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Study of Angiotensin Converting Enzyme (ACE) Gene Polymorphism and its Correlation with Serum Angiotensin Converting Enzyme Activity in Primary Hypertension

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ABSTRACT

Background: Renin angiotensin system (RAS) being the most vital pathogenic mechanism of hypertension is mediated by a key component; the angiotensin converting enzyme (ACE).The angiotensin-converting enzyme (ACE) gene in humans has an insertion-deletion (I/D) polymorphic state in intron 16 on chromosome 17q23. This polymorphism has been widely investigated in different diseases. The present study was aimed to know the relationship of ACE gene polymorphism and the possible risk of development of hypertension in the study population.**Methods:**50 hypertensive patients were studied for ACE I/D polymorphism against 50 age/sex matched controls taken from general population. The polymorphisms of ACE gene were investigated using polymerase chain reaction for detection of ACE I/D genotype. Correlation of serum Angiotensin Converting Enzyme (ACE) activity with ACE genotype and correlation of serum Angiotensin Converting Enzyme (ACE) level with severity of hypertension were studied.**Results:**D/D genotype in the hypertensive patients was found significant compared to the control group (p = 0.0001) which indicates that ACE (D/D) genotypes are more prone for the development of hypertension.**Conclusion:**The Angiotensin Converting Enzyme D/D genotype is positively associated with hypertension in our study population.

Keywords: Hypertension, ACE, Polymorphism, correlation.

INTRODUCTION

Each year a theme is selected by WHO on 7th April to highlight a priority area public health. It provides an opportunity for individuals in every community to get involved in activities that can lead to better health. The theme for world health day 2013 is "Blood pressure – take control." Hypertension has become one of the most common non-communicable global health problem with pandemic trend. It is well known risk factors for various cardiovascular, peripheral vascular and renal event in our body. Primary hypertension accounts for > 90% cases of total hypertension.[1]Hypertension is defined as a systolic blood pressure equal to or above 140 mm Hg and/or diastolic blood pressure equal to or above 90 mm Hg. Normal levels of both systolic and diastolic blood pressure are particularly important for the efficient function of vital organs such as the heart, brain and kidneys and for overall health and wellbeing.[2]Worldwide, raised blood pressure is estimated to cause 7.5 million deaths, about 12.8% of the total of all deaths.About 33% urban and 25% rural Indians are hypertensive.[3]A number of genes are implicated in the pathogenesis of cardiovascular disease and hypertension. Primary hypertension is a polygenic disorder resulting from interaction of several genetic and environmental factors. The Angiotensin converting enzyme (ACE) gene can regulate the Angiotensin Converting Enzyme (ACE) of Renin Angiotensin Aldosterone System(RAAS) regulating fluid and electrolyte balance and Blood pressure(BP).[4]In Homosapiens, the gene encoding ACE gene is located on the long arm of chromosome 17(17q23). The gene is 21 kilo base (kb) long and comprises of 26 exons and 25 introns.[5]ACE is a zinc metalloenzyme. Zinc is essential for its activity. The primary source of ACE is the endothelial lining of lungs. ACE plays a central role in (RAAS) in maintaining salt and water balance.ACE converts decapeptide Angiotensin I to octapeptide Angiotensin II. Angiotensin II is potent vasoconstrictor can increase the BP. ACE also degrades the Bradykinin in Kinin – Kallikrein System.[6]The ACE genotypes includes the presence (I allele) or (D allele)of a 287 bpalu repeat sequence in intron 16, resulting in 3 genotype (D/D, I/I & I/D). An I/D polymorphism of ACE gene at this region correlates with circulating ACE activity.Higher ACE activity is observed in subjects with ACE D/D genotype. A raised plasma ACE activity may elevate the blood pressure through increased production of angiotensin II.Studies have demonstrated ACE polymorphisms are associated with common disease like hypertension,diabetic nephropathy, coronary heart disease, cardiomyopathy and ischemic stroke.[7]

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Aims & objectives

1. To evaluate association of ACE genotype in hypertensive cases & normal controls.
2. To study level of serum Angiotensin Converting Enzyme (ACE) in cases and controls.
3. Correlation of serum Angiotensin Converting Enzyme (ACE) activity with ACE genotype.
4. To correlation of serum Angiotensin Converting Enzyme (ACE) level with severity of hypertension.
5. To study association of serum lipid profile, serum electrolyte, serum urea, serum creatinine in cases and controls.

MATERIALS AND METHODS

This study was conducted in Department of Biochemistry, M.K.C.G. Medical College in collaboration with Department of Medicine, M.K.C.G. Medical College and Hospital. Written approval was obtained from Institutional Ethical Committee and written informed consent was taken from all cases and control.

Study design:
Prospective, Case - Control, Hospital based study.
The study was carried out on 50 patients with H/O hypertension, who attended the outpatient Department of Medicine of M.K.C.G. Medical College and Hospital, Berhampur during the period of October 2015 to October 2017. Fifty age and sex matched normotensive people were taken as control.

Inclusion criteria:
Hypertensive male and female patient of 20 to 60 year of age

Exclusion criteria:
Elderly age >60 years, cases with diabetes mellitus, chronic kidney disease, thyroid disease, autoimmune disease and any other chronic diseases were excluded.

Collection of sample:
A morning sample of venous blood (8ml) was collected after overnight fast by sterile disposable syringe under aseptic condition from each case and control. 5ml blood was kept in EDTA vial for DNA isolation. Rest 3 ml of the sample was placed in a plain vial without any anticoagulant and was allowed to clot. After retraction of the clot serum was separated by centrifugation.Serum was used for estimation of ACE enzyme activity in Transasia semi-autoanalyzer and other risk factors like lipid profile, renal function test were done in Toshiba FR 120 autoanalyzer. Serum electrolyte was estimated in electrolyte analyzer I – Smart 30 having ion sensitive electrode.DNA Isolation by Non-Enzymatic Method.

PCR – Protocol:
ACE gene locus is located on human chromosome 17q23.

Template: 150 ng of genomic DNA/reaction volume of 10µl.

Forward primer:
5'-CTGGAGACCACTCCCATCCTTTCT-3' 25ng / reaction

Reverse primer:
5'GATGTGGCCATCACATTCGTCAGAT-3' 25 ng / reaction
dNTPs: Final concentration 200µM each
Buffer: Final concentration 1.5mM MgCl2, 50 mM KCl, 10 Mm TrisHCl, PH 7.6-8.0

Taq DNA
Polymerase:1.25U / reaction volume of 10µl.
PCR cycling profile: 94°C (5 min)- Genomic denaturation (30 cycles) 94°C (30 sec)- Denaturation 50°C (30 sec)-Annealing72°C (1 min)-Extension72°C (5 min)-Final extension
Gel:2%Agarose in 1X TE
Buffer
Product:490bp (Insertion)
190bp (Deletion)
DNA Marker:ϕ X174 RF DNA Hae III
PCR products were resolved using 2%agarose gel.
Gel electrophoresis was done and the image was showing different genotypes (II, ID, DD) for ACE locus.

Sample purity:

1. Nanodrop ND-2000 was used to determine sample purity. We also used it to determine sample concentration.
2. Purified DNA samples were used for PCR. Data from Nanodrop helped in troubleshooting whether the impurities were present in the sample had an effect on the quality.

Statistical analysis:
Statistical analysis was done by SPSS 21 Version Software. For each variable, values were expressed as Mean ± SD. The groups were compared by students 't' test. Correlations were calculated by Karl Pearson's Coefficient. A p value < 0.05 was considered significant.

RESULTS

[Table 1] shows that, all the biochemical parameter are higher in cases except HDL which is low in cases.TheMean±SD of Total Cholesterol between hypertensive and control group are 191.1 ± 37.3 and 158±32.48 respectively. The Mean±SD of Total Triglyceride between hypertensive and control group are 191.1±76.9 and 148.9±94.23 respectively.). The Mean±SD of HDL Cholesterol between hypertensive and control group are 37.12±9.1 and 41.92±7.03 respectively. The Mean±SD of LDL Cholesterol between hypertensive and control group

are 107.12±27.8 and 89.4±15.7 respectively. The Mean±SD of sodium between hypertensive and control group are 141.96±6.4 and 134.9±5.00 respectively. The Mean±SD of potassium between hypertensive and control group are 4.2±0.63 and 3.8±0.56 respectively. The Mean±SD of urea between hypertensive and control group are 32.70±23.52 and 23.5±8.4 respectively. The Mean±SD of creatinine between hypertensive and control group are 1.01±0.22 and 0.91±0.24 respectively. On comparison the difference in the sodium level between healthy individuals and hypertensive patients was found to be statistically significant. The levels of Total cholesterol, Total triglyceride, LDL Cholesterol and, Serum urea, Serum creatinine, serum potassium were significantly higher in patient group as compared to controls, ($p<0.05$). The levels of HDL Cholesterol was found to be significantly lower in healthy control as compared to hypertensive patient. The Mean ± SD of ACE the control and patient groups was 94.3 ± 14.63 and 58.1± 12.37 respectively. The ACE level was found to be higher in hypertensive patients in comparison to controls ($p = 0.001$), which is statistically significant.

Table 1: Comparison of biochemical parameters of hypertensive cases & controls

Parameters	Case(Mean ± SD)	Control(Mean ± SD)	't' value	'r' value	p value
CHO	191.1±37.3	158±32.48	4.6	0.478	0.000
TG	191.18±76.9	148.9±94.23	2.4	0.327	0.016
HDL	37.12±9.1	41.92±7.03	2.9	0.088	0.004
LDL	107.2±27.8	89.4±15.7	3.9	0.080	0.002
Na	141.9±6.4	134.9±5.0	6.0	0.767	0.000
K	4.2±0.63	3.8±0.56	3.5	0.380	0.001
UREA	37.70±23.52	23.5±8.4	4.1	0.006	0.002
CREAT	1.01±0.22	0.91±0.24	2.1	0.653	0.032

Data is represented as Mean ± SD.

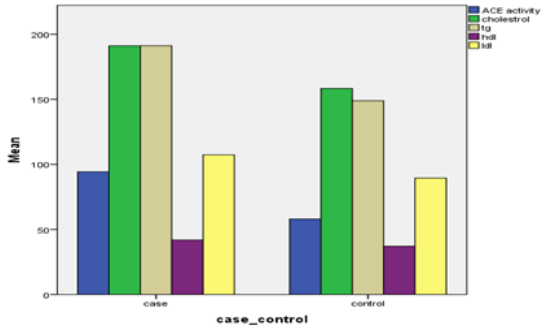

Figure 1: Comparison of biochemical parameter & serum ACE enzyme activity level in cases & controls.

[Figure 1] Shows serum ACE activity and TC, TG, LDL has higher in cases and HDL is low in cases than controls.

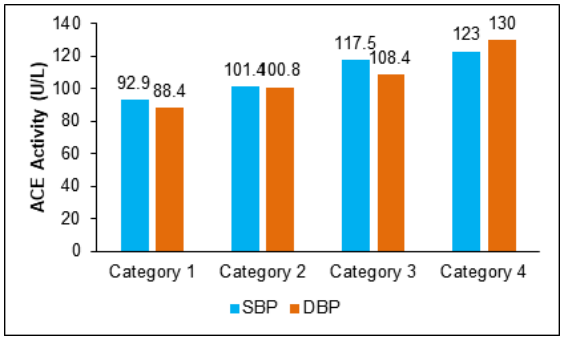

Figure 2: Correlation of serum ACE enzyme activity with SBP and DBP in different categories

Cat -1 SBP-120-139 mmHg,DBP – 80-89 mmHg; Cat -2 SBP- 140-159 mmHg,DBP- 90- 99 mmofhg.;Cat -3 SBP- 160-179 mmofhg,DBP- 100-109 mmHg.;Cat -4 SBP- ≥ 180 mmHg, DBP- ≥ 110 mmHg. [Figure 2] shows with severity of hypertension, the serum ACE enzyme activity is found to be higher.

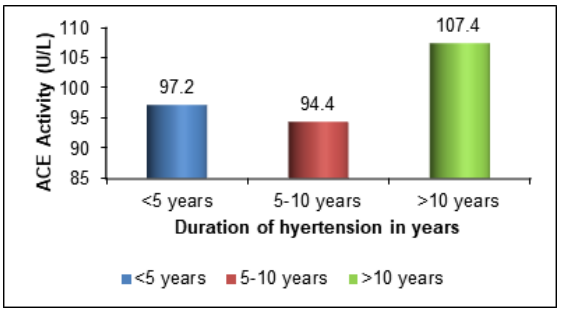

Figure 3: Correlation of serum ACE enzyme activity level in duration of hypertension in years.

[Figure 3] shows serum ACE enzyