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# RESISTANT HYPERTENSION IN TYPE 2 DIABETES: PREVALENCE AND PATIENT CHARACTERISTICS

**DANA MIHAELA CIOBANU[1], HÉLÈNE KILFIGER[2], BOGDAN APAN[3], GABRIELA ROMAN[1,3], IOAN ANDREI VERESIU[1,3]**

**[1]Department of Diabetes, Nutrition and Metabolic Diseases, Faculty of Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania**
**[2]Faculty of Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania**
**[3]Cluj County Emergency Clinical Hospital, Center of Diabetes, Nutrition and Metabolic Diseases, Romania**

***Abstract***

***Background and aims****. Resistant hypertension is defined as failure to achieve blood pressure lower than 140/90 mmHg when using three antihypertensive agents or controlled blood pressure with four or more drugs. We aimed at assessing the prevalence of resistant hypertension and to describe a type 2 diabetes population with resistant hypertension.*

***Methods.*** *The retrospective observational study included (n=73) type 2 diabetes subjects with resistant hypertension selected from (n=728) subjects admitted to the Centre of Diabetes, Cluj, Romania.*

***Results.*** *The subjects (70% women) had a mean age of 65.0±8.9 yrs. and diabetes duration 11(6-19) yrs. Prevalence of resistant hypertension was 10%. Chronic diabetes complications and cardiovascular disease were present in 77% and 56% of subjects respectively. On admission, antihypertensive drugs used were: angiotensin-converting enzyme inhibitors or angiotensin II receptors blockers 93%, β-blockers 88%, diuretics 78%, calcium channels blockers 59%, adrenergic α-antagonists 11%. Systolic and diastolic blood pressure were lower in the last compared to first admission day. Diuretics and calcium channels blockers were the most frequently newly added antihypertensive agents.*

***Conclusion.*** *Although the prevalence of resistant hypertension in type 2 diabetes did not differ from the general population, we observed that these patients had increased frequency of chronic diabetic complications. Angiotensin-converting enzyme inhibitors or angiotensin II receptors and β-blockers were the most used antihypertensive drugs, while the most frequently newly prescribed drugs were diuretics and calcium channel blockers.*

**Keywords**: diabetes mellitus, hypertension, antihypertensive agents, diabetic complications

## Background and Aims

Resistant hypertension is an increasingly clinical problem that is often heterogeneous in etiology, risk factors, and comorbidities [1]. A proportion of poorly controlled hypertensive subjects have resistant hypertension, defined as failure to achieve the goal BP <140/90 mmHg when patients adhere to an appropriate regimen of three or more than three antihypertensive agents of different classes or controlled blood pressure with four or more medications.

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Address for correspondence: birsan.dana@umfcluj.ro

Ideally, one of the three agents should be a diuretic and all agents should be prescribed at optimal dose amounts [2,3]. Although resistant hypertension is quite common, the exact prevalence remains unknown. Data derived from cross-sectional studies and post hoc analyses of clinical trials have estimated that the prevalence of resistant hypertension is about 10%–35% of all patients being treated for hypertension [2]. Data from NHANES indicate that the prevalence of resistant hypertension was 9-12% [4,5]. In the ACCOMPLISH study between 25% to 28% of subjects remained uncontrolled during the study in spite of treatment intensification [6].

Resistant hypertension has been linked with type 2 diabetes [7], obesity and chronic kidney disease [8]. The presence of diabetes and/or chronic kidney disease can be both causes and consequences of resistant hypertension. These associations predispose resistant hypertension subjects to high risk of cardiovascular events and mortality rates compared to controlled hypertension subjects [9].

Evidence from randomized controlled trials show that blood pressure lowering treatment reduces the risk of cardiovascular morbidity in hypertensive subjects, regardless of the classes of antihypertensive drugs used [10]. Recent guidelines recommend angiotensin-converting enzyme inhibitors or angiotensin II receptors blockers as first-line antihypertensive agents for their favorable outcomes in subjects with chronic kidney disease [11] and diabetes [3]. Therefore, we aimed at assessing the prevalence of resistant hypertension and to describe a type 2 diabetes population with resistant hypertension.

