

Full Length Research Paper

Prevalence and characteristics of resistant hypertension among Greek type 2 diabetic subjects

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It is well documented that hypertension is more prevalent among type 2 diabetic (T2D) subjects. Successful tight blood pressure control allows to significantly reducing the incidence of microvascular and cardiovascular complications in T2D subjects; unfortunately, adequate blood pressure control is reportedly not achieved in up to 50–75% of diabetic patients. Therefore, we performed a retrospective analysis in order to estimate the prevalence of resistant hypertension among Greek T2D subjects. We performed a retrospective analysis of the medical records of 664 T2D subjects (mean age \pm standard deviation: 65.5 \pm 9.8 years, 341 females / 323 males) with arterial hypertension attending the diabetes outpatient clinic of our hospital during the period from 1 January 2010 to 30 September 2010. Of the study participants, 20.8% (n=138) had resistant hypertension. The antihypertensive treatment of the diabetic subjects with and without resistant hypertension was, respectively; 59.4% vs. 47.9% on angiotensin-converting enzyme inhibitors (ACE-I) (P=0.01), 45.7% vs. 21.9% on angiotensin II receptor blockers (ARBs) (P<0.001), 52.2% vs. 23.0% on β -blockers (P<0.001), 12.3% vs. 1.5% on centrally acting antihypertensives (P<0.001), and 71.0% vs. 29.7% on calcium channel blockers (P<0.001). Of the diabetic subjects without resistant hypertension 39.53% was on treatment with diuretics. Multivariate logistic analysis adjustment resistant hypertension was associated with body mass index (BMI) (OR: 1.06, 95% CI: 1.02-1.11, P<0.001), presence of coronary artery disease (OR: 1.83, 95% CI: 1.21-2.77, P=0.004), and insulin therapy (OR: 1.78, 95% CI: 1.15-2.75, P=0.01). In conclusion, the present study showed that a significant percentage of T2D subjects have resistant hypertension that is related with body mass index, presence of coronary artery disease and insulin treatment.

Keywords: Resistant hypertension, type 2 diabetes mellitus, coronary artery disease, body mass index, insulin treatment.

INTRODUCTION

It is well documented that hypertension is more prevalent among type 2 diabetic (T2D) subjects (Arauz-Pacheco et al., 2003; McFarlane et al., 2003). It is noteworthy that about 50% of subjects with T2D have hypertension at the time of diagnosis (Klein et al., 1996). The coexistence of T2D and hypertension is associated with increased risk of microvascular complication as well as cardiovascular

disease (Bakris et al., 2000). Successful tight blood pressure control (systolic blood pressure < 130 mmHg and/or diastolic blood pressure < 80 mmHg) allows to significantly reduce the incidence of microvascular and cardiovascular complications in T2D subjects (UKPDS 38, 1998); unfortunately, adequate blood pressure control is reportedly not achieved in up to 50–75% of diabetic patients (Hansson, 2002; Saydah et al., 2004). In addition, achieving blood pressure control in subjects with T2D frequently requires the use of more than 3 antihypertensive agents (Bloomgarden, 2001; Calhoun et al., 2002).

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Table 1. Demographic and clinical characteristics of diabetic subjects with and without resistant hypertension (RH).

	RH (+)	RH (-)	P
Males % (n)	52.2 (625)	47.7 (261)	0.35
Age (years)	67.1 ± 8.6	65.1 ± 10.0	0.03
Current smokers % (n)	32.3 (49)	37.4 (158)	0.001
Duration of diabetes (years)	12.0 ± 7.8	11.2 ± 9.3	0.32
HbA1c (%)	7.5 ± 1.6	7.8 ± 2.0	0.04
Body mass index (Kg/m ²)	33.1 ± 5.6	31.2 ± 5.3	<0.001
Systolic blood pressure (mm Hg)	148.6 ± 15.7	138.8 ± 17.8	<0.001
Diastolic blood pressure (mm Hg)	79.9 ± 8.7	79.1 ± 10.4	0.41
Coronary artery disease (yes) % (n)	43.5 (40)	26.2 (158)	0.001
Dyslipidemia (yes) % (n)	72.5 (90)	54.4 (296)	<0.001
Treatment for diabetes	-	-	-
Antidiabetic tablets % (n)	68.8 (103)	75.1 (387)	0.13
Insulin (%)	35.5 (29)	19.2 (121)	<0.001

P values for the comparison between subjects with and without RH by independent samples *t*-test for continuous variables or by Pearson χ^2 for nominal variables.

