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Prevalence of Resistant Hypertension in Patients of Type 2 Diabetes Mellitus Visiting OPD/IPD in Smhs Hospital Srinagar J&K

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ABSTRACT

The purpose of the present study was to find the prevalence of resistant hypertension in patients of type 2 diabetes.The impact of different risk factors like obstructive sleep apnoea, obesity, chronic kidney disease, duration of diabetes and hypertension, albuminuria, etc. on development of resistant hypertension was also studied. A total of 408 cases were studied; 216 males and 192 females, amounting to 53% and 47%, respectively. The mean population age was 59.8 ± 5.9 years. The prevalence of resistant hypertension was found to be 11.5%. In males it was higher (13.4%) than in females (9.3%). Age (>70 years) was found to have strong impact (84.8%) on development of resistant hypertension. Out of the 408 subjects, 138 were having dyslipidemia accounting for 33.8% of the population, while the rest 66.2% were not having this condition. Out of the dyslipidemic population, 18.1% had resistant hypertension as against 8.1% in non-dyslipidemic population. This revealed a significantly ($p<0.005$) higher association of dyslipidemia for development of resistant hypertension. BMI ≥ 30 group comprised of the highest number of resistant hypertensive patients ranging to 23.5%. Out of the 92 OSA positive subjects, 17 were experiencing resistant hypertension, amounting to 18.5%, in contrast to only 9.8% resistant hypertensive cases from OSA negative sub-population. Of the hypertensive heart diseased patients, 17.3% had resistant hypertension which was significantly ($p<0.005$) higher than 7.3% resistant hypertension cases observed in the population not suffering from hypertensive heart disease. 33.8% patients suffering form CKD were having resistant hypertension, far higher than 6.1% of the resistant hypertensive patients from non-CKD population. 39.8% of >10 year hypertensive population were experiencing resistant hypertension which was significantly ($p<0.005$) higher than the proportion of resistant hypertensives (0.6%) in sub-population having hypertension for <10 years. From the population group suffering from diabetes for more than 10 years, 46.6% was found to have resistant hypertension as against 4.6% resistant hypertensive patients in <10 year diabetic group. Out of 44 patients who had diabetes and hypertension for more than 10 years, 61.3% were found to be resistant hypertensive in contrast to 5.4%, who had duration of diabetes and hypertension for less than 10 years. The prevalence of resistant hypertension (66.6%) was higher in nephrotic range proteinuria group (>3g/day) as compared to subnephrotic range proteinuria groups.

KEYWORDS Resistant Hypertension, Type 2 DM.

INTRODUCTION

Hypertension is regarded as an important public health challenge through out the world, primarily because of its high frequency and concomitant risk of cardiovascular and kidney diseases. It has been identified as the leading risk factor for mortality, and is ranked as third major cause of disability-adjusted life-years **(Kearney et al. 2005)**.Resistant hypertension (RHT) is taken as the high blood pressure (BP) that requires ≥3 medications for treatment **(Acelajado et al., 2012)**. The exact definition of resistant hypertension is variable, subject to treatment regimen and the target BP to be achieved. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High BP defined resistant hypertension as failure to achieve BP to target despite adherence to appropriate treatment with full doses of at least 3 drug regimens including a diuretic. However, the National Institute for Health and Care Excellence as well as the European Society of Hypertension guidelines do not include the use of a diuretic in their definitions. A recent scientific statement from the American Heart Association (AHA) defined resistant hypertension as blood pressure that remains above goal despite the concurrent use of 3 different antihypertensive medication classes, one ideally being a diuretic, with all agents prescribed at doses that provide optimal benefit **(Daugherty et al., 2012)**. Thus, RHT includes all the patients whose BP is uncontrolled or controlled after use of ≥4 medications; the later proportion of patients being identified as a unique phenotype distinct from the broader group of patients whose BP can be controlled. This unique form of RHT is known as refractory hypertension **(Acelajado et al., 2012)**.Despite the huge impact of resistant hypertension in developing world countries, little is known about its prevalence and its association with other co-morbidities. The scaricity of such knowledge in our country, especially in Kashmir province, paved the way for designing the present study with following objectives: **1)** To assay the general prevalence of resistant hypertension and its association with age and gender. **2)** To study the impact of co-morbidities like obstructive sleep apnoea, obesity, chronic kidney disease, duration of diabetes and hypertension, albuminuria, etc. on development of resistant hypertension.