## Patients and Methods

### *Patients*

We performed a retrospective observational study. We selected a number of 73 subjects after evaluating a total of 728 patients' files according to inclusion and exclusion criteria. The subjects were hospitalized at the Centre of Diabetes, Nutrition and Metabolic Diseases, Emergency Clinical County Hospital, Cluj-Napoca, Romania, between July 2013 and February 2014. Inclusion criteria were: adults (>18 years old) with type 2 diabetes and blood pressure on the first admission day that was above goal (≥140/90 mmHg) in spite of concurrent use of three antihypertensive agents of different classes or controlled blood pressure (<140/90 mmHg) with four or more medications. Exclusion criteria were: secondary hypertension, estimated glomerular filtration rate <30 ml/min/1.73 $m^2$, severe infections and lack of antihypertensive treatment adherence. All study procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the Helsinki Declaration. All participants provided written informed consent.

### *Study Protocol*

Patients' medical files were accessed and data related to personal and medical history were collected: age, gender, type 2 diabetes duration, glycated hemoglobin (HbA1c), presence of chronic diabetic complications (neuropathy, retinopathy and diabetic chronic kidney disease) and cardiovascular disease. The chronic diabetic complications were diagnosed using Toronto score for diabetic neuropathy, retinal photography for diabetic retinopathy, and estimated glomerular filtration rate<60 ml/min/1.73 $m^2$ and/or present albuminuria for diabetic chronic kidney disease [12]. The cardiovascular disease was defined as the presence of at least one of the following: ischemic heart disease, history of stroke or myocardial infarction. The diagnosis of ischemic heart disease was established in the cardiology department. Antihypertensive medication classes were recorded in the first and last admission days. The blood pressure lowering medications classes taken into consideration were: angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptors blockers (ARB), β-blockers, diuretics, calcium channel blockers (CCB) and adrenergic α-antagonists. Height, weight and waist circumference were recorded and body mass index (BMI) was calculated. Blood pressure was measured using an automatic device (Colin Press-Mate BP-8800C Sphygmomanometer Monitor, Japan). Blood pressure readings were measured twice daily (8 am and 6 pm) during the hospital admission period with the patient seated, the arm at heart level and the cuff correctly placed on the arm circumference, after 5 minutes of rest. In order to assess changes in blood pressure values during the hospitalization period, we recorded the blood pressure values in the first and the last admission days.

### *Statistical analysis*

Data analyses were performed using Microsoft Office Excel 2010 and IBM SPSS ver.22 for Windows. The normality of variables distribution was evaluated using Kolmogorov–Smirnov test. Continuous data were expressed as means +/− standard deviation (SD) when normally distributed or as median and interquartile range (IQR) for non-parametric data. The categorical or dichotomous variables were expressed as absolute values and percentages. Group comparisons of all variables were performed using t- test for paired samples for normally distributed data or Mann–Whitney test for groups with data not normally distributed. Correlation analyses between variables were evaluated using non-parametric Spearman rank coefficient. A $p$ values less than 0.05 was considered statistically significant.

## Results

### *Characteristics of the study population.*

The characteristics of type 2 diabetes subjects with resistant hypertension are presented in Table I.

The prevalence of resistant hypertension in type 2 diabetic study population was 10%. The chronic microvascular complications of the type 2 diabetes

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

| Variables | Subjects (n=73) |
|---|---|
| Age (years) | 65.0±8.9 |
| Female Gender (n, %) | 51 (70%) |
| Diabetes duration (years, IQR) | 11 (6-19) |
| Body mass index (kg/m2) | 25.8±4.3 |
| Waist circumference (cm) | 95.1±13.2 |
| Glycated hemoglobin - HbA1c (%) | 9.5±2.5 |

Values are means+/− S.D, as medians (IQR) or percentages.

subjects are presented in Figure 1. About 77% of the type 2 diabetes subjects had at least one chronic microvascular complication of diabetes. The cardiovascular disease had the following prevalence: ischemic heart disease (43%), history of stroke (21%), history of myocardial infarction (4%). A percent of 56% of subjects had at least one of the cardiovascular disease previously listed.

