

Predisposing Factors for Prevalence of Hypertension in Discrete Population of Type 2 Diabetes Mellitus Patients

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Abstract

Hypertension is an extremely common complication in patients with type 2 diabetes mellitus. Hypertension (HTN) is an increase in blood pressure from normal to more than 120/80. With time, high blood pressure can damage arteries that feed the heart. HTN in Type 2 Diabetes Mellitus (T2DM) is associated with an increased risk of premature death from cardiovascular disease (CVD), because of the strong linkage of the two conditions. Therefore, it is essential to treat hypertension in patients with type 2 diabetes mellitus. The main rationale of the case-control study is to identify the at-risk population for hypertension among the discrete diabetic population through genetic and biochemical predisposition. This is done by simultaneous detection of two missense single nucleotide polymorphisms (T207M or rs4762 and M268Tor rs699) in Angiotensinogen gene.

The study showed the deviation of Lipid profile from normal and the absence of T207M or rs4762 in the diabetes population and M268Tor rs699 is present in 48% of the diabetic population of Telangana and Andhra Pradesh states in India.

Keywords: *Angiotensinogen Gene; Hypertension; rs4762; rs699; Andhra Pradesh; Telangana*

Introduction

Several studies report a genetic linkage between the angiotensinogen gene (AGT) and essential hypertension [1]. Approximately 30% of the changes in blood pressure are attributable to genetic heritability [2]. Type 2 diabetes mellitus (T2DM) is the accumulation of high blood sugar content in blood. It results in several adverse conditions. Hypertension (HTN) is one such condition which is responsible for premature deaths in developed countries, it is the fourth (4th) contributor in developing countries it is the seventh contributor they are important predisposing factor for each other. The reduced blood supply to heart walls due high triglyceride content results in blockage of arteries resulting in massive heart attack which is sometimes fatal. Globally around 17 million deaths occur in a year are due to cardiovascular diseases (CVDs) nearly complications of HTN accounts for one-third of 9.4 million deaths worldwide every year [3-7]. The proportion of the global burden of hypertension is increased from about 4.5% in 2000, to 7% in 2010. Two-thirds of patients with type 2 diabetes mellitus (T2DM) have hypertension. They are important predisposing factors for each other [8-13]. In the Framingham Heart Study, A 2 - 4 fold increased risk of myocardial infarction (MI), congestive heart failure, peripheral arterial disease, stroke, and death is seen in T2DM patients [14] (AGT) and hypertension Coexistent HTN and DM were associated with higher costs and resource utilization. The burden of illness of hypertension and comorbid diabetes is immense [15]. This makes HTN the single most important cause of morbidity and mortality globally.

This study is an attempt to validate the association of angiotensin polymorphisms (rs699 and rs4762) with complementation of Biochemical parameter of Lipid profile in T2DM patients. This association is reported worldwide population [16] in and other parts of India.

Factors involved in the pathogenesis of both hypertension and type 2 diabetes include inappropriate activation of the renin-angiotensin-aldosterone system, oxidative stress, inflammation, impaired insulin-mediated vasodilatation, augmented sympathetic nervous system activation, altered innate and adaptive immunity and abnormal sodium handling by the kidney. Alarmingly, diabetic women also have a higher relative risk for death from CVD than diabetic men [17]. Fatal complications of hypertension with T2DM include increased risk of cardiovascular disease. It is essential to treat patients with and type 2 diabetes mellitus.

T2DM (Type 2 Diabetes Mellitus)

About 5% of all the deaths occur each year due to diabetes. It is resulting from improper insulin utilization due to resistance or improper secretion, or both. This condition can be depicted by elevated blood glucose levels with hindrance to carbohydrate, fat and protein metabolism [18-20]. A total of about 1.56 billion people are going to be diabetic by 2025 and by 2030 around 366 million will have diabetes. For all the age-groups worldwide the prevalence was estimated to be 2.8% in 2000 and 4.4% in 2030 [21].

HTN (Hypertension)

The Condition in which the arteries have persistently elevated blood pressure is called Hypertension. It is the most common non-communicable chronic diseases affecting developed and developing countries around the world. Type 2 Diabetes mellitus and hypertension. The most important cause of premature death worldwide according to WHO rating is HTN [22,23]. This is responsible for 57% of all stroke deaths and 24% of all coronary heart disease (CHD) deaths [24-27].

AGT gene (Angiotensinogen)

The Angiotensinogen gene, AGT is an essential component of the renin-angiotensin system (RAS) that regulates blood pressure, body fluid and maintains electrolyte homeostasis is reported in studies from 1969 - 2011. Pre-angiotensinogen the precursor angiotensinogen is coded by the gene which on cleavage produces peptide hormone derivative angiotensin. The variation in plasma angiotensinogen levels is due to a defect in the gene. The first candidate gene linked to hypertension is AGT gene [28] is expressed in many tissues. AGT polymorphism shows varying results in multiple populations [29-33].

Aim of the Study

To identify at risk population for hypertension among the discrete Type 2 Diabetes Mellitus patients.

