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Prevalence of Primary Aldosteronism and Complications in Type 2 Diabetes Mellitus Patients with Resistant Hypertension: A Prospective Observational Single Centre Study Protocol

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Research Article

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Abstract

Primary hyperaldosteronism (PA) has been thought to be an uncommon cause of hypertension, with an estimated prevalence of 2% among the general hypertensive population but is much higher, especially in resistant hypertension (RH) patients. Recent studies, however, have suggested that the prevalence of PA may be as high as 30% in RH populations. PA is associated with higher morbidity rates than matched essential hypertension patients. RH is more common in type 2 diabetes mellitus (T2DM). PA is generally remediable by treatment with an aldosterone antagonist or, in the case of adrenal adenoma, by adrenalectomy, knowing the true prevalence of PA is important for early diagnosis and treatment.

Aim: This study aims to evaluate the prevalence of PA and cardiovascular (CVD) and renal complications in T2DM mellitus patients with resistant hypertension .

Method: Prospective observational single centre study, in outpatient (OPD) settings in a tertiary care hospital.

The primary outcome of the study is to estimate the prevalence of primary aldosteronism in T2DM patients with resistant hypertension. The secondary outcome is to evaluate the difference in prevalence of complications / comorbidities like CVD, left ventricle hypertrophy(LVH) , atrial fibrillation (AF), chronic kidney disease (CKD) in T2DM patients with and without PA hyperaldosteronism .

T2DM patients aged more than 18 years with RH will be included in the study. Patients with type 1 diabetes mellitus or secondary causes of diabetes mellitus, acute diabetic complications, severe underlying systemic diseases, chronic kidney disease stage ≥4 , known secondary causes of hypertension, pregnancy and lactation and on medications like oral contraceptives, spironolactone, eplerenone, amiloride, triamterene will be excluded.

Study subjects with plasma aldosterone to renin ratio of value ≥ 1.6 ng/dl/μIU/ml and plasma aldosterone concentration (PAC) of value ≥ 10 ng/dl with suppressed renin, will be considered to be positive on a screening test. Patients, those positive on a screening test will undergo seated saline suppression test (SST). Repeat plasma aldosterone concentration (PAC) with value ≥ 6 ng/dl will be confirmatory test for PA.

Conclusion: RH specially in T2DM high-risk phenotype, which may be further aggravated by underlying PA . Thus we want to estimate the prevalence of PA in T2DM patients with RH. We also want to highlight any difference in prevalence of CV and renal complications due to in T2DM patients with and without PA, which may support early screening and diagnosis of PA and targeted treatment of PA to prevent its aggravating effects on chronic diabetes complications.

Keywords: T2DM; Primary Aldosteronism; Chronic Kidney Disease

Abbreviations: PAC: Plasma Aldosterone Concentration; PA: Primary Aldosteronism; CKD: Chronic Kidney Disease; AF: Atrial Fibrillation; LVH: Left Ventricle Hypertrophy; T2DM: Type 2 Diabetes Mellitus; RH: Resistant Hypertension; ARR: Aldosterone Renin Ratio; OPD: Observational Study in Outpatient; SST: Saline Suppression Test; HPP: Hypokalemic Periodic Paralysis.

Introduction and Background

Primary aldosteronism (PA) is characterized by excessive and autonomous aldosterone production, which classically manifests as hypertension and hypokalemia [1]. Excess level of aldosterone with sodium excess is associated with worse cardiovascular outcomes than essential hypertension at comparable blood pressure levels [1]. A recent meta-analysis suggests that PA is associated with an increased risk of coronary artery disease, stroke, atrial fibrillation, heart failure, diabetes mellitus, metabolic syndrome and left ventricular hypertrophy [1]. The prevalence rates of PA in the routine hypertensive population in the two large series are 7.2%–19.5% and 3.9%–11.8%, using aldosterone renin ratio (ARR) as the screening test followed by confirmatory testing [2,3]. A recent study using oral sodium suppression test regardless of baseline aldosterone and renin levels showed the prevalence of 11.3%–22% across the spectrum from normotensives to resistant hypertension [4].

Type 2 diabetes mellitus (T2DM) frequently coexists with hypertension. Patients with type 1 diabetes mellitus usually develop hypertension after nephropathy sets in, whereas hypertension in T2DM is due to associated obesity, higher risk of atherosclerosis, nephropathy and higher sympathetic drive due to insulin resistance [5]. The development of hypertension in T2DM increases cardiovascular risk, renal failure and other target organ damage. Underlying PA can lead to a worsening of hypertension and glycemia and may escalate cardiovascular risk [6]. Studies in T2DM patients with resistant or difficult to control hypertension have shown a higher prevalence of PA (13%–14%). The studies on the prevalence of PA in T2DM patients without resistant hypertension are a few with conflicting results; studies from Japan (n = 124) and China (n = 256) reported the disease burden of 11.3% and 19%, respectively, while other studies (n = 61, n = 551) have reported a very low prevalence (0%–0.93%) [7-12].

Thus, there are a few studies with varying evidence on PA in patients with T2DM and hypertension. A couple of studies from the Indian sub- continent show high PA prevalence in hypertensives , but none specifically investigated patients with T2DM and hypertension. In addition, Asian Indians have a different phenotype with higher abdominal fat, insulin resistance and dyslipidemia , which predisposes them to an increased risk of T2DM and coronary artery disease. Therefore, to elucidate the prevalence and contribution of possible underlying PA, we aimed to screen patients with T2DM and RH for PA. Diabetes is an epidemic disease that poses a serious threat to human health. Micro-vascular and macro-vascular complications caused by diabetes are the major reasons for disability and mortality. Several studies have reported that the prevalence of hypertension is 40% to 60% in diabetes patients [13]. Furthermore, both hypertension and diabetes mellitus increase the risk of complications, which can cause cardiovascular and chronic kidney diseases and eventually lead to death [14]. In patients with diabetes, PA accompanied by severe hypertension may cause more serious organ damage. The prevalence of PA in hypertensive patients is estimated to be around 5% to 10% [15-17]. In patients with resistant hypertension, the prevalence of PA is much higher, reaching 17% to 23% [18]. However, few studies have investigated whether patients with both diabetes and hypertension had a higher prevalence of PA. Recently, PA has been directly associated with abnormal glucose metabolism [19]. Excess aldosterone may inhibit insulin secretion [20]. Hypokalemia in PA is another element that decreases insulin secretion [21]. Aldosterone affects insulin sensitivity in adipose and vascular tissues, thus inducing insulin resistance. It seems that there is a close relationship between diabetes and primary aldosteronism.

Lacunae in Literature

There is gross under diagnosis of PA across the world with very limited literature on PA from India. There is no literature on prevalence of PA and complications in T2DM with RH, from India.

Research Questions

What is the prevalence of PA in T2DM with RH? How does PA affect complications of T2DM diabetes mellitus? What percentages of PA versus non PA study subjects have CV and renal comorbidities like LVH, stroke, myocardial infarction (MI), chronic kidney disease (CKD)?

Aims and Objectives

This study aims to evaluate the prevalence of PA and cardiovascular (CVD) and renal complications in T2DM mellitus patients with resistant hypertension.

Our primary objective is to calculate the prevalence of PA in T2DM subjects with RH. Secondary objective is to estimate the difference in prevalence of complications / comorbidities like LVH, stroke, myocardial infarction (MI), chronic kidney disease (CKD), in T2DM patients with and without PA.

Study Design

Prospective observational study in outpatient (OPD) settings in a tertiary care hospital.

Material and Methods

Outpatient setting, clinical presentation including blood pressure (BP), plasma aldosterone concentration (PAC), Plasma Renin Activity (PRA) / Direct Renin , Aldosterone Renin Ratio (ARR), sodium, potassium, creatinine, aldosterone concentration post salt loading confirmatory test, complications at baseline will be evaluated. Patients with plasma aldosterone to renin ratio of value ≥ 1.6 ng/dl/μIU/ml and plasma aldosterone concentration (PAC) of value ≥ 10 ng/dl with suppressed renin, will be considered to be positive on a screening test. Patients, those positive on a screening test will undergo seated saline suppression test (SST). Repeat plasma aldosterone concentration (PAC) with value ≥ 6 ng/dl will be confirmatory test for PA.