In our country the evidence regarding the prevalence of resistant hypertension among T2D subjects are lacking. Therefore, we performed a retrospective analysis in order to estimate the prevalence of resistant hypertension among Greek T2D subjects.

METHODS

We performed a retrospective analysis of the medical records of 664 T2D subjects (mean age ± standard deviation: 65.5 ± 9.8 years, 341 females / 323 males) with arterial hypertension attending the diabetes outpatient clinic of our hospital during the period from 1 January 2010 to 30 September 2010. According to routine clinical practice at our center, each medical record contains patient's demographic characteristics, a detailed medical history as well as information about the presence of cardiovascular disease, current medication, other diseases and smoking habits. In addition, an HbA1c, systolic (SBP) and diastolic (DBP) blood pressure and a weight measurement are performed at every scheduled examination and then body mass index (BMI) is calculated.

Only patients with at least six months of follow-up by the medical staff at the center, prior to the recorded visit, and patients who had at least one previous examination during this time period were included. When more than one patient visit (fulfilling the above criteria) was recorded during the same year, the first one was selected. Patients with type 1 diabetes were excluded from the study, based on physician indications on each patient's file.

According to the current guidelines, resistant hypertension is defined by a failure to achieve goal blood pressure despite appropriate adherence to a three antihypertensive drug regimen (Calhoun et al, 2008). It is advised but not strictly required that one of the three

agents is a diuretic and all agents are prescribed at optimal doses; this definition was used in the present study (Calhoun et al, 2008). Target blood pressure is <140/90 mmHg except for those with diabetes and chronic kidney disease where the goal is <130/80 mmHg (Chobanian et al., 2003).

The Hospital's ethical committee provided approval for this study. The study was in accordance with the Helsinki declaration.

Statistical analysis

Statistical analysis was performed using programs available in the SPSS statistical package (SPSS 15.0, Chicago, USA). All variables were tested for normal distribution of the data. Data are shown as mean ± SD, unless it is stated otherwise. A two sample *t*-test was used to assess differences in continuous variables, while a chi-square test was used for categorical variables. Univariate logistic regression analysis was performed to look for the relationship between resistant hypertension and the variables of interest in the sample population. Then, multivariate logistic regression analyses were performed (backward stepwise method) to look for independent associations between resistant hypertension and the variables of interest. All independent variables in the multivariate analyses were tested for multicollinearity. *P*<0.05 (two-tailed) was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the study participants are shown on Table 1. Diabetic subjects with resistant hypertension, compared to those without

Table 2. Univariate and multivariate logistic regression analysis: the association between various parameters with resistant hypertension in the study population.

	<i>Univariate analysis</i>			<i>Multivariate analysis</i>		
	Odds ratio	95% Confidence Intervals	P-value	Odds ratio	95% Confidence Intervals	P-value
Age	1.02	1.00-1.04	0.03	-	-	-
Sex	1.24	0.86-1.83	0.24	-	-	-
Body mass index	1.06	1.03-1.10	<0.001	1.06	1.02-1.11	<0.001
Coronary artery disease	2.16	1.46-3.19	<0.001	1.83	1.21-2.77	0.004
Dyslipidemia	2.21	1.46-3.19	<0.001	-	-	-
HbA1c	0.91	0.82-1.01	0.07	-	-	-
Duration of diabetes	1.03	0.99-1.05	0.08	-	-	-
Smoking	0.77	0.59-1.02	0.07	-	-	-
Insulin therapy	2.31	1.53-3.48	<0.001	1.78	1.15-2.75	0.01
Oral antidiabetic therapy	1.02	0.66-1.55	0.95	-	-	-

resistant hypertension, were older (67.1 ± 8.6 vs. 65.1 ± 10.0 years, respectively, $P=0.03$), had higher BMI (33.1 ± 5.6 vs. 31.2 ± 5.3 Kg/m², respectively, $P<0.001$), had more often coronary artery disease (CAD) (43.5 vs. 26.2%, respectively, $P=0.001$), dyslipidemia (72.5 vs. 54.4%, respectively, $P<0.001$) and were more often on insulin therapy (35.5 vs. 19.2%, respectively, $P<0.001$). It is noteworthy that diabetic subjects without resistant hypertension, compared to those with resistant hypertension, were more often current smokers (37.4 vs. 32.3%, respectively, $P=0.001$) and had higher values of HbA1c (7.81 ± 2.0 vs. 7.5 ± 1.6 %, respectively, $P=0.04$).

