis of BP control against WC, the subgroups of men with values between 86 and 93.5 cm and

of women with values range 72–79.5 cm were taken as the reference (0). The increase in the risk of uncontrolled hypertension was rising from 2.81 in men with values 94–101.5 cm to 5.09 in those with values ≥118 cm, while in

Table 3. Models of univariate and fully adjusted multivariate logistic regression analyses for uncontrolled hypertension

	Level (N)	Uncontrolled hypertension, N (%)	Univariate models, OR (95% CI)	Model with BMI ≥ 30 kg/m ² , OR (95% CI)	Model with WC $\geq 80/94$ cm, OR (95% CI)	Model with WC $\geq 88/102$ cm, OR (95% CI)
Age ≥ 65 yr	Y (4,465) N (7,824)	3,019 (67.6) 5,032 (64.3)	1.16 (1.07–1.25) [^] Ref.	–	–	–
Gender	M (6,126) W (6,163)	4,111 (67.1) 3,940 (63.9)	1.15 (1.07–1.24) [^] Ref.	1.26 (1.12–1.42) [^] Ref.	1.25 (1.14–1.36) [^] Ref.	–
Active or passive smokers	Y (4,355) N (7,934)	3,188 (73.2) 4,863 (61.3)	1.73 (1.59–1.87) [^] Ref.	1.44 (1.27–1.64) [^] Ref.	1.81 (1.65–1.99) [^] Ref.	2.29 (2.06–2.56) [^] Ref.
Alcohol consumers	Y (4,039) N (8,250)	2,520 (62.4) 5,531 (67.0)	0.82 (0.75–0.88) [^] Ref.	0.73 (0.64–0.83) [^] Ref.	0.63 (0.57–0.69) [^] Ref.	0.59 (0.53–0.66) [^] Ref.
Sedentary lifestyle	Y (9,337) N (2,952)	6,324 (67.7) 1,727 (58.5)	1.49 (1.37–1.62) [^] Ref.	1.35 (1.19–1.53) [^] Ref.	1.31 (1.19–1.44) [^] Ref.	1.41 (1.27–1.57) [^] Ref.
BMI ≥ 30 kg/m ²	Y (N = 5,139) BMI 18.5–24.9 (1,893)	3,901 (75.9) 968 (51.1)	3.01 (2.70–3.36) [^] Ref.	2.57 (2.26–2.93) [^] Ref.	–	–
WC ≥ 80 cm (W) 94 cm (M)	Y (8,155) N (4,134)	5,814 (71.3) 2,237 (54.1)	2.11 (1.95–2.28) [^] Ref.	–	1.79 (1.64–1.94) [^] Ref.	–
WC ≥ 88 cm (W) 102 cm (M)	Y (5,265) WC $< 80/94$ (4,134)	3,850 (73.1) 2,237 (54.1)	2.31 (2.12–2.52) [^] Ref.	–	–	1.95 (1.77–2.15) [^] Ref.
HA treatment > 5 yr	Y (5,582) N (6,707)	3,793 (68.0) 4,258 (63.5)	1.22 (1.13–1.31) [^] Ref.	–	–	–
Diabetes	Y (2,980) N (9,309)	2,234 (75.0) 5,817 (62.5)	1.80 (1.64–1.97) [^] Ref.	1.52 (1.32–1.75) [^] Ref.	1.61 (1.46–1.79) [^] Ref.	1.66 (1.48–1.87) [^] Ref.
Dyslipidaemia	Y (6,082) N (6,207)	4,547 (74.8) 3,504 (56.5)	2.29 (2.12–2.47) [^] Ref.	1.64 (1.46–1.83) [^] Ref.	2.01 (1.85–2.19) [^] Ref.	1.69 (1.54–1.86) [^] Ref.
CAD or PAD	Y (4,183) N (8,106)	3,080 (73.6) 4,971 (61.3)	1.76 (1.62–1.91) [^] Ref.	2.10 (1.83–2.43) [^] Ref.	1.63 (1.48–1.80) [^] Ref.	1.59 (1.43–1.78) [^] Ref.
HF	Y (1,382) N (10,907)	951 (68.8) 7,100 (65.1)	1.18 (1.05–1.33) [*] Ref.	–	–	–
Severe CKD	Y (873) N (11,416)	655 (75.0) 7,396 (64.8)	1.63 (1.39–1.91) [^] Ref.	–	1.38 (1.16–1.64) [^] Ref.	1.85 (1.52–2.26) [^] Ref.
Polytherapy	Y (9,437) N (2,852)	6,093 (64.6) 1,958 (68.7)	0.83 (0.76–0.91) [^] Ref.	0.58 (0.48–0.70) [^] Ref.	0.70 (0.62–0.79) [^] Ref.	0.68 (0.59–0.79) [^] Ref.
β -adrenolytics	Y (6,180) N (6,109)	4,320 (69.9) 3,731 (61.1)	1.48 (1.37–1.59) [^] Ref.	0.80 (0.71–0.91) [^] Ref.	–	–
CCBs	Y (5,614) N (6,675)	3,455 (61.5) 4,596 (68.9)	0.72 (0.67–0.78) [^] Ref.	0.52 (0.46–0.59) [^] Ref.	0.63 (0.58–0.69) [^] Ref.	0.55 (0.49–0.61) [^] Ref.
ACEIs	Y (7,255) N (5,034)	4,672 (64.4) 3,379 (67.1)	0.89 (0.82–0.96) [*] Ref.	–	0.64 (0.56–0.73) [^] Ref.	0.69 (0.59–0.80) [^] Ref.
Diuretics	Y (5,627) N (6,662)	3,725 (66.2) 4,326 (64.9)	1.06 (0.98–1.14) Ref.	0.70 (0.62–0.80) [^] Ref.	0.84 (0.77–0.92) [^] Ref.	0.79 (0.71–0.88) [^] Ref.
ARBs	Y (2,458) N (9,831)	1,580 (64.3) 6,471 (65.8)	0.93 (0.85–1.02) Ref.	0.67 (0.57–0.79) [^] Ref.	0.72 (0.65–0.81) [^] Ref.	–