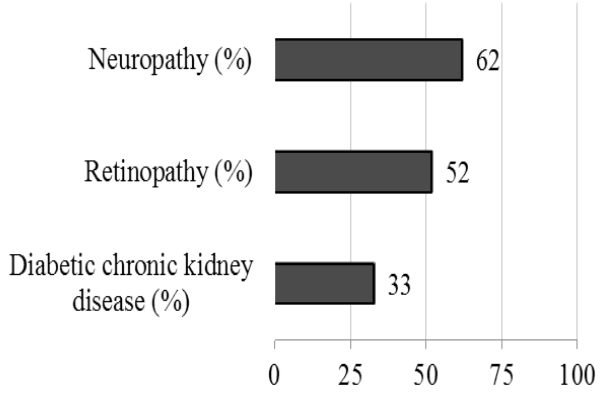


**Figure 1.** Chronic microvascular complications of diabetes.

***Antihypertensive agents***

Blood pressure lowering medication classes recorded in the first and last admission days are presented in Figure 2. A percent of 43% of subjects had four or more antihypertensive drugs. We observed that ACE-I or ARB (93%) were the most frequently used antihypertensive agents, followed by β-blockers and diuretics. Diuretics (p=0.006) and CCB (p=0.012) were the most frequently newly prescribed blood pressure lowering drugs. ACE-I or ARB remained the most frequently used antihypertensive agents in the last admission day (99%). ARB were used by 11% of the type 2 diabetes subjects in the first admission day and by 34% of the type 2 diabetes subjects in the last admission day.

***Blood pressure in the first and last admission days***

We observed that both systolic blood pressure (148.5±19.7 *vs* 139.7±22.5 mmHg; p=0.04) and diastolic blood pressure (82.8±13.6 *vs* 79±11 mmHg; p=0.02) were significantly reduced in the last admission day compared to the first admission day (Figure 3). Blood pressure control was obtained by modifying the medication doses or by introducing new antihypertensive agents.

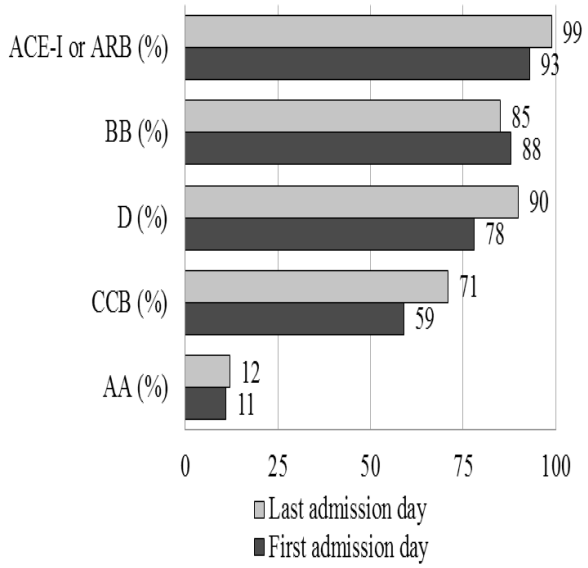


**Figure 2.** Antihypertensive agents in the first and last admission days. Angiotensin-Converting Enzyme Inhibitors - ACE-I; Angiotensin II Receptors Blockers – ARB; Adrenergic β-Blockers – BB; Diuretics – D; Calcium Channel Blockers – CCB; Adrenergic α-Antagonists – AA.

