

Special Issue: Diabetic Nephropathy

Resistant Hypertension in Diabetes Mellitus

Pedro Armario^{1,2*}, Pedro Blanch^{1,3}, Pere Castellanos^{1,2}, Raquel Hernandez del Rey^{1,2}, Carlos Jericó^{1,2}, Oana Rap^{1,4}, Carmen Martin-Castillejos¹, Antonio Mestrón^{1,5} and Lluís Vila^{1,5}

¹Vascular Risk Area. Hospital Moisès Broggi- Consorci Sanitari Integral, University of Barcelona, Spain

²Department of Internal Medicine- Hospital Moisès Broggi- Consorci Sanitari Integral, University of Barcelona, Spain

³Department of Cardiology -Hospital Moisès Broggi- Consorci Sanitari Integral, University of Barcelona, Spain

⁴Department of Nephrology- Hospital Moisès Broggi- Consorci Sanitari Integral, University of Barcelona, Spain

⁵Department of Endocrinology -Hospital Moisès Broggi- Consorci Sanitari Integral, University of Barcelona, Spain

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***Corresponding author:** Pedro Armario, Vascular Risk Area and Department of Internal Medicine Hospital Mosès Broggi Sant Joan Despi- Consorci Sanitari Integral, Jacint Verdaguer, 90. 08970 Sant Joan Despi. Barcelona, University of Barcelona, Tel: + 34 935531200; 8602; Fax: + 34 93 553 12 17; Email: pedro.armario@sanitatintegral.org

Abstract

Diabetes Mellitus (DM) confers an increase of cardiovascular risk, independently from other conventional risk factors. The risk of cardiovascular events is 4-fold higher in patients with both diabetes and hypertension, compared with the normotensive controls. Compared with data from the general population or hypertensive individuals, a higher frequency of Resistant Hypertension (RH) has been observed in subjects with type 2 diabetes. Moreover, subjects with resistant hypertension had a higher prevalence of diabetes as compared with patients treated and controlled with three or less drugs.

In this review, the burden of RH in subjects with diabetes and the ratio between benefit and risk of spironolactone according to the renal function and or Hyperkalemia has been examined. In addition, this review focus in the possible role of new non-pharmacological techniques used in recent years in the control the RH, and its effect on office blood pressure and the most controversial and heterogeneous effects on ambulatory BP. Some studies have shown promising results on the metabolism of glucose and insulin repetition, but these promising results need to be confirmed in large randomized studies.

Keywords: Resistant Hypertension; Diabetes; Spironolactone

Introduction

A great number of clinical trials have shown the benefits of reducing Blood Pressure (BP) to prevent cardiovascular morbidity and mortality and these are directly proportional to the BP levels achieved. Despite this, BP is poorly controlled in most countries. Several factors have been associated with poor control, some of which involve the characteristics of the patients themselves, such as socioeconomic factors, poor unsuitable lifestyles, but other factors are related to hypertension or to associated comorbidity and the control rate is even lower in high-risk hypertensive patients such as diabetic patients and patients with chronic kidney disease [1,2]. But uncontrolled hypertension and Resistant Hypertension (RH) are not synonymous.

Uncontrolled hypertension includes patients who have not met targets because they failed to adhere to treatment or who are not treated adequately.

RH is defined as office blood pressure that remains above the goal despite the concurrent use of 3 antihypertensive agents, at full doses, one of them being a diuretic [3]. In addition, the term RH has been suggested for those patients with true RH and values above normal limits, after a careful exclusion of secondary causes, and in whom adequate adherence to medication has been evaluated [4,5]

Prevalence and Incidence of Resistant Hypertension

Data about the prevalence of RH have been reported from the Spanish ABPM Registry, the epidemiological community and the National Health and Nutrition Examination Survey (NHANES) from the United States, to establish that the prevalence of RH in treated hypertensive population is around 12-14% [6,7]. This condition is of clinical importance, because it is associated with a worse prognosis.

The prevalence of RH is higher in a number of clinical conditions such as obesity, diabetes mellitus, or chronic renal disease or target organ damage [4,8].

In a retrospective cohort study of 205,750 patients with incident hypertension, 1.9% developed RH within a median of 1.5 years from their initial treatment (0.7 cases per 100 person-years of follow-up). Over 3.8 years of median follow-up, and after adjustment for patients and clinical characteristics, cardiovascular event rates were significantly higher in RH patients [9].

Role of Ambulatory Blood Pressure Monitoring (ABPM) in Resistant Hypertension

The definition of RH is based on office measurements.

However, the use of ABPM has allowed for the recognition of pseudoresistant hypertension. It is estimated that more than a third of patients with suspected RH have white coat or isolated office RH, showing a normal daytime or 24-hour ABPM values⁶. These subjects are characterized by a lower prevalence of target organ damage [10,11]. On the other hand, several prospective studies have shown a better prognosis in patients with pseudoresistant hypertension compared with subjects with true RH [12-14].

Furthermore, ABPM add some information on the circadian BP pattern. The non dipper or risers pattern are more frequent in subjects with true RH than in subjects with white coat RH and there is wide evidence on the value of nocturnal BP as the parameter that best correlates with organ target damage [15], and as an independent predictor of the occurrence of cardiovascular disease during follow-up[16]. On the other hand, the group of Muxfeldt et al. [17] in a prospective study of 547 subjects with RH followed during 4.7years, have shown the prognosis of 24h-ambulatory arterial stiffness index. Therefore, the role of ABPM is central both in the initial diagnosis of subjects with RH and during the follow-up.

Diabetes and Resistant Hypertension

DM confers an increase of cardiovascular risk. A collaborative meta-analysis of 102 prospective studies [18] has shown that DM confers about a two-fold excess risk for coronary heart disease, major stroke subtypes, and deaths attributed to vascular causes, independently from other conventional risk factors. Hypertension is present in more than 50% of patients with DM and contributes significantly to both microvascular and macrovascular disease. The risk of cardiovascular events is 4-fold higher in patients with both DM and hypertension, compared with the normotensive controls [19]. DM and hypertension share several pathophysiological mechanisms including inappropriate activation of the renin-angiotensin-aldosterone system, increased sympathetic nervous system activation, insulin resistance and hyperinsulinemia, oxidative stress, inflammation, impaired insulin-mediated vasodilatation, and abnormal renal processing of sodium[19,20]. On the other hand, some research has suggested a direct association between DM and primary hyperaldosteronism. Umpierrez et al. [21] observed a prevalence of 14% of primary aldosteronism in diabetic patients with poorly uncontrolled hypertension taking ≥ 3 antihypertensive agents.

Compared with data from the general population or hypertensive individuals, a higher frequency of RH has been observed in subjects with type 2 diabetes. The RIACE study enrolled 15,773 patients consecutively visiting 19 diabetes clinics during the years 2007-2008, and RH was detected in 2,363 subjects (15% of the whole RIACE cohort [22], 17.4% of hypertensive individuals, and 21.2% of treated hypertensive patients). Moreover, subjects with RH from the Registry of the Spanish Society of Hypertension [11] have shown a high prevalence of DM (38.6%), and metabolic syndrome (63.8%). In an analysis of 27,897 hypertensive subjects [23], those with RH had a higher prevalence of DM as compared with patients

treated and controlled with three or less drugs (35.1% vs 18.8% respectively).

The burden of RH in people with type 1 diabetes has also been examined. A cross-sectional study[24] including a nationally representative cohort of patients with type 1 diabetes (n=3,678) from the Finnish Diabetic Nephropathy Study in Finland has shown that the prevalence of RH was 1.2% in the normoalbuminuric, 4.7% in the microalbuminuric, 28.1% in the macroalbuminuric, 36.6% in the dialysis and 26.3% in the kidney transplant groups.

Treatment of Resistant Hypertension in Diabetic Patients

Following are some steps in the management of hypertension difficult to control in diabetic patients, being necessary to confirm a good adherence to lifestyle changes and drug treatment, exclude secondary causes of hypertension, and confirm the lack of control by ambulatory BP-24h (Figure 1 and Table 1).

The definition of RH implies that one of the 3 drugs must be a diuretic, since the resistance of hypertension is often due, at least in part to inadequate control of volume expansion. Studies have shown that diuretic use is associated with improved BP control. The main classes of diuretic agents used in hypertension are thiazide or thiazide-like diuretics or loop diuretics in patients with a reduction of renal function (glomerular filtration rate < 40 mL/min)[25] Not all thiazide diuretics are equally efficacious. Chlortalidone, a longer-acting thiazide-like diuretic and indapamide have been recommended, especially in patients with poor control of hypertension [26]. A systematic review and meta-analysis [27] has shown that the use of thiazide-like diuretics was associated with additional risk reduction of 12% for cardiovascular events, and the incidence of adverse events was comparable among thiazide and thiazide-like diuretics.