MATERIALS AND METHODS

The present study conducted with the aim of finding the prevalence of resistant hypertension in patients of type 2 diabetes and hypertension of age ≥18 years visiting OPD/IPD of SMHS hospital was accomplished using the material and methods to be discussed in the present chapter. The study was prospective and observational, conducted for a period of 2 years. It included patients of type 2 diabetes and hypertension visiting OPD/IPD of SMHS, hospital, Srinagar. The standard study ethics were maintained and all the patients were informed of the ongoing study and a written consent was obtained. A total of 408

patients were selected for the study which comprised of 216 (53%) males and 192 (47%) females.

3.1 Place of study

The study was conducted on the patients visiting OPD/IPD of SMHS, hospital, Srinagar who gave a written consent for the study and fulfilled the parameters of our inclusion/exclusion criteria. All the associated baseline as well as special investigations were performed within the SMHS and associated hospitals.

3.2 Exclusion criteria

The subjects were evaluated for their inclusion or exclusion in study population. The subjects with following criteria were excluded from the study: **1)** Patients suffering from serious medical co-morbidities like myocardial infarction, cerebro-vascular accident, unstable angina etc. **2)** Those patients suffering from mental illness that could hamper therapeutic adherence. **3)** Patients of age less than 18 and those who didn't give consent for the study. **4)** All pregnant women. **5)** Patients with a recent change in anti-hypertensive medication and their dosage (less than a month). **6)** Patients who were unaware of the antihypertensive medication they were taking.

3.3 Study population

The study population was thus identified which comprised of 408 individuals. These included 216 males and 192 females, amounting to 53% and 47%, respectively. The population was divided into three main age groups viz., ≤65 years, 66-70 years and > 70 years. The age groups comprised of 79%, 17% and 3% of the population, respectively. The mean age of the population was 59.8±5.9The population was also categorized based on BMI into four groups:<18.5; 18.5-24.9; 25-29.9 and ≥ 30.

3.4 Statistical analysis

All statistical analysis was done using the Statistical Package for Social Sciences (SPSS version 20). Continuous data was described as mean and standard deviation if the distribution was normal. When the data was a skewed distribution, median and interquartile range (25-75th percentiles) was used. Categorical data was reported as proportions (percentage). Chi-square test were used for the categorical or dichotomous variables. All variables with the p-value of less than 0.25 in the univariate analyses as well as clinically significant variables were entered into the multivariate logistic regression. The dependent variable was resistant hypertension (yes or no). The independent variables were age, gender, BMI, hypertensive heart disease, chronic kidney disease, dyslipidemia, duration of hypertension, duration of diabetes and albuminuria. All analyses were done with 95% confidence intervals (CI), and the level of significance was set at p<0.05.

