Research Article

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Estimating the Prevalence of Resistant Hypertension among Patients Attending Public Health Care Services in Trinidad

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Abstract

Background

The rate of resistant hypertension (RH) in Trinidad is unknown. Several studies have shown that 12% to 30% of patients with hypertension in western countries may have RH. This is the first study to describe RH in Trinidad. RH increases the risk of type 2 diabetes, chronic kidney disease, coronary heart disease, heart failure and stroke.

Objective

The aim of the study is to measure the proportion of patients with hypertension who meet the criteria for RH among patients attending primary health care facilities in Trinidad and describe its epidemiological features.

Design and methods

We used a cross-sectional study design. Participants were selected using a clustered sampling technique from primary care clinics throughout the island. Data were collected by the administration of a pretested structured questionnaire. Apart from demographics, data was collected on the duration of hypertension and predisposing risk factors, and the presence of chronic kidney disease (CKD) and the metabolic syndrome.

Results

Initially 428 patients with hypertension were recruited, however only 391 entered the study of which 64 (16.4%, 95% CI 13- 20.3) met the criteria for RH. RH was found to be more common in patients 61-70 years, females and patients of African descent. Half of the patients classified as resistant hypertensive were obese, both CKD abd the metabolic syndrome were higher in patients with RH compared to non-resistant hypertension.

Conclusion

We provide evidence for the first time that the occurrence of RH in patients attending primary health care facilities in Trinidad was 16%. RH in Trinidad patients is associated with overweight/obesity, type 2 diabetes, chronic kidney disease and the metabolic syndrome. (266 words)

Introduction

The emergence of Non communicable diseases (NCDs) as the predominant challenge to global health is undisputed [1]. This situation is emphasised in the 2010 report on the global status of the challenges presented by NCDs, which states that NCDs accounted for 63% of the 57 million deaths that occurred in 2008 [2]. This number increased to 68% in 2012 [3]. NCD's particularly cardiovascular diseases, type 2 diabetes (T2DM), hypertension, chronic kidney disease (CKD) and cancer, are the leading cause of mortality in Trinidad.

Both the American Heart Association and the European Society of Cardiology as well as the Eighth Joint National Committee (JNC 8) define RH as uncontrolled blood pressure (BP) despite patient adherence to 3 anti-hypertensive drugs (including a diuretic), or controlled BP using ≥4 anti-hypertensive drugs [4-6]. Hypertension is common in Trinidad, in which the population consists of two major diaspora Africans and South East Asians (SEA) each representing close to 40% of the population respectively. Although hypertension is more common among Africans, the prevalence of RH in Trinidad is unknown. Cross sectional studies and hypertension outcome studies suggest however, that RH is not rare. Egan et al. reported that the prevalence of RH has progressively increased over the last several decades specifically from 5.5% in 1988-1994, to 8.5% in 1999-2004, and 11.8% in 2005-2008 (NHANES) [7].

It is important to differentiate between RH and uncontrolled hypertension [8,9]. Patients who are non-compliant or not adequately treated with a therapeutic plan should not be classified as having RH as this is better termed pseudo-resistance [9]. Bunker et al. determined that only 4F0% of patients referred to a specialist hypertension centre with uncontrolled hypertension despite the use of three or more drugs actually had true RH [10]., while Ceral et al. reported non-adherence in about two thirds of patients [11].

Patients are more likely to develop RH if they are older, non-Hispanic black, female or obese [12,13]. Patients with a high baseline systolic blood pressure (SBP), T2DM, CKD or left ventricular hypertrophy (LVH) were also found to be more likely to develop RH [9]. Additionally, obstructive sleep apnea (OSA) and primary aldosteronism, are secondary causes of RH [9,14].

RH is one of the most important modifiable risk factors for cardiovascular diseases [15]. Persell et al. reported that patients with RH have an increased risk of T2DM, reduced renal function, coronary heart disease (CHD), heart failure and stroke [8]. Further RH is associated with a 36% increased risk of heart failure, a 25% increased risk of myocardial infarction (MI), a 10% increased risk of stroke, and a 24% increased risk of end-stage renal disease (ESRD) [16].

RH requires a comprehensive management strategy as its etiology is multifactoral [17-20]. Pharmacological agents should be chosen with a medication strategy targeting the pathogenesis of RH [21]. A typical regimen should ideally include a diuretic, an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB), a calcium channel blocker (CCB) and a β-blocker (BB) [21]. It has been proven that a diuretic is essential to maximize BP control as patients with RH often have inappropriate volume expansion which add to their treatment resistance [18]. Aldosterone antagonists in particular are useful in the treatment of RH as primary aldosteronism is often an underlying cause [21,22], BBs are preferred in patients with coronary artery disease, congestive heart failure and post-MI [14] as they are usually needed to overcome the reflex tachycardia when administering direct vasodilators [21].

It is recommended that lifestyle interventions such as weight loss, regular exercise, low salt diet, moderation of alcohol and caffeine intake and smoking cessation [18,21,22]. accompany the therapeutic options for the treatment of RH as they are able to lower BP in patients with RH [23].

The aim of this study is to measure the proportion of patients with RH among patients attending primary health care facilities in Trinidad and describe its epidemiological features.

Methodology

We used a cross-sectional study design to estimate the occurrence of resistant hypertension in the Trinidad population. In Trinidad there is a two tier system of health care delivery: a private health care system based on a fee for service model and a public health care system financed by the state and free from all cost including medication. The study was confined to hypertensive patients accessing the public health care system as this provides a lager representative population of patients. Patients accessing private health is limited in number and logistically difficult to access.

The island is divided into four Regional Health Authorities (RHA). Each RHA delivers care at the primary level through a network of primary care facilities (PCF). Hypertensive management is delivered at these PCF. Thus in the first stage of selection of study participants we created a database of all the 100 PCF in all of the four RHA. This database was used to randomly select 20 PCF each representing a cluster. All patients >18 years at each cluster were invited to participate in the study. If the patient accepted to participate in the study, written informed consent was obtained. Inclusion criteria were a) patients with a physician diagnosis of hypertension defined as a BP >140/90mmHg and currently receiving treatment, b) patients with hypertension not controlled to target (i.e. <140/90 mmHg): defined as a clinic systolic BP ≥ 5 mmHg above target under one of the following conditions: i) treatment for at least 3 months with 3 antihypertensive agents at maximum dosage, and ii) are receiving additional drugs to manage their hypertension. Patients were excluded if they were visiting the health centre for the first time, did not have hypertension, or had secondary or accelerated hypertension, were too ill or unable to respond to the questionnaire, pregnant, had a diminished mental capacity, a recent cardiovascular event requiring hospitalization or did not give informed consent. In addition treatment with any of the following medications: oral corticosteroids within 3 months of screening, chronic use of non-steroidal anti-inflammatory agents and alpha-blockers with the exception of afluzosin and tamsulosin for prostatic symptoms. T2DM was considered controlled if the HbA1c level was ≤ 7%. Metabolic syndrome was assessed using the 2005 International Diabetes Federation (IDF) global definition and based on central obesity, defined by waist circumference (men ≥120 cm, women ≥80cm), along with any two of the following: elevated triglycerides (≥150 mg/dl or 1.7 mmol/l) or the use of a lipid-lowering drug; reduced high-density lipoprotein (HDL)-cholesterol (<40 mg/dl or 1.03 mmol/l in men;<50 mg/dl or 1.29 mmol/l in women) or specific treatment for this lipid abnormality; elevated fasting plasma glucose (≥ 100 mg/dl or 5.6 mmol/l) or previously established diagnosis of type-2 diabetes [24]. Although hypertension (SBP ≥130 mmHg or DBP ≥85 mmHg) or the use of an antihypertensive is part of the definition all our participants at entry would have met this criterion. Serum creatinine was measured using standard method and the values were used in the formula186 x $(Creat / 88.4)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.210 if black) to calculate the eGFR [25, 26].

A pretested structured interview questionnaire was administered to collect data on the patient's duration of hypertension, possible predisposing factors, as well as barriers to optimal BP control. We report means with standard deviations (SD), proportions with 95% confidence intervals (CI) and a Kaplan-Meir survival analysis. We used the Mann-Whitney test to determine significant differences, at a level of $p < 0.05$, ethical approval for the study was obtained from The University of the West Indies Ethics Committee.

Results

We recruited 428 patients who satisfied the entry criteria. However 37 patients refused to participate resulting in a non-response rate of 8.6%, hence 391 patients were available for analysis. The majority of patients in the study were in the age groups 61-70 years (141, 36.1%) and 51-60 years (115, 29.4%), (Table 1). The mean age of the sample was 62years (SD ±11.2) and the interquartile range was 55-69 years. There were more females (288, 73.7%) than males (103, 26.3%) with a f:m ratio of 2.8:1. Half (203, 51.9%) of the patients had hypertension for ≥ 7 years, the remainder of patients had hypertension for ≤ 6 years. Using the WHO criteria (2015) [27] for obesity and overweight the majority of patients were either overweight (153, 39.1%) or obese (151, 38.6%). Due to the age range of our sample it was not unusual that most subjects were unemployed (145, 37.1%) or retired (160, 40.9%). In Trinidad there are 2 major diasporas Africans and East Indians each representing approximately 40% of the population respectively. Our sample had more East Indians (184, 47.1%) than Africans (139, 35.5%).

Of the 391 patients entered into the study, 64 patients or 16.4% (95% CI 13.0 - 20.3) met the criteria for RH. The majority of the patients with RH were in the age groups 51-60 (17, 26.6%) and 61-70 (21, 32.8%), and RH was more common among females than males (f:m 4:1), (Table 2). Among patients with RH, approximately half were obese

(31, 48.3%) and one-third were overweight (22, 35.0%). Although the sample had more SEA, there was a significant (p<0.05) ethnic disparity in the distribution of RH being more common in Africans (32, 50%) compared with East Indians (22, 34.4%) as well as all other races (32, 50% vs 10, 15.6%).

RH occurred more commonly (40, 62.5%) in patients with hypertension for more than 7 years. However, a physician diagnoses of RH was only recorded in 6 (9.4%) patients and only 3 (4.7%) were aware that they had RH (3, 4.7%).

T2DM was established as the most common comorbid condition among patients with either hypertension (195, 49.9%) or RH (37, 60.7%), (Table 3). Among the 37 patients with both RH and T2DM, in a half (20, 51.3%) of these patients the T2DM was also uncontrolled. Obesity was a major comorbid factor in both hypertensive patients and patients with RH, (Table 3). Nutritional therapy is the first line therapy for T2DM as recommended by both the American Diabetes Association and the European Association for the Study of Diabetes (EASD) [28,29]. Among obese patients, 98 (25.3%) were advised to lose weight and among patients with RH and obesity, 22 (34.4%) were advised to lose weight. Dyslipidemia was also common among patients with hypertension (109, 27.9%) and RH (15, 23.4%), (Table 3).

A significant difference (p ≤ 0.05) was also found between patients who had hypertension and progressed to the development of T2DM (74, 37.9%), compared to those with T2DM who progressed to hypertension (51, 26.2%). Using the Kaplan-Meier time to an event analysis [30]., the median time for the development of T2DM after the onset of hypertension was found to be 7 years (95% CI 5.2-8.3).

Using an internationally valid questionnaire, "Epworth Sleepiness Scale" [31]. for assessing OSA, we found only 3.3% of patients with hypertension who met the criteria for OSA. Similarly, only 1 patient with RH satisfied the criteria for OSA, (Table 3).

All patients had their serum creatinine measured by standard methods. Using the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease [32], 165 (42.1%) patients had normal renal function, however 226 were in the various stages of CKD, (Table 4). As much as 14% (54) of patients had already advanced to stage 3 and 4. Among the patients with RH, a significantly higher proportion (33%, p<0.05) were in stage 3 and 4. The occurrence of the metabolic syndrome was similar among patients with hypertension (18, 4.6%) and RH (3, 4.7%).

Discussion

An important finding of the study is the relatively high proportion (16%, 95% CI 12.9-20.5) of RH among patients with hypertension attending PCF throughout the four RHA in Trinidad. In other words, 1 in 6 patients with hypertension developed RH. This finding is marginally higher than developed countries such as USA and Spain which reported prevalence rates of RH between 12-15%, and exceedingly higher than China (1.9%) [8,33-37]. Among developing countries the pattern is similar, studies in Brazil reported a prevalence of 11% [38,39]. at the lower end while in Sri Lanka rates of 19.1% have been reported [40,41]. This finding has important policy implications particularly for PHF, which has to be strengthened in an effort to provide additional promotive, preventive, curative, and rehabilitative services. Other implications include poor outcomes for patients with hypertension and RH, such as increased risk of cardiovascular morbidity and mortality

Characteristic	n(%)	Characteristics	n(%)
Age (yr)		**Gender**	
≤45	32 (8)	Male	103 (26.3)
>45	359(92)	Female	288 (73.7)
Total	391 (100)	Total	391 (100)
BMI (kg/m²)		**Ethnicity**	
normal	87 (22.3)	African	139 (35.5)
overweight	153 (39.1)	SEA	184 (47.1)
obesity	151 (38.6)	Other	68 (17.4)
Total	391 (100)	Total	391 (100)

Table 1: Sample characteristics of patients with hypertension.

Characteristics of patients with RH	n(%)	Characteristics of patients with RH	n(%)	Male	Female	
Age (yr)		**BMI (kg/m²)**				
≤45	10 (15.6)	Normal	11 (17.2)	0 (0.0)	1 (2.0)	
>45	54 (84.4)	overweight	22 (34.4)	5 (38.5)	5 (9.8)	
		obese	31 (48.4)	7 (53.8)	15(29.4)	
Total	64 (100)	Total	64 (100)	1 (7.7)	30(58.8)	
				13(100)	51(100)	
Gender		**Ethnicity**				
Male	14 (21.9)	African	32 (50.0)			
Female	50 (78.1)	East Indian	22 (34.4)			
Total	64 (100)	Other	10 (15.6)			
		Total	64 (100)			
Weight Status		**Income Status**				
Underweight	1 (1.7)	Unemployed	28 (43.8)			
Normal	10 (15.0)	Retired	24 (37.5)			
Overweight	22 (35.0)	Non-white	9 (14)			
Obese	31 (48.3)	White collar	3 (4.7)			
Total	64 (100)	Total	64 (100)			

Table 2: Characteristics of patients with RH.

Hypertensive Patients	n(%)	Patients with RH	n(%)
T2DM	195 (49.8)	**T2DM**	37 (57.8)
Dyslipidemia	109 (27.9)	**Dyslipidemia**	15 (23.4)
IHD	27 (6.9)	**IHD**	7 (10.9)
Thyroid Disease	18 (4.6)	**Thyroid Disease**	2 (3.1)
Proteinuria	11 (2.8)	**Proteinuria**	3 (4.7)
OSA	13 (3.3)	**OSA**	1 (1.6)
Obesity	131 (33.5)	**Obesity**	29 (45.3)
Metabolic Syndrome	18 (4.6)	**Metabolic Syndrome**	3 (4.7)

Table 3: Prevalence of comorbidities among patients with hypertension and RH.

CKD stage	n (%)
Normal	165 (42.1)
CKD Stage 1	10 (2.3)
CKD Stage 2	162 (41.5)
CKD Stage 3	44 (11.3)
CKD Stage 4	10 (2.6)
CKD Stage 5	0 (0.0)
Total	391 (100)

Table 4: Prevalence of CKD Stages 0 -5 among hypertensive patients attending primary health care facilities in Trinidad.

and CKD.

RH was more common in females (ratio: 4:1), older patients (59% 51-70 years) and patients of African ethnicity (50%). Recently in the Women's Ischemia Syndrome Evaluation (WISE) study [42], females with RH had a greater long-term risk of adverse events when compared to females without RH. This finding is also consistent with the findings of the ALLHAT study which showed that women and African-Americans had greater resistance to treatment [13]. We also report a significant ethnic disparity in the distribution of RH. We now provide evidence that not only is hypertension more common in African patients but is also more common than any other ethnic group. In addition RH was also more common in elderly patients a finding consistent with the literature [13,43]. Others have shown that while in younger age groups hypertension was more common in men than women, in older age groups especially female African-Americans had higher hypertension rates than other ethnic groups and thus a higher risk of developing RH [12]. Further Hung et al. concluded that gender and age can be used to predict the cardiovascular risk in patients with RH. Thus our findings imply that gender, age and ethnicity can be used to predict the cardiovascular risk in patients with RH. While this is the first study to describe the relationship between gender, age, and ethnicity in patients with RH, further research is needed to confirm this relationship and to identify the exact mechanisms involved. Although we did explore salt intake or other dietary factors Powless et al. showed that salt intake in the Caribbean was estimated at 3.5g/day and did vary by age or gender [44].

The major strengths of this study are that the research subjects were sampled from a large community cohort, and information regarding levels of BP and duration of hypertension were available for all patients thus reducing white-coat hypertension or isolated office RH, reported to as high as 37.5% [45]. However several limitations should be considered when interpreting the present study. A major limitation was patient adherence to drugs could not be adequately assessed and thus we relied on patient reporting. Further, the study could not adjust the optimal dosing of each medication as this was entirely within the domain of the attending physician. However, medication use in the present study represents real-world management choices.

In conclusion this is the first study to estimate the occurrence of RH in Trinidad. We provide evidence that RH is common. Age, gender and ethnicity are important predictors of RH. In addition RH

in Trinidadian patients is associated with overweight/obesity, type 2 diabetes, chronic kidney disease and the metabolic syndrome.

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