Original Article

Evaluation of the Causes of Resistant Hypertension in Non-dialysis Chronic Kidney Disease Patients

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DOI: https://doi.org/10.3329/bccj.v10i1.59199

Abstract:

Background: *In Chronic Kidney disease (CKD), resistant hypertension (RH) is a common condition due to a combination of factors including sodium retention, increased activity of the renin-angiotensin system, and enhanced activity of the sympathetic nervous system. The aim of the study was to determine the causes of resistant hypertension in non-dialysis Chronic Kidney Disease Patients.*

Methods: *This descriptive cross-sectional study was conducted in the department of Nephrology & Internal Medicine of Dhaka Medical College Hospital from 18th January 2016 to 20th may 2016. Patients aged above 18 years admitted with resistant RH and CKD were enrolled in the study after fulfilling the inclusion and exclusion criteria. The study involved 50 CKD patients who had RH. Purposive consecutive type of sampling technique was applied for sample collection. Detail socio-demographic data were collected and recorded in a predesigned questionnaire. Clinical examination and relevant investigations were done. Data was analysed with SPSS version 22.0. P value of <0.05 was considered significant.*

Result: *Maximum number of patients 23(46.0%) were between 46-60 years age group, mean age of the patient was 53.17 ± 8.42 years. Male: female ratio was 1.63:1. Study showed that frequency of RH and CKD gradually increased with age. In case of both sexes, 46-60 years age group showed the highest incidence for CKD. The mean systolic and diastolic blood pressures (BP) were 133.04 ± 12.91 mmHg and 81.07 ± 6.41 mmHg respectively. Those with diabetes mellitus, obesity (BMI > 27.5 kg/m2) and those who were older than 55 years were significantly higher in the RHT group than in the non-RHT group.*

Conclusion: *RH in CKD patients was significantly associated with the presence of obesity, diabetes mellitus and increased age. These factors should always be kept in mind while treating HTN in CKD patients.*

Key words: *Resistant Hypertension, Non-dialysis Chronic Kidney Disease Patient.*

Introduction

High blood pressure (hypertension) is one of the most important preventable causes of morbidity and mortality in the Bangladesh. Hypertension is a major risk factor for ischemic and hemorrhagic stroke, myocardial infarction, heart failure, chronic kidney disease, cognitive decline and premature death. Untreated hypertension is usually associated with a progressive rise in blood pressure. The vascular and renal damage caused by this can culminate in a treatment-resistant state. Blood pressure is normally distributed in the population and there is no natural cut-off point above which 'hypertension' definitively exists and below which it does not. The risk associated with increasing blood pressure is continuous, with each 2 mmHg rise in systolic blood pressure associated with a 7% increased risk of mortality from ischemic heart disease and a 10% increased risk of mortality from stroke. Hypertension is remarkably common in the Bangladesh and the prevalence is strongly influenced by age.

In any individual person, systolic and/or diastolic blood pressures may be elevated. Diastolic pressure is more commonly elevated in people younger than 50. With ageing, systolic hypertension becomes a more significant problem, as a result of progressive stiffening and loss of compliance of larger arteries. At least one quarter of adults (and more than half of those older than 60) have high blood pressure.[1]

Resistant hypertension (RH) (see operational definition under methodology) is a common clinical problem faced by both primary care clinicians and specialists. While the exact prevalence of resistant hypertension is unknown, clinical trials suggest that it is not rare, involving perhaps 20% to 30% of study participants. As older age and obesity are two of the strongest risk factors for uncontrolled hypertension, the incidence of resistant hypertension will likely increase as the population becomes more elderly and heavier. The prognosis of resistant hypertension is unknown, but cardiovascular risk is undoubtedly increased as patients often have a history of

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Received : September 13, 2019; Accepted : December 07, 2021

long-standing, severe hypertension complicated by multiple other cardiovascular risk factors such as obesity, sleep apnea, diabetes, and chronic kidney disease. The diagnosis of resistant hypertension requires use of good blood pressure technique to confirm persistently elevated blood pressure levels.

Pseudo-resistance, including lack of blood pressure control secondary to poor medication adherence or white coat hypertension, must be excluded. Resistant hypertension is almost always multifactorial in etiology. Successful treatment requires identification and reversal of lifestyle factors contributing to treatment resistance; diagnosis and appropriate treatment of secondary causes of hypertension; and use of effective multidrug regimens. As a subgroup, patients with resistant hypertension have not been widely studied. Observational assessments have allowed for identification of demographic and lifestyle characteristics associated with resistant hypertension, and the role of secondary causes of hypertension in promoting treatment resistance is well documented; however, identification of broader mechanisms of treatment resistance is lacking. In particular, attempts to elucidate potential genetic causes of resistant hypertension have been limited. Recommendations for the pharmacological treatment of resistant hypertension remain largely empiric due to the lack of systematic assessments of 3 or 4 drug combinations.