RESULTS

The present study was aimed to study the prevalence of resistant hypertension in patients of type 2 diabetes. Its association with age, gender, duration of diabetes and hypertension were also studied. The impact of various co-morbidities, presumed to be the secondary causes of resistant hypertension like obstructive sleep apnoea, chronic kidney disease, dyslipidemia, obesity, and albuminuria on development of resistant hypertension was also examined. The final goal was to evaluate the relative effect of these factors on development of resistant hypertension in patients of Kashmir province, visiting the OPD of our hospital. **4.1 Gender distribution of the population under study** During our study period, a total of 408 patients having type 2 diabetes mellitus and hypertension were studied. Out of these, 216 were males and the rest 192 females, amounting, respectively, to 53% and 47% of the population). Out of the total 408 patients, 47 (11.5%) were found to have resistant hypertension. **4.2 Age distribution of the population under study** The study population was classified into 3 age groups: (1) ≤65 years; (2) 66-70 years; and (3) >70 years. Out of total 408 patients, majority (325) belonged to group 1 (≤ 65 years) while as 70 and 13 patients belonged to group 2 and group 3 respectively. This amounted to 79.6%, 17.1% and 3.1%, respectively, for the three age groups. The mean population age of our study group was 59.8 ± 5.9. **4.3 Effect of gender on development of resistant hypertension** A total of 47 patients were found to have resistant hypertension, amounting to a general prevalence of 11.5%. 29 out of 216 males were having resistant hypertension, amounting to a prevalence of 13.4%. In female population `18 out of 192 were having resistant hypertension, amounting to a prevalence of 9.3%. **4.4 Effect of age on development of resistant hypertension** In our study we found least prevalence of resistant hypertension in age group ≤65 years. The prevalence in this group was just 1.8% (6/325), as compared to 42.8% (30/70) in 66-70 year age group. The highest prevalence was observed in >70 age group, measuring about 84.6% (11/13). **4.5 Effect of dyslipidemia on development of resistant hypertension** Out of the 408 subjects, 138 were having dyslipidemia accounting for 33.8% of the population, while the rest 270 (66.2%) were not having dyslipidemia. 18.1% (25/138) of the dyslipidemic population was experiencing resistant hypertension as against 8.1% (22/270) of resistant hypertension cases in non-dyslipidemic population, which was more than twice than in non dyslipidemic group. **4.6 Effect of obesity on development of resistant hypertension** Based on the body mass index (BMI), we classified our study population into three groups: i) BMI <25 (normal); ii) BMI = 25 to 29.9 (overweight); and iii) BMI ≥ 30 (Obese). 27.4% (112/408) of our study population belonged to BMI <25 group, while 55.8% (228/408) were overweight (BMI of 25-29.9). 16.7% (68/408) were obese (BMI ≥30). The prevalence of resistant hypertension in the three BMI groups was 4.4%, 11.4% and 23.5% respectively (Table 8 and Figure 8).The prevalence in obese group was about 5 times than in normal weight group.

DISCUSSION

This chapter presents the relevant discussion for the observations and results which we obtained in present study, aimed to find the prevalence of resistant hypertension in patients of type 2 diabetes and hypertension. The reported studies, whether in confirmity or otherwise to our results are discussed herein to corelate our inferences and findings. **5.1 Prevalence of resistant hypertension** A total of 47 patients were found to have resistant hypertension, amounting to a general prevalence of 11.5%. Our results are in accordance with various prevalence estimates which show that anywhere from 3% to 30% of patients with hypertension require ≥ 3 medications to achieve BP control **(Hajjar and Kotchen, 2005; Cushman et al., 2002; Persell. 2008)**. However, small observational studies estimate the prevalence from 5 to 50%, while data from large clinical trials estimate it from 20 to 35% (Epstein, 2007). **5.2 Effect of gender on development of resistant hypertension** The prevalence in male population was 13.4%, while for female population it measured to 9.3%. Out of the 47 resistant hypertensive patients, 29 were males and 18 females, amounting respectively to 61.7% and 39.3%. Our results are in conformity with de la Sierra et al. (2011) who reported higher prevalence in males than in females (51.4% males and 48.6% females). **5.3 Effect of age on development of resistant hypertension** We observed highest prevalence of resistant hypertension in age group of >70 years (84.6%), the prevalence of resistant hypertension was comparatively lower in age group of 66 to 70 (42.8%) and least in age group of less than 65 years (1.8%). Our results revealed that age is one of the most important factors for development of resistant hypertension and a hypertensive patient of older age (>70 years) has several fold higher chances of being resistant to medications than his/ her younger counterpart. Our results are in accordance with previous studies which aimed to find association of age with resistant hypertension. For example **(Llyod-Jones et al., 2000)** in an analysis of Framingham study data found that the strongest predictor of the lack of blood pressure control was older age. The study concluded that participants with >75 years age were one-fourth less likely to have systolic blood pressure controlled compared with participants ≤60 years of age. Another study by **(Cushman et al., 2002)** also suggested older age to be associated with treatment resistance for hypertension as defined by the need for 2 or more antihypertensive medications to achieve the control. It has also been found that the disparity of systolic versus diastolic blood pressure control worsens with increasing age such that systolic control rates exceed 60% for younger participants (≤60 years) but was <40% in older subjects (>75 years) **(Kearney et al., 2005)**. ALLHAT studies also demonstrated a similar difficulty in controlling systolic blood pressure in that only 67% of the participants had their systolic blood pressure lowered to <140