Of the study participants 20.8% ($n=138$) had resistant hypertension. No sex difference was observed in study participants regarding the prevalence of resistant hypertension (19.2% males / 22.9% females, $P=0.24$). The antihypertensive treatment of the diabetic subjects with and without resistant hypertension was, respectively; 59.4% vs. 47.9% on angiotensin-converting enzyme inhibitors (ACE-I) ($P=0.01$), 45.7% vs. 21.9% on angiotensin II receptor blockers (ARBs) ($P<0.001$), 52.2% vs. 23.0% on β -blockers ($P<0.001$), 12.3% vs. 1.5% on centrally acting antihypertensives ($P<0.001$), and 71.0% vs. 29.7% on calcium channel blockers ($P<0.001$). Of the diabetic subjects without resistant hypertension 39.5% was on treatment with diuretics.

Univariate logistic analysis showed that resistant hypertension was associated only with age [odds ratio (OR): 1.02, 95% Confidence Intervals (95% CI): 1.00-1.04, $P=0.03$], BMI (OR: 1.06, 95% CI: 1.03-1.10, $P<0.001$), presence of coronary artery disease (OR: 2.16, 95% CI: 1.46-3.19, $P<0.001$), presence of dyslipidemia (OR: 2.21, 95% CI: 1.46-3.19, $P<0.001$), and insulin therapy (OR: 2.31, 95% CI: 1.53-3.48, $P<0.001$). No significant associations were found between resistant hypertension and gender, duration of diabetes, HbA1c, smoking, and oral antidiabetic therapy.

After multivariate adjustment resistant hypertension was associated with BMI (OR: 1.06, 95% CI: 1.02-1.11,

$P<0.001$), presence of coronary artery disease (OR: 1.83, 95% CI: 1.21-2.77, $P=0.004$), and insulin therapy (OR: 1.78, 95% CI: 1.15-2.75, $P=0.01$) (Table 2).

DISCUSSION

This study found that 20.8% of our cohort of Greek patients with T2D had resistant hypertension. It is known that only a minority of diabetic patients achieve target blood pressure of 130/80 mmHg (Hansson, 2002). Nearly 75% of diabetic patients do not achieve good blood pressure control (Hajjar et al., 2003). The NHANES 1999-2000 study showed that only 35.8% of participants achieved the target of SBP less than 130 mmHg and DBP less than 80 mmHg, while 40.4% had hypertensive blood pressure levels (Saydah et al., 2004). The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that 34% of participants had above goal blood pressure on an average of 2 medications and 51% of participants required 3 or more medications (Cushman et al., 2002). Small studies have demonstrated that the prevalence of resistant hypertension in the general population from 5% in general medical practice to 50% in nephrology clinics (Kaplan, 2005).

Primary aldosteronism is common in diabetic patients with resistant hypertension, with a prevalence of 14% (Umpierrez et al., 2007). This evidence has been confirmed by other studies showing that hyperaldosteronism is a common cause of resistant hypertension in diabetic subjects (Bloomgarden, 2001; Mukherjee et al., 2010). These findings indicate that diabetic subjects with poorly controlled hypertension who are taking more or equal to 3 antihypertensive agents should be screened for primary aldosteronism (Umpierrez et al., 2007; Mukherjee et al., 2010). Other reasons for poorly controlled hypertension in diabetic subjects include poor patient compliance, cost and side effects of

antihypertensive medications, presence of co-morbidities, and physicians' lack of adherence to practice guidelines for managing hypertension (Wang et al., 2005).

We found that main determinants of the presence of resistant hypertension were BMI, presence of coronary artery disease and insulin therapy. According to the AHA scientific statement for resistant hypertension (Calhoun et al., 2008), based on the results of Framingham and ALLHAT studies, among the strongest predictors of resistant hypertension were older age and obesity. One of the underlying mechanisms linking resistant hypertension and obesity is increased sympathetic nervous system activity (Tsioufis et al., 2011). In addition, it is well documented that subjects with resistant hypertension have increased risk of cardiovascular events, most likely due to the long term history of poorly controlled blood pressure and the common association of resistant hypertension with diabetes (Lewington et al., 2002).

A recent article confirmed our findings showing that the development of resistant hypertension in individuals with metabolic syndrome that is characterized by insulin resistance and obesity (Chaudhary et al., 2010). Another study showed that hyperinsulinaemia is the main factor linking resistant hypertension, obesity and T2DM (Isaksson et al., 1994). In the same study the authors showed that resistant hypertension was associated to an increased risk of target organ damage, including cardiovascular disease (Isaksson et al., 1994).

In conclusion, the present study showed that a significant percentage of T2D subjects have resistant hypertension that is related with BMI, presence of coronary artery disease and insulin treatment.

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