Spirolactone is a nonselective antagonist of aldosterone and potassium-sparing diuretic. Despite its short half-life, the onset of action of aldosterone is slow, since it usually begins 48 hours after the initial dose, and the maximum effect on BP is observed after 3-4 weeks, and persists for at least one week after the suppression of the same, due to the presence of active metabolites. In recent years, evidence has been accumulated on the role of spironolactone at a dose of 25-50 mg per day in the management of RH. Although most of these studies were open, uncontrolled, or retrospective analyses, a significant reduction in BP (20-25 mm Hg systolic and 10-12 mm Hg for diastolic BP) was observed. This reduction was higher than would be expected by the simple addition of another antihypertensive [28]. A meta-analysis has been recently published [29] and 13 eligible studies were identified involving a total of 2,640 patients (3 randomized controlled trials and 10 observational studies without a control group). In controlled studies, there was a reduction in mean systolic and diastolic BP of -16.5 (95% confidence interval: -30.0 to -3.0mm Hg) and -4.1 (95% CI -7.8 to -0.32 mm Hg), respectively. In this meta-analysis, it has been observed that the use of an aldosterone antagonist was associated with a mild but significant increase in serum potassium and creatinine. Diabetic

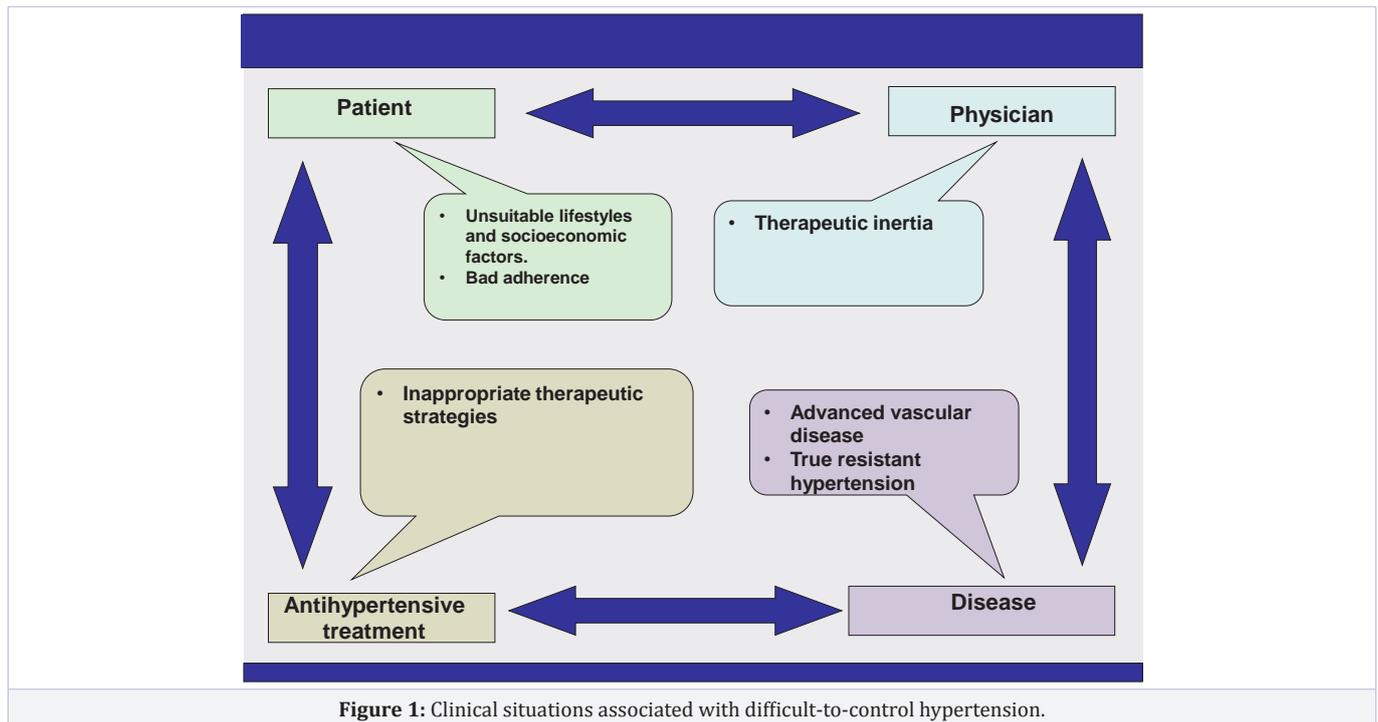


Figure 1: Clinical situations associated with difficult-to-control hypertension.