Studies of RH are limited by the high cardiovascular risk of patients within this subgroup, which generally precludes safe withdrawal of medications; the presence of multiple disease processes (e.g., sleep apnea, diabetes, chronic kidney disease, and atherosclerotic disease) and their associated medical therapies, which confound interpretation of study results; and the difficulty in enrolling large numbers of study participants. Expanding our understanding of the causes of RH and thereby potentially allowing for more effective prevention and/or treatment will be essential to improve the long-term clinical management of this disorder.[2]

The prevalence of RH is unknown. Cross- sectional studies and hypertension outcome studies suggest, however, that it is not uncommon. In a recent analysis of National Health and Nutrition Examination Survey (NHANES) participants being treated for hypertension, only 53% were controlled to <140/90 mm Hg. In a cross-sectional analysis of Framingham Heart Study participants, only 48% of treated participants were controlled to <140/90 mm Hg and less than 40% of elderly participants (>75 years of age) were at a goal blood pressure.[3] Among higher- risk populations and, in particular, with application of the lower goal blood pressures recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) for patients with diabetes mellitus or chronic kidney disease (CKD) (see operational definition under methodology), the proportion of uncontrolled patients is even higher. Of NHANES participants with chronic kidney disease, only 37% were controlled to <130/80 mm Hg[4] and only 25% of participants with diabetes were controlled to <130/85 mm Hg.[5]

Uncontrolled hypertension is not synonymous with RH. The former includes patients who lack blood pressure control secondary to poor adherence and/or an inadequate treatment regimen, as well as those with true treatment resistance. To accurately determine the prevalence of resistant hypertension, a forced titration study of a large, diverse hypertensive cohort would be required. The aim of the study was to determine the causes of resistant hypertension in non-dialysis CKD patients.

Methodology

This observational descriptive study was done in the department of Medicine and Nephrology, Dhaka Medical College Hospital, Dhaka from 18th January 2016 to 20th may 2016. Purposive consecutive type of non-probability sampling was applied. All the data were recorded in a preformed structured questionnaire. CKD patients with resistant hypertension who were not undergoing dialysis, having an age of more than 18 years willing to give voluntary consent were included in the study. Those unwilling to give voluntary consent were excluded from the study. Prior to the commencement of this study, the research protocol was approved by the ethical committee of Dhaka Medical College Hospital. The aims and objectives of the study along with its procedure, method, risks & benefits of this study explained to the respondents in easily understandable local language and then informed written consent was taken from each patient or relatives. Necessary investigations were done and recorded in the data collection sheet.

Operational definitions:

Resistant Hypertension: Hypertension is defined "resistant" (RH) when blood pressure (BP) levels persist above the therapeutic target (<140/90 mmHg for general population and <130/80 mmHg for patients with diabetes mellitus or chronic kidney disease (CKD)), despite the use of at least three antihypertensive drugs at full dose, including the diuretic. Furthermore, according to the current definition, also hypertensive patients who reach BP target by means of four or more drugs are considered resistant.[6,7]

CKD: Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR or GFR <60 mL/min/1.73m2 for ≥3 months, with or without kidney damage.[8]

Statistics:

After collection of all the required data, they were checked, verified for consistency and then tabulated and analyzed by the computer using the SPSS version 22.0. (SPSS Inc., Chicago, Illinois, USA). Variables were expressed as frequencies and percentages. Binary logistic regression analysis was done to evaluate the probable risk factors of RH in non-dialysis CKD patients. A p-value of <0.05 was considered as significant.

Results

Three hundred and ten non-dialysis CKD patients with hypertension were invited for the study, of which 277 consented to participate in the study and completed the

questionnaires (response rate – 86.6%). Among them 50 had RH and 227 did not have RH . Among the patients with RH maximum number of patients 23(46.0%) were between 46-60 years age group with a mean age of 53.17 ± 8.42 years. Male: female ratio was 1.63:1. Study showed that frequency of RH and CKD gradually increased with raised age.