BP, blood pressure; BM, body mass; WC, waist circumference; CAD, coronary artery disease; CKD, chronic kidney disease; HF, heart failure; PAD, peripheral artery disease; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; OR, odds ratio.
^{*} $p < 0.01$. [^] $p < 0.001$.

Fig. 1. Risk of uncontrolled BP against BMI categories, analysed separately for men and women. The subgroups with values between 20 and 22.4 kg/m² served as the reference. BP, blood pressure; OR, odds ratio.

women, the increase was much smaller and significant only in the last 2 subgroups – from 1.83 (WC: 96–103.5 cm) to 1.93 (WC ≥104 cm) (Fig. 2). Similarly as for BMI, for each 8-cm increase in WC, there was a 0.09/0.15 mean increase in the number of antihypertensive drugs and 3.4/7.2% in the frequency of the use of diuretics (in men and women, respectively).

Diverse Effect of BM on the Occurrence of Uncontrolled Hypertension in Men and Women

The analysis of BM was performed with a shift of 15 kg reflecting the gender-related difference in BM in the Polish population. The subgroups with BM below 65 kg for women and below 80 kg for men served as the reference. As shown in Table 4, the increase in the occurrence of

uncontrolled hypertension was found for subjects with a BM of 80 kg or more, regardless of gender. The increase in the risk in the subsequent subgroups was slower in women than in men. However, in the last categories (≥110 kg for women and ≥125 kg for men), the values were quite similar: OR = 10.47 (95% CI: 5.05–21.71) and OR = 9.66 (5.86–15.94), respectively (Fig. 3).

Discussion

The reported data in this study extend our knowledge concerning the factors affecting the control of hypertension among treated patients, pointing out, yet poorly characterizing obesity-related differences between men

Fig. 2. Risk of uncontrolled BP against WC categories, analysed separately for men and women. The subgroup of men with values between 86 and 93.5 cm and of women with values ranging from 72 to 79.5 cm served as the reference subgroups (category 0). The categories refer to the values in Table 4. BP, blood pressure; WC, waist circumference; OR, odds ratio.

and women. In line with the previously published studies, we showed that obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) remains a significant independent factor affecting BP control [11, 12, 20]. Our data show that the deterioration of BP control is already observed in normal-weight men with $\text{BMI} 22.5\text{--}24.9 \text{ kg/m}^2$ when compared with those with $\text{BMI} 20\text{--}22.4 \text{ kg/m}^2$, adopted as a reference in our study. The risk of uncontrolled hypertension was increasing from $\text{OR} = 1.78$ (in the aforementioned subgroup) to 8.58 in men with $\text{BMI} \geq 35 \text{ kg/m}^2$. A similar analysis performed for WC detected the deterioration of BP control for men with WC values corresponding to the IDF cut-off. The risk of uncontrolled hypertension was increasing from $\text{OR} =$