mmHg as compared to 92% of the participants who achieved a goal diastolic blood pressure of <90 mmHg. Thus, it could be concluded that it is the difficulty to control systolic blood pressure, and not the diastolic blood pressure, with increasing age that leads to development of resistant hypertension as the age advances **(Cushman et al., 2002)**. Increasing age (>65 years) is presumed to be associated with a higher prevalence of arterial stiffening which is responsible for both falsely elevated systolic blood pressure as well as the true elevations **(Chobanian, 2003; Sarafidis and Bakris, 2008)**. Current guidelines for systolic BP goals of <140 mmHg are more difficult to achieve in patients with isolated systolic hypertension and are more difficult with increasing age because of the natural history of arteriosclerosis **(Chobanian, 2003)**. **5.4 Effect of dyslipidemia on development of resistant hypertension** The prevalence of resistant hypertension was more than double in dyslipidemic patients (18.1%) as compared to those not having dyslipidemia (8.1%). Our results are in confirmity to a previous study conducted by **(Acelajado et al., 2012)**. In this study it was reported that out of 275 patients with controlled hypertension, 133 were dyslipidemic, amounting to 48.4% of the population, while out of the 29 refaractory hypertensive patients, 15 were experiencing dyslipidemia which amounted to 51.7% of the population. Thus, a strong association seems to exist between dyslipidemia and development of hypertension, both resistant as well as refractory. **5.5 Effect of obesity on development of resistant hypertension** Our results show a strong and statistically ($p<0.05$) significant association between BMI / obesity and development of resistant hypertension. The association was found to be of the magnitude that obese patients (23.5%) had more than 5 times prevalence of resistant hypertension than normal weight patients It has been found in both cross-sectional studies and treatment trials that obesity is associated with the use of an increased number of antihypertensive medications and a decreased likelihood of achieving blood pressure control **(Aucott et al., 2005)**. Obese individuals have increased sympathetic activity, higher cardiac output, and high peripheral vascular resistance due to reduced endothelium dependent vasodilation. The level of plasma aldosterone and endothelin are also increased, while elevated level of adipose tissue results in increased intrarenal pressures and changes in renal architecture **(Hall, 2003)**. With the increase in body mass index (BMI), higher doses of antihypertensive drugs are required to control blood pressure **(Redon et al., 1998)**. **(Rexrode et al., 1996)** have concluded that overweight persons are 3-times more likely to have hypertension than normal weight individuals. Risk estimates from the Framingham Heart Study suggested that 78% of new cases of hypertension in men and 65% in women are related to excess body weight. It has further been delineated that every 10-pound weight gain is associated with an estimated 4.5-mmHg increase in systolic blood pressure **(Rexrode et al., 1996; Garrison et al., 1987)**. A greater sympathetic activity has been observed with increasing body weight which in turn increases blood pressure, heart rate, cardiac output and renal tubular sodium reabsorption **(Grassi et al., 1998; Vaz et al., 1997; Masuo et al., 2001; Reaven et al., 1996)**. It has also been evidenced that leptin from adipocytes increases sympathetic stimulation of the kidney and brown adipose tissue in rats; though it is less conclusive in humans **(Rumantir et al., 1999)**. Another reason by which obesity might cause sympathetic activation is by inducing obstructive sleep apnea **(Narkiewicz, et al., 2014)**. Excess visceral fat has also been shown to elevate aldosterone levels by synthesis of angiotensinogen in fat cells whichis inturn cleaved to angiotensin by rennin **(Cassis et al., 1988)**. **5.6 Effect of obstructive sleep apnoea on development of resistant hypertension** From our results, it could be inferred that OSA plays a significant role in development of resistant hypertension, comparison showing prevalence of resistant hypertension twice more common in OSA group (18.5%) than in non-OSA group (9.8%). A high degree of co-relation has been reported between obstructive sleep apnoea and hypertension, particularly among patients with resistant hypertension **(Murray, 2007)**. Cross-sectional studies have indicated that more severe the sleep apnea, the less likely blood pressure is controlled despite the use of an increasing number of medications **(Lavie and Hoffstein, 2001; Somers et al., 1995)**. OSA prevalence rates up to 50% have been reported in patients with hypertension **(Silverberg and Oksenberg, 2001)**. OSA is listed as one among the identifiable causes of hypertension, and its screening is justifiable in the clinical practice. In another