Methodology

Hypothesis

This study is a part of case control study undertaken for identifying genetic and non-genetic risk factors for T2M and its related complications. This involves Biochemical and SNP validation study for AGT polymorphism in the diabetic population. The consistency of the polymorphism in SNPs and abnormality of lipid profile shows HTN susceptibility in diabetic population.

Ethical considerations

As per ICMR Ethical guidelines there is a waiver of consent for using leftover blood samples.

Sample collection

The left over blood samples were collected from of subjects aged between 15 - 85 years the population of Telangana and Andhra Pradesh state in India was collected from diagnostic centers. Subjects with History of Diabetes disease were selected as cases and normal subjects were selected as controls. On the basis of pre-prandial and post-prandial glucose levels, 90 diabetic cases and 90 controls were selected.

Field work

Written informed consent was obtained from each of the subjects after explaining the objectives of the study. The subjects were enrolled after preliminary screening by Blood Glucose Estimation (FBS and PPBS) in accordance to WHO criteria for T2DM diagnosis Fasting Blood Sugar value of more than 126 mg/dl and post-prandial blood Sugar value of more than 200 mg/dl following inclusion and exclusion criteria. The Pre-Prandial and Post Prandial Blood Sugar value was estimated by glucose oxidase and peroxidase (GOD-POD) method.

Processing of sample

The biochemical parameters of HDL, LDL, triglycerides and total cholesterol were examined and recorded in both diabetic cases and control groups using auto analyzer for identifying the biochemical predisposing factors for cardiovascular disease. The colour formed is measured spectrophotometrically.

For analyzing the genetic predisposition factors blood samples will be collected and was processed for PCR technique, This is done by DNA isolation, amplification and sequencing. The leucocyte component of the blood samples will be processed for isolation of genomic DNA using modified Sambrook., *et al.* protocol. The polymorphism specific portion of the AGT was amplified by PCR using specially designed primers. Sequencing the amplified PCR products was done by Sanger sequencing method.

The sequences were investigated for polymorphisms in SNP. The sequenced portion of the gene will be further analyzed by using different computational tools and statistical methods. The consistency of the polymorphism in SNPs was checked for the blood samples of both cases and controls.

Statistical analysis

The mean and stand deviation for numerical outputs for each of the Biochemical parameters investigated was calculated with the help of IBM SPSS v.21 Software.

Results

The study showed that the lipid profile values HDL, LDL, Total cholesterol and Triglycerides was found to be high in both the diabetic cases and controls. The HDL levels showed the decreased value.

The SNP validation study for AGT polymorphism rs699 and rs4762 in the discrete diabetic population identified only rs699 and not rs4762 T174M as a risk factor for hypertension. The results are tabulated below in table 1-3.

Parameter	T2DM cases Mean ± SD	Controls Mean ± SD	Normal Range	p value
FBS	152 ± 92.8	92 ± 11.7	70 - 110	0.8
PPBS	229.3 ± 67.6	131.2 ± 18.8	170 - 200	0.7

Table 1: Blood sugar values.

Parameter	T2DM cases Mean ± SD	Controls Mean ± SD	Normal Range	p value
Total Cholesterol	176.8 ± 50.3	163 ± 51.7	130 - 250	0.09
Triglycerides	198.1 ± 87.7	141 ± 56.9	50 - 150	0.1
HDL	42.5 ± 4.7	43.2 ± 5.9	35 - 70	0.05
LDL	86.4 ± 25.8	44 ± 28.6	10 - 40	0.09
VLDL	41.8 ± 20.7	28.6 ± 13.6	Upto140	0.09

Table 2: Lipid profile values.

Gene	Amplicon	Reported SNP	Reference Sequence	Affected Population
AGT	230710528 - 230710030	C/T	0699	48.7%
			rs4672	Not reported

Table 3: Distribution of AGT polymorphism.

Discussion

This study demonstrated that the T2DM patients are more prone to cardiovascular diseases in form of HTN. The metabolic syndrome of insulin resistance, central obesity and dyslipidemia is accompanied by HTN. Both macrovascular and microvascular complications risk is substantially increased. The risk of coronary events is twofold among diabetic men and fourfold in diabetic women. Globally, Cardiovascular diseases (CVDs) accounts for approximately 17 million deaths a year, nearly one third of the total. Of these, complications of HTN account for 9.4 million deaths worldwide every year. It is reported to be the fourth(4th) contributor to premature death in developed countries and the seventh in developing countries [3-6].

The proportion of the global burden of disease attributable to HTN has significantly increased. This makes HTN the single most important cause of morbidity and mortality globally and highlights the urgent need of action to address the problem [34]. Varying association between hypertension and the M235T, T174M variants of AGT gene. 235T polymorphism is shown by different ethnic populations. The highest frequency has been observed in Africans (84 - 94%) followed by Asians (70 - 73%) and Caucasians (20 - 45%) [35]. Hypertension may be the causal affect T2DM but the relationship from HTN to T2D is not causal [36].

Conclusion

We conclude from the results of our study that T174M polymorphic variants of AGT gene do not predispose hypertension. Only M23T is a predisposing factor for hypertension in our study population. The increased biochemical parameters in cases the controls make them susceptible to type 2 diabetes and to hypertension. This study can be extended to a large population size.

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