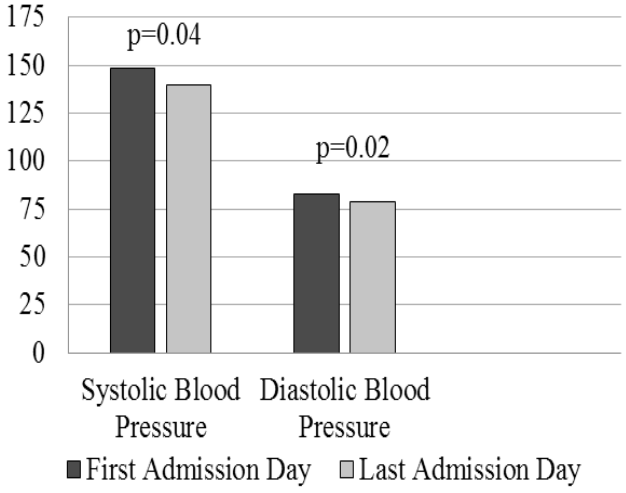


**Figure 3.** Systolic and Diastolic blood pressure in the first and last admission days.

***Correlations***

Diabetes duration was directly associated with the presence of diabetic peripheral neuropathy (r=0.37 [95% CI 0.15 to 0.58]; p=0.001) and diabetic retinopathy (r=0.46 [95% CI 0.25 to 0.64]; p<0.001). Diabetic retinopathy was directly associated with the use of ARB both in the first admission day (r= 0.29 [95% CI 0.18 to 0.58]; p=0.001) and last admission day (r=0.29 [95% CI 0.06 to 0.49]; p=0.013). The presence of cardiovascular disease was associated with the use of ARB in the last admission day (r=0.23 [95% CI 0.03 to 0.45]; p=0.05). There was no association between the cardiovascular disease and the use of β-blockers.

## Discussion

We found that the prevalence of resistant hypertension in the type 2 diabetes study population was 10%. Our result showing the prevalence of resistant hypertension was similar with previous reports in the general population [2,4,5]. The main difference between our study and these studies is that we analyzed a type 2 diabetes population. In the RIACE study, the prevalence of resistant hypertension in the type 2 diabetes population was 15% [7]. We would have expected higher resistant hypertension prevalence considering the high prevalence of hypertension in type 2 diabetes subjects compared to the general population [13]. Resistant hypertension needs to be differentiated form "pseudo-resistance" which is a consequence of inadequate hypertension management. In an analysis of the Spanish ambulatory blood pressure monitoring registry with patients treated for hypertension, 12.2% of subjects were diagnosed with resistant hypertension. Out of these subjects, a percent of 37.5% were found to have pseudo-resistant HTN when examining blood pressure with ambulatory blood pressure monitoring [14].

A large retrospective cohort study described the use of antihypertensive agents in patients with resistant hypertension. The most frequently prescribed antihypertensive classes were ACE-I and/or ARB in 96.2%, diuretics in 93.2%, CCB in 83.6%, and β-blockers in 80.0% of patients [15]. In comparison, in our study we found that the most frequently used antihypertensive drugs were ACE-I or ARB in 93%, followed by β-blockers in 88% and diuretics in 78%. ACE-I or ARB were first-line hypertension medication in the type 2 diabetes subjects, as recommended by the guidelines [3,16]. According to the Eighth Joint National Committee guideline, if goal BP is not reached within a month of treatment, the clinicians should increase the dose of the initial drug or add a second drug from one of the classes in recommendation (thiazide-type diuretic, CCB, ACE-I, or ARB) [11]. In our study, we found that β-blockers were the second more used drugs, although the JNC 8 does not include β-blockers in the list of first four recommended drugs. We hypothesized that the increased use of β-blockers was related to increased prevalence of cardiovascular disease in the study populations. Thus, we found no association between the use of β-blockers and the presence of cardiovascular disease. Moreover, in diabetic subjects the use of β-blockers might be limited due to their negative metabolic effects such as masking of hypoglycemia [17]. Diuretics were the third most frequently used drugs in our study. One prospective study found that occult volume expansion is an underlying condition in resistant hypertension and that forced titration of diuretics can improve hypertension control [18]. Thiazide diuretics are effective antihypertensive agents in the majority of patients, but in the presence of chronic kidney disease loop diuretics should be considered. Moreover, the increase use of diuretics can be explained by the recent recommendation guidelines that place diuretics on the first line therapy in most hypertensive subjects [3,11]. Minimally efficacious combinations, such as an ACE-I and an ARB, were prescribed in 15.6% of the subjects included in the previously mentioned cohort study [15]. We found that none of the patients included in our study had both ACE-I and ARB at the same time.