case series **(Logan et al., 2003)**, 83% of patients with resistant hypertension had OSA, defined as apnea-hypopnea index (AHA) ≥ 10 episodes per hour. This study, however, precluded controls for confounding factors like gender, age and obesity. OSA causes hypertension by intermittent hypoxemia, and/or increased upper airway resistance, thereby inducing a sustained increase in sympathetic nervous system (SNS) activity **(Grassi et al., 2005; Lavie et al., 2003)**, which raises blood pressure through increase in cardiac output and peripheral resistance as well as by increased fluid retention. In addition, sleep apnoea has been associated with increase in reactive oxygen species with concomitant reduction in nitric oxide bioavailability **(Lavie et al., 2003; Duchna et al., 2005)**. Hypoxia is also reported to increase plasma aldosterone concentration independent of increase in plasma rennin activity **(Raff et al., 1988)**. **5.7 Association of hypertensive heart disease and resistant hypertension** The associatin of hypertensive heart disease with resistant hypertension was clearly reflected in our study, as patients of established hypertensive heart disease had twice more prevalence of resistant hypertension than in those without hypertensive heart disease (17.3%vs 7.3%)., reflecting a significantly higher association of resistant hypertension with hypertensive heart disease, are in agreement to the previous ones which have reported 7% prevalence of resistant hypertension in congestive heart disease, whereas a mere 11% of the cases the hypertension was controlled with use of ≥3 antihypertensive drugs, one being a diuretic. In stroke paptients, it has been reported that 8% of the population are resistant to antihypertensive treatment as against 22% of the patients who responded to drugs and had controlled hypertension **(Acalajado et al., 2012)**. In an ALLHAT study, left ventricular hypertrophy has been shown to lead to development of treatment resistance as defined by need of 2 or more antihypertensive patients. **5.8 Effect of CKD on development of resistant hypertension** We observed that 33.8% of the CKD patients were having resistant hypertension which was far higher than 6.1% of the resistant hypertensive patients from non-CKD population. CKD is at the same time both a cause and consequence of poorly controlled hypertension. A prevalence of 23-25% of true resiatant hypertension has been reported in CKD patients **(Nicola et al. 2011)**. This corresponds to prevalence three times greater than that reported in essential hypertension (~8%). The reported prevalence of 23-24% is, however, lesser than what we have observed in our study. This could probably be due to the more stringent criteria applied by the researchers to exclude pseudoresistance which is typically encountered in early stages of CKD but virtually disappears in CKD stage 5. Other studies have reported prevalence of 26% to 38% in CKD patients which is in closer agreement to our observations **(Nicola et al., 2011)**. The pathogenesis of resistant hypertension in CKD patients is presumed to be multifactorial involving a combination of factors like sodium retention, increased activity of the renin-angiotensin system and enhanced activity of the sympathetic nervous system **(Minutolo et al., 2007)**. The most frequent pathophysiological disorder is the salt and water retention occurring in majority of patients with reduced glomerular filtration rate (GFR). The resulting expansion of the ECV allows preserving the external balance of sodium, but with consequent development of persistent and often refractory hypertension. **5.9 Effect of duration of hypertension on development of resistant hypertension** Our study demonstrated that patients with long duration of hypertension(>10 years) were 40 times more prone to develop resistant hypertension than in those having a duration of less than 10 years (39.8% vs 0.6%), clearly reflecting the positive impact of hypertension duration on development of resistant hypertension. It has been reported that 10% to 15% of the general hypertensive population develop resistant hypertension **(McAdam Marx et al., 2009)**. The positive association with duration could presumably be due to more target organ (renal and cardiovascular) damage, that hypertension causes as an accrue. **5.10 Effect of duration of type 2 diabetes on development of resistant hypertension** We observed significantly higher proportion of resistant hypertension cases in patients having type 2 diabetes for more than 10 years as compared to those with lesser duration (46.6% vs 4.6%). A study conducted by **(Ciobanu et al., 2015)** reported prevalence of resistant hypertension at 10% in type 2 diabetes population. A high frequency of both chronic microvascular complications of diabetes (neuropathy, retinopathy, diabetic chronic kidney disease) and cardiovascular disease in the type 2 diabetes was found in the study population. The duration of