Table 1: Recommended steps in the management of resistant hypertension in diabetic patients.

1. Improve lifestyle changes
2. To evaluate adherence
3. To exclude pseudo-resistance hypertension with ambulatory blood pressure monitoring
4. Re-check for secondary causes,
5. Optimize pharmacological therapy
6. Consider new strategies for the management of resistant hypertension: renal sympathetic denervation or stimulation of the carotid baroreceptors.

patients could develop hyperkalaemia during treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in combination with low doses of spironolactone, more frequently than other non-diabetic hypertensive patients. However, low dose spironolactone exerts a significant BP and urinary albumin creatinine ratio thereby lowering the effects in high-risk patients with RH and type 2 diabetes mellitus [30]. Oxlund et al. [31], in a multicentre, double-blind, randomized, placebo-controlled trial study of 112 patients with RH, confirmed these results, and they observed that adverse events during the treatment with a low dose of spironolactone in these diabetic patients with RH and near normal renal function were infrequent and no unexpected adverse effects were seen.

RH is frequently associated with chronic kidney disease, but in this population the frequency of occurrence of hyperkalaemia during treatment with spironolactone is higher, especially when the estimated Glomerular Filtration Rate (eGFR) is <45 ml/min/1.73 m², and this treatment is not recommended when the GFR is <30 ml/min/1.73 m². Finally, some patients do not respond to spironolactone, and other therapeutic regimens can be used, based more on clinical experience than on the results of controlled studies.

New Strategies for the Management of RH

Sympathetic overactivity is seen in a wide array of medical conditions including RH. The contribution of renal afferent and efferent sympathetic activity on the development and progression of hypertension has been demonstrated in both preclinical studies and humans in various models of hypertension, myocardial infarction and chronic renal disease [32].

In recent years, two new techniques have been developed and evaluated in managing RH: renal sympathetic denervation and stimulation of the carotid baroreceptors.

Renal denervation therapy: The European Societies of Hypertension [33] and Cardiology [34] have been positioned on the role of this technique in the management of RH, establishing a series of indications and recommendations. On the other hand, in the last 2013 Guidelines of the European Society of Hypertension and European Society of Cardiology [35], it is recommended that its use may be indicated in selected cases, always when there is a lack of response to antihypertensive treatment, but according to the current data, the definite role and indications of this treatment are not clear. There is a scientific rationale for the procedure, and the magnitude of BP reduction was significant,

but the effects of this procedure on blood pressure levels obtained during the ABPM are less clear [36]. Some argued that the absence of a positive finding in Symplicity HTN-3 was mainly related to adding a sham procedure and blinding of patients, and others tried to provide other explanations [37].

Baroreflex activation therapy: Treatment based on baroreceptor activation is consistent with electrical stimulation located in the carotid sinus technique, resulting in reduced sympathetic outflow to the heart, vascular system and kidneys as well as an increase in parasympathetic tone [38]. Today, we have the results of two studies: the Device-Based Therapy in Hypertension trial (Debut-TH) [39] and the Rheos Pivotal Trial [40,41], which have shown promising results, although some complications directly related to the surgical procedure were observed. More recently, a system of baroreflex activation of second generation has been introduced, and 33 patients with RH were evaluated in 7 centers in Europe and Canada with a baseline BP of 172/100 mm Hg, and in which a reduction in BP was observed at 6 months of 26/12 mm Hg [42]. During the procedure, only 3 minor complications appeared within the first 30 days of implanting the device, and all were resolved without sequelae.

Some studies have shown that renal denervation improves glucose metabolism, and insulin sensitivity in addition to significantly reducing blood pressure in resistant hypertensive patients [43,44], but these promising results need to be confirmed in large scale, randomized studies.

In summary, RH is highly prevalent in patients with diabetes and contributes to increased morbidity and mortality. Spironolactone a low doses can improve the control rate of RH. However it should be used with caution in patients with diabetes because of the risk of hyperkalemia. Interesting perspectives could be open in the treatment of RH with renal denervation therapy and baroreflex activation therapy, but its role in diabetic patients with RH need to be confirmed in large scale, randomized studies.

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