The mean systolic and diastolic blood pressures (BP) were 133.04 ± 12.91 mmHg and 81.07 ± 6.41 mmHg respectively and 74% (n = 37) of them were admitted to hospital at least once due to a complication arising from hypertension (heart failure, cardio-/cerebrovascular disease, renal failure, hypertensive emergency, and etc.). Those with diabetes mellitus, obesity (BMI > 27.5 kg/m^2) and those who were older than 55 years were significantly higher in the RH group than in the non-RH group. Majority of the study population had one or more comorbidities. Ischemic heart disease (90.6%), hyperlipidemia (49.1%) and diabetes mellitus (69.9%) were the commonest co-morbidities. Among the 50 cases of RH with non-dialysis CKD patients, 32% were in the older age group, 42% were diabetic and 68% had a history of Nonsteroidal anti-inflammatory drugs ingestion for long duration. Obstructive sleep apnea and obesity was seen in 12% and 14% of cases respectively. Among these 50 patients, with resistant hypertension, 37 of them were using 3 antihypertensive drugs including a diuretic and 13 were having 4 or more anti-hypertensive drugs.

In this study majority of patients (74%) were in stage IV of CKD and 24% were in stage III of CKD. Patients are generally admitted in tertiary level hospital after development of sign, symptoms or referred from primary/secondary level hospitals, so stage I was nil in our study. All the patients with resistant hypertension were compliant with their therapeutic regime and majority (93.9%) of the patients in the non-resistant hypertensive group was also compliant. Table 1 summarizes the anti-hypertensive drugs and other drugs used in the study population. The most commonly used anti-hypertensive drug was ACE inhibitors (54.5%) followed by β-blockers (51.6%) and Calcium Channel Blockers (CCBs) (47.3%). In the resistant hypertension group, the most commonly used anti-hypertensive drug was β-blockers (71.7%) followed by ACE inhibitors (69.8%) and CCBs (54.7%). The usage of ACE inhibitors, α-blockers, β-blockers, furosemide, spironolactone and thiazide diuretics were more common in the RH group than in the non RH group (Table 1).

No significant difference was observed between the RH and non-RH groups for the following modifiable and non-modifiable cardio-vascular risk factors: gender, family history, high salt intake, smoking, alcohol consumption and hyperlipidemia (Table 2). Those with diabetes mellitus, obesity (BMI > 27.5 kg/m2) and those who were older than 55 years were significantly higher in the resistant hypertension group than in the non-resistant hypertension group.

In the binary logistic regression analysis older age (OR: 1.36, 95%CI 1.14–1.56), longer duration of hypertension (OR: 1.76, 95% CI 1.26– 2.28), presence of diabetes mellitus (OR: 1.67, 95% CI 1.31–1.97) and being obese (OR: 1.84, 95% CI 1.04–3.26) were significantly associated with resistant hypertension in non-dialysis CKD patients.(Table 3)

Table 1:

Name of drug	Number of patients (%)			p-value*
	All (n = 277)	Resistant (n = 50)	Non resistant (n = 227)	
ACEI	151(54.5%)	37(69.8%)	114(50.9%)	<0.05
α-blockers	21 (7.6%)	14(26.4%)	7 (3.1%)	<0.001
ARB	94 (33.9%)	22(41.5%)	72 (32.1%)	NS
β-blockers	143(51.6%)	38(71.7%)	105(46.9%)	<0.01
CCBs	131(47.3%)	29(54.7%)	102(45.5%)	NS
Furosemide	59 (21.3%)	26(49.1%)	33 (14.7%)	<0.001
Spironolactone	8 (2.9%)	6 (11.3%)	2 (0.9%)	<0.01
Thiazide	34 (12.3%)	16(30.2%)	18 (8.0%)	<0.001
Other drugs				
Anti-platelets	201(72.6%)	37(69.8%)	174(77.7%)	NS
Lipid lowering drugs	152(54.9%)	25(47.1%)	127(56.7%)	NS
Nitrates	139(50.2%)	26(49.1%)	113(50.4%)	NS

ACEI: Angiotensin Converting Enzyme Inhibitors, ARB: Angiotensin-II Receptor Blockers, CCB: Calcium Channel Blockers, NS: Not Significant.