2.81 in the subgroup with WC of 94–101.5 cm to 5.09 in men with values $\geq 118 \text{ cm}$. Notwithstanding, the deterioration of BP control was not detected within the normal weight interval and was observed for the first subgroup ($25\text{--}27.4 \text{ kg/m}^2$) of overweight women. The risk of uncontrolled hypertension was increasing slower from 1.37 in the mentioned subgroup to 3.63 in women with $\text{BMI} \geq 35 \text{ kg/m}^2$. The deterioration of BP control was not corresponding to the IDF and even NCEP ATP III cut-offs for WC. It was significant for subgroups with $\text{WC} \geq 96 \text{ cm}$ with a weak increase (from 1.83 to 1.93) in the next subgroup ($\text{WC} \geq 104 \text{ cm}$). Of interest, regardless of gender, we found the deterioration of BP control in individuals

Fig. 3. Risk of uncontrolled BP against BM categories, analysed separately for men and women. The subgroup of men with values below 65 kg for women and below 80 kg for men served as the reference subgroups (category 0). BP, blood pressure; BM, body mass; OR, odds ratio.

with body weight ≥ 80 kg. Similarly to BMI and WC, the increase was slower in women than in men. In the last distinguished categories (≥ 110 kg for women and ≥ 125 kg for men), the risk of uncontrolled hypertension was extremely high but quite similar: OR = 10.47 (95% CI: 5.05–21.71) in women and OR = 9.66 (5.86–15.94) in men. The ORs were even higher than those observed in subgroups with the BMI ≥ 35 kg/m², especially in women. Therefore, we think that body size is neglected by the majority of physicians during the decision-making process regarding the pharmacotherapy of hypertension, including the use of diuretics. The current guidelines, as well as the summaries of products' characteristics of antihypertensive drugs, recommend dose adjustment depending

on the effect achieved, but omitting the aspect of body size that seems important.

The lack of BP control in obese patients with hypertension is certainly multifactorial and only to a small extent explained by the higher occurrence of the so-called resistant hypertension which prevalence increases with the severity of obesity [12]. It is believed that impaired response to antihypertensive drugs in the obese is due to the excessive salt intake (increased volemia), increased volume of distribution (especially for lipophilic drugs), and lower plasma levels of active forms of drugs with standard doses used. However, the evidence for an altered pharmacokinetic profile of antihypertensive medication is scarce. The volume of distribution in obese people is increased,

Table 4. BP control in BMI and WC and BM subgroups

Class	BMI, kg/m ²	Men (<i>N</i> = 6,126)		For uncontrolled BP OR (95% CI)	BMI, kg/m ²	Women (<i>N</i> = 6,163)		For uncontrolled BP OR (95% CI)
		BP control				BP control		
		yes	no			yes	no	
−1	<20.0	9	18	2.96 (1.24–7.08)*	<20.0	35	71	2.21 (1.40–3.48) [#]
0	20.0–22.4	80	54	Reference	20.0–22.4	194	178	Reference
1	22.5–24.9	221	266	1.78 (1.21–2.63)**	22.5–24.9	405	390	1.05 (0.82–1.34)
2	25.0–27.4	664	634	1.41 (0.99–2.03) ^{\$}	25.0–27.4	611	768	1.37 (1.09–1.72)**
3	27.5–29.9	451	1,028	3.38 (2.35–4.85) [#]	27.5–29.9	330	717	2.37 (1.86–3.01) [#]
4	30.0–32.4	325	951	4.33 (3.00–6.26) [#]	30.0–32.4	320	725	2.47 (1.94–3.15) [#]
5	32.5–34.9	159	546	5.09 (3.45–7.50) [#]	32.5–34.9	161	535	3.62 (2.77–4.74) [#]
6	≥35.0	106	614	8.58 (5.74–12.83) [#]	≥35.0	167	556	3.63 (2.78–4.74) [#]
WC, cm				WC, cm				
−1	<86	656	676	0.99 (0.85–1.16)	<72	256	345	0.91 (0.74–1.11)
0	86–93.5	552	573	Reference	72–79.5	433	643	Reference
1	94–101.5	433	1,263	2.81 (2.39–3.30) [#]	80–87.5	493	701	0.96 (0.81–1.13)
2	102–109.5	233	816	3.37 (2.80–4.07) [#]	88–95.5	544	864	1.07 (0.91–1.26)
3	110–117.5	71	413	5.60 (4.24–7.40) [#]	96–103.5	276	752	1.83 (1.53–2.20) [#]
4	≥118	70	370	5.09 (3.84–6.74) [#]	≥104	221	635	1.93 (1.59–2.35) [#]
BM, kg				BM, kg				
0	<80	484	498	Reference	<65	377	513	Reference
1	80–94	977	1,652	1.64 (1.42–1.91) [#]	65–79	1,091	1,539	1.04 (0.89–1.21)
2	95–109	466	1,366	2.85 (2.42–3.35) [#]	80–94	560	1,221	1.60 (1.36–1.89) [#]
3	110–124	70	416	5.76 (4.35–7.66) [#]	95–109	187	553	2.17 (1.76–2.69) [#]
4	≥125	18	179	9.66 (5.86–15.94) [#]	≥110	8	114	10.47 (5.05–21.71) [#]