diabetes was found to be significantly associated with the presence of diabetic neuropathy and diabetic retinopathy which could be the confounding factors for development of resistant hypertension. **5.11 Effect of duration of diabetes and hypertension on development of resistant hypertension** Out of 44 patients who had diabetes and hypertension for more than 10 years, 27 were found to have resistant hypertension, in contrast to only 20 out of the 364 subjects who had diabetes and hypertension but for less than 10 years. The prevalence of resistant hypertension (61.3%) was significantly ($p<0.01$) higher in the former as compared to later, signifying the influence of duration of these conditions. This could probably be due to more target organ damage, especially kidneys and heart over the time. **5.12 Effect of urinary albumin on development of resistant hypertension** We observed highest prevalence of resistant hypertension in patients with more than 3gm/day proteinuria (66.6%), followed subsequently by 0.5 to 3 gm/day (56%). Least prevalence was found in patients with a proteinuria of less than 150 mg/day. The association of albuminuria with resistant hypertension is clear, based on the relation between kidney disease and heart disease. The presence of albuminuria is regarded as a predictor of worse outcomes for both kidney and heart patients **(Koroshi, 2007)**. It is taken as an indicator of insulin resistance and increased renal and cardiovascular risk associated with metabolic syndrome. Microalbuminuria is generally the first clinical sign of renal dysfunction in diabetes. A positive link is reported between high blood pressure and albuminuria, as high blood pressure may cause albuminuria by increasing glomerular filteration pressure and subsequent renal damage. It is presumed that the development of albuminuria is a marker for pathophysiologic events that aggravate blood pressure or impair the response to blood pressure lowering drugs leading to development of resistant hypertension, as observed in our study. Alternatively, the increasing systemic arterial BP transmits a higher pressure to the glomerular and peritubular capillaries (in the presence of afferent arteriolar dilation), thereby promoting abnormal glomerular permselectivity or changes in tubular albumin processing **(Glassock, 2006)**. Even high normal blood pressure is associated with significant higher frequency of microalbuminuria and this way may be a biomarker of increased cardiovascular risk **(Knight et al., 2003)**. There may be also common genetic factors that predispose to both high BP and microalbuminuria.

Conclusion: -

From the population group suffering from diabetes for more than 10 years, 46.6% was found to have resistant hypertension as against 4.6% resistant hypertensive patients in <10 year diabetic group. Out of 44 patients who had diabetes and hypertension for more than 10 years, 61.3% were found to be resistant hypertensive in contrast to 5.4%, who had duration of diabetes and hypertension for less than 10 years. The prevalence of resistant hypertension (66.6%) was higher in nephrotic range proteinuria group (>3g/day) as compared to subnephrotic range proteinuria groups. Finally, we analyzed the impact of different predictors on development of resistant hypertension. The order of association of these risk factors with resistant hypertension was found to be: Dyslipidemia < obesity < obstructive sleep apnoea < hypertensive heart disease < chronic kidney disease < duration of hypertension (>10years) < duration of diabetes (>10 years) < albumiuria < age (>70 years). There relative impact on development of resistant hypertension is depicted in the pie-diagram .

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