We observed that both systolic and diastolic blood pressures were significantly reduced in the last admission day in comparison to the first admission day. The reduction in blood pressure was obtained by modifying actual antihypertensive medication doses or by prescribing newly antihypertensive classes. Diuretics and CCB were the most frequently newly prescribed drugs and were introduced according to the recommendations of recent guidelines [3,11]. Another possible explanation for the blood pressure reduction during hospitalization was the low sodium regimen [19]. This regimen might have contributed to the blood pressure lowering, but we have no data on the amount of sodium intake before and during the hospitalization period.

We found a high frequency of both chronic microvascular complications of diabetes (neuropathy, retinopathy, diabetic chronic kidney disease) and cardiovascular disease in the type 2 diabetes study population. In comparison, other studies found lower frequencies of overall chronic complications of diabetes: 44% [20], 69% [21], 52% [22], and cardiovascular disease: 11% [21], 30% [22]. A possible explanation for these differences is the higher complication rates in hospitalized subjects compared to subjects evaluated in the out-patient clinic.

Diabetes duration was significantly associated with the presence of diabetic neuropathy and diabetic retinopathy. These data are confirmed in the UKPDS study [23]. Diabetic retinopathy was directly associated with the use of ARB in the first and last admission days. No other antihypertensive medication was associated with diabetic retinopathy. A meta-analysis published in 2015 concluded that ARB were associated with a higher possibility of diabetic retinopathy regression, although they had no effect on disease progression [24]. We hypothesized that the patients with diabetic retinopathy included in our study might have higher chances of retinopathy regression due to the use of ARB. The presence of cardiovascular disease was directly associated with the ARB in the last hospitalization day. Results of clinical trials sustain the use of ARB in subjects with diabetic microvascular complications [25,26] and cardiovascular disease [27].

## Conclusions

We found that the prevalence of resistant hypertension in the type 2 diabetes study population was 10%. Also, we observed a high prevalence of both

diabetic chronic complications (neuropathy, retinopathy and diabetic chronic kidney disease) and cardiovascular disease in the study population. We found that angiotensin-converting enzyme inhibitors or angiotensin II receptors blockers were the most frequently used antihypertensive agents, while diuretics and calcium channel blockers were the most frequently newly prescribed antihypertensive agents.

### Perspectives

Resistant hypertension is a challenging clinical condition in the management of hypertension, particularly in the presence of type 2 diabetes. In order to improve blood pressure control, efficient health services for the detection and screening of hypertensive subjects should be promoted. The next steps are to investigate the lifestyle and biological factors that contribute to failure to achieve blood pressure control, such as poor treatment compliance, inadequate lifestyle, dietary sodium intake and use of medication (such as, non-steroidal anti-inflammatory drugs and antidepressants) or caffeine consumption.

### Limitations of the study

The retrospective study design may have limited our evaluation. Office blood pressure was measured in the first and last admission days. Patients with pseudo-hypertension are better identified using 24 hours ambulatory blood pressure monitoring than using office blood pressure. At the time of the study, 24 hours ambulatory blood pressure monitoring was not accessible to all patients admitted to our clinic. We evaluated type 2 diabetes subjects with long term hospitalization in the Diabetes Centre Cluj that might have had higher rates of chronic diabetic complications and cardiovascular disease.

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