BP, blood pressure; BM, body mass, WC, waist circumference; OR, odds ratio. ^{\$} $p < 0.1$. * $p < 0.05$. ** $p < 0.01$. [#] $p < 0.001$.

but to a lesser extent, even for lipophilic β -adrenolytics, there would have been the result of the conversion of the dose per kilogram of the BM [21]. Similar data, for altered obese pharmacokinetics, are available for some other drugs. The exposure to subcutaneous sumatriptan, a drug used in migraine headaches, was significantly reduced [22]. Therefore, it seems necessary to adjust the drug doses based on BMI, or even better BM, and titrate up to the maximal doses recommended by the Summary of Product Characteristics. It seems possible that inadequate drug doses in obese men, showing BM much greater than women, may explain at least partially, worse BP control. However, we cannot verify this hypothesis as the survey did not collect data concerning the prescribed drug doses.

Worse BP control, especially in obese men, may be also a consequence of more frequent non-adherence among men [23, 24], physician inertia (observed up to 70% of patients with uncontrolled BP) [25], and poorly studied

patient reluctance in prescribing multidrug therapy including diuretics observed in daily clinical practice. We have shown that more than half of patients with uncontrolled hypertension were prescribed with any diuretic. It seems that the lack of oedema may prevent some physicians from prescribing diuretic for obese patients with uncontrolled hypertension due to “invisible hypervolaemia.” This reluctance is partially explained by lower long-term adherence to diuretics [26], raised in analyses of the trend of prescription patterns in other countries [27].

In our study, there was a stronger relation between frequency in diuretics use with BMI but weaker with WC among men than among women. Therefore, we think that the lack of BP control is more related to the prescribed diuretic doses than the frequency of diuretics uses per se. In addition, the mean increase in the number of antihypertensive drugs was less driven by WC than BMI in men.

Study Limitations

The study enrolled almost exclusively Caucasians as the consequence of Polish population structure; therefore, the results cannot be generalized to non-Caucasian populations. We cannot exclude selection bias resulting in an overrepresentation of hypertensive patients with uncontrolled hypertension, more often using medical services and more frequently attending cardiology outpatients' clinics. Moreover, the survey did not collect the data concerning generic names and doses of antihypertensive drugs and results of home BP monitoring. The office BP measurements were performed with validated, however different, sphygmomanometers. We did not assess the adherence to antihypertensive therapy; therefore, we cannot analyse to what extent worse BP control in obese/viscerally obese men is affected by nonadherence.

Conclusions

(1) Obesity and visceral obesity limit the effectiveness of hypertension therapy more in men than in women. (2) This phenomenon should be taken into account in the prescription of adequate doses of antihypertensive drugs.

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Statement of Ethics

According to the Polish law, surveys are not medical experiments and as such do not require either Bioethical Committee approval or the need to obtain written informed consent from the patients for inclusion. The patients gave oral consent for the participation in the survey and processing of the anonymised medical data. The data (BP values and clinical information) were collected as part of routine clinical practice.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Concept and study design: J. Chudek and M. Olszanecka-Glinianowicz. Project administration: Z. Walencka and A. Almgren-Rachtan. Statistical analysis: A.J. Owczarek. Data analysis: J. Chudek and M. Olszanecka-Glinianowicz. Manuscript preparation: A. Chudek and J. Ficek. Manuscript editing: K. Wiczkowska-Tobis.

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