Prevalence of hypokalemia, hypokalemic periodic paralysis (HPP), duration and number of antihypertensives, duration and to be noted. Prevalence of complications like CKD (by albumin creatinine ratio and estimated GFR, LVH by ECG or ECHO, history/ presence of coronary artery disease (CAD) , atrial fibrillation(AF), cerebrovascular accident (CVA), obstructive sleep apnea (OSA) will be evaluated as per regular diabetes guidelines.

Statistical Analysis

All continuous variables will be expressed as mean±sd or median (IQR) as appropriate and qualitative variables as no.s and percentages. If required, continuous variables will be compared by using independent t-test for normally distributed data and for non-normal data Mann-Whitney U test will be used. Qualitative variables will be compared between groups by Chi-square test or Fisher's exact test as appropriate .

A p-value <0.05 will be considered as statistically significant. SPSS 26.0 will be used for statistical analysis.

Eligibility Criteria

A. Inclusion Criteria

Patients aged more than 18 years and either sex. Patients willing to give written informed consent. Patients who have T2DM with blood pressure >140/90 mmHg despite the use of ≥3 antihypertensive agents or whose blood pressure is controlled on 4 or more antihypertensive agents (resistant hypertension).

B. Exclusion Criteria

Patients with type 1 diabetes mellitus or secondary causes of diabetes mellitus (receiving glucocorticoids,pancreatitis). Type 2 diabetes mellitus with acute diabetic complications (diabetic ketoacidosis, hyperosmolar nonketotic hyperglycemia). Any severe underlying systemic diseases. Chronic kidney disease stage ≥4 (eGFR <30 mg/dl). Patients on oral contraceptives or hormone replacement therapy, spironolactone, eplerenone, amiloride, triamterene. Pregnancy and lactation.Patients with other known secondary causes of hypertension (renovascular hypertension, pheochromocytoma, cushing's syndrome, acromegaly etc).

Discussion

Prevalence of primary aldosteronism is high and largely unrecognized. Unregulated aldosterone production (high ARR) is seen in 5-10% of patients with hypertension in 20% of resistant hypertension patients. Hallmark presentation and diagnosis of PA is hypertension with hypokalemia with inappropriate production of aldosterone suppression leading to suppression of renin.

PA is a common syndrome, manifesting with a broad spectrum of presentation from mild severity hypertension -to-severe resistant hypertension with hypokalemia. Clinical manifestations depend on the severity and duration of hyperaldosteronism, genetic makeup and other comorbidities [14]. In patients with diabetes, PA accompanied by severe hypertension may cause more serious organ damage. The prevalence of PA in hypertensive patients is estimated to be around 5% to 10% [15-17]. In patients with resistant hypertension, the prevalence of PA is much higher, reaching 17% to 23% [18]. However, few studies have investigated whether patients with both diabetes and hypertension had a higher prevalence of PA. Recently, PA has been directly associated with abnormal glucose metabolism [19]. Excess aldosterone may inhibit insulin secretion [20]. Hypokalemia in PA is another element that decreases insulin secretion [21]. Aldosterone affects insulin sensitivity in adipose and vascular tissues, thus inducing insulin resistance. It seems that there is a close relationship between diabetes and primary aldosteronism [22-29].

Conclusion

RH specially in T2DM high-risk phenotype, which may be further aggravated by underlying PA . Thus we want to estimate the prevalence of PA in T2DM patients with RH. We also want to highlight any difference in prevalence of CV and renal complications due to in T2DM patients with and without PA, which may support early screening and diagnosis

of PA and targeted treatment of PA to prevent its aggravating effects on chronic diabetes complications.

Our main objective is to estimate the case load, to do early diagnosis and to start targeted treatment of primary aldosteronism and to prevent its aggravating effects on chronic diabetic complications (if any).

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