Table 2

Risk factors	Number of patients (%) All (n = 277)	Resistant (n = 50)	Non resistant (n = 227)	p-value
Non modifiable				
Age (> 55 years)	202(72.9%)	46(86.8%)	156 (69.6%)	<0.05
Gender – Male	139(50.2%)	28(52.8%)	111 (49.5%)	NS
Gender – Female	138(49.8%)	25(47.2%)	113 (50.4%)	NS
Family history	126(45.5%)	29(54.7%)	97 (43.3%)	NS
Modifiable				
High salt intake	61 (22.0%)	12(22.6%)	49 (21.9%)	NS
Tobacco smoking	16 (5.8%)	1 (1.9%)	15 (6.7%)	NS
Hyperlipidemia	142(51.3%)	24(45.3%)	118 (52.7%)	NS
Diabetes mellitus	111(40.1%)	30(56.6%)	81 (36.2%)	< 0.01
Obesity (BMI > 27.5 kg/m^2)	18 (66.8%)	42(79.2%)	143 (63.8%)	< 0.05
Alcohol consumption	29 (10.5%)	7 (13.2%)	22 (9.8%)	NS

BMI Body Mass Index, NS Not Significant;

Table 3

Risk factor	β-coefficient (95% CI)	p-value
Age	1.36 (1.14 – 1.56)	<0.05
Gender – female	Reference	
male	1.52 (0.67 – 3.47)	NS
Duration of hypertension	1.76 (1.26 – 2.28)	<0.05
Current smoking - non-smoker	Reference	
smoker	1.51 (0.25 – 9.01)	NS
Alcohol consumption - no	Reference	
yes	2.81 (0.96 – 8.20)	NS
Diabetes Mellitus – absent	Reference	
present	1.67 (1.31 – 1.97)	<0.05
IHD – absent	Reference	
present	0.59 (0.12 – 2.50)	NS
CKD – absent	Reference	
present	0.79 (0.39 – 1.58)	NS
Hyperlipidemia - absent	Reference	
present	1.16 (0.54 – 2.48)	NS
Obesity - BMI <27.5	Reference	
BMI > =27.5	1.84 (1.04 – 3.26)	<0.05
High salt intake – absent	Reference	
present	1.96 (0.94 – 2.95)	NS

IHD: Ischemic Heart disease NS: Non significant

Discussion

Maximum number of patients 23(46.0%) were between 46-60 years age group. Mean age of the patient was 53.17 ± 8.42 years. Male: female ratio was 1.63:1. Study shows that frequency of resistant HTN in CKD patient gradually increased with raised age. In case of male and female 46-60 years showed the highest incidence for CKD. Findings correlate with the results of similar studies at home and abroad, e.g., with the results of Kumara et al (2013).[9]

In developed countries the prevalence of RH in non-dialysis CKD patients increase with age and the peak incidence is found in 7th and 8th decades. In our study we found that the incidence of disease declined sharply after the age of 60 years. This difference may be due to the fact that in our country life expectancy is lower than those of the developed countries due to the poor health-care facilities and lack of confidence of patient's attendance regarding the prolong time and lengthy treatment procedure of such disease. The reason for disparity in peak age range among RH in non-dialysis CKD patients from developed countries and our study population may be related to genetics, sociocultural factors, access to diagnostic tools, therapeutic modalities and the pattern of diseases causing RH.

Our results demonstrate that blood pressure control rates are suboptimal in 41.1% of the hypertensive population, similar to reports from developed western countries[10-12]. This suboptimal hypertension control includes two different entities; uncontrolled/poorly controlled hypertension and RH. Uncontrolled hypertension is lack of blood pressure control secondary to poor adherence and/or an inadequate therapeutic regimen, while treatment of resistance is suboptimal blood pressure control despite using optimal therapy. Many studies have suggested the prevalence of uncontrolled hypertension to be around 50% of patients being treated for hypertension[13,14].

In the present study, deficiencies in the quality of hypertension management were observed despite the fact that patients were assessed frequently and had satisfactory compliance. The proportion of poorly controlled hypertensive patients with sub optimal drug management was 27.8%. It is the physicians' failure to increase the intensity of treatment among patients with uncontrolled hypertension, a phenomenon known as therapeutic inertia. Distinguishing therapeutic inertia from other causes for uncontrolled hypertension is an important initial step to identify strategies to improve care offered to these patients. Majority of patients in both resistant (79.2%) and non-resistant (63.8%) hypertension groups were obese. Obesity is recognized as the sixth most important risk factor contributing to the overall burden of HTN worldwide[15]. Studies have shown that the cardiovascular risks in those with obesity are not significantly increased unless hypertension is present[16]. This observation emphasizes the role of hypertension as a mediator through which obesity may cause cardiovascular disease. Our results also demonstrate that obesity was a significant factor associated with resistant hypertension in the logistic regression analysis. Obesity is associated with more severe hypertension, a need for an increased number of medications and a decreased likelihood of achieving blood pressure control [2]. The impact of body weight change on the prognosis in these patients is potentially of relevance when planning future treatment strategies for uncontrolled hypertension and its cardiovascular consequences.

This epidemic of obesity and obesity-related hypertension is paralleled by an alarming increase in the incidence of diabetes mellitus and CKD. We observed a statistically significant relationship between diabetes mellitus and resistant hypertension in the logistic regression analysis. Hypertension in diabetics interferes with the rate of development and progression of diabetic complications, which in turn aggravates the hypertensive disease. It appears to be universally accepted that the tight treatment regimens for hypertension in diabetics reduces cardiovascular risk and slows the rate of progression of diabetic complications such as diabetic nephropathy. Hypertension is usually linked with renal disease and it is both a cause and a complication of hypertension. Furthermore, blood pressure, plasma glucose, and lipids are continuous variables that exert a dose-dependent effect on cardiovascular risk[17].

RH represents a different phenotype to the general population and it is reasonable to assume that genetic factors play a greater role in pathogenesis. In one of the few genetic evaluations of patients with resistant hypertension, investigators in Finland found that 2β ENaC and γENaC gene variants were significantly more prevalent in the patients with resistant hypertension than in the normotensive controls[18]. A particular allele of the CYP3A5 enzyme that plays an important role in the metabolism of cortisol and corticosterone has been associated in African-American patients with higher systolic blood pressure levels in normotensive participants and in hypertension that is more resistant to treatment[19, 20].

Inducible nitric oxide synthase (iNOS) is another important enzyme regulating blood pressure . Studies have shown that the g.2087G > A polymorphism in the iNOS gene affects the susceptibility to hypertension. Moreover, the S-C-A haplotype is also associated with responsiveness to antihypertensive therapy[21]. The calcium/calmodulin-dependent kinase IV (CaMKIV) seems to be involved in blood pressure regulation mediated via the control of endothelial nitric oxide synthase activity[22]. In addition, the Angiotensinogen AGT 235 T allele has also been shown to be an independent risk factor for resistant hypertension[23].

The heptahelical G-protein-coupled receptors (GPCRs) represent one of the largest classes of cell-surface receptors, a wide variety of GPCRs are involved in blood pressure control. In addition, several intermediaries involved in the GPCR desensitization process, like the G-protein-coupled receptor kinases (GRKs) are important in the regulation of vascular tone. Of the seven mammalian GRKs, GRK2 seems to be the most relevant isoform at the cardiovascular level[24].

Identification of genetic influences on resistance to current therapies might also lead to development of new therapeutic targets. However, it is important to understand that a single

genetic variant may not reveal significant associations with resistant hypertension because their effects may be dependent on gene-gene or gene-environment interactions.

There are a wide range of anti-hypertensive available for the treatment of hypertension. Among them diuretics play major role in blood pressure control. However, most of the patients (63.5%) in our study sample were not on any diuretic, including furosemide, spironolactone and thiazide diuretics. It has been said that combinations of the thiazide-type and potassium-sparing subclasses may be highly effective, providing nearly optimal therapy for some, and might be considered more often in the treatment of hypertension[25]. Treatment of hypertension using a diuretic-based strategy has been effective in preventing stroke and cardiac disease, a consistent finding from the earliest randomized clinical trials (1960s) to present-day large multi-centered studies such as ALLHAT [26].

In our study sample β-blockers were the second commonly used anti-hypertensive and there were 9 patients on sole β-blockers therapy of which 4 had uncontrolled blood pressure. ACE inhibitors are some of the most commonly prescribed medications for hypertension. ACE inhibitors are seen as more appropriate for first-line use when other high-risk conditions are present, such as diabetes. It is clear that it has an important role in the treatment of hypertension. In our study sample ACE inhibitors were the most commonly used anti-hypertensive drug. There were 13 patients on sole ACE inhibitor therapy, out of which 6 were having diabetes mellitus and 7 had uncontrolled blood pressure.

Conclusion

Prevalence of RH in non-dialysis CKD patients is increasing day by day. Several factors seem to contribute to this rising prevalence. Among all of them the presence of obesity and diabetes mellitus and increasing age was significantly associated with the development of RH in non-dialysis CKD patients as proved by the binary logistic regression analysis. Therapeutic inertia seems to contribute significantly towards the presence of uncontrolled blood pressure, its role and causative factors need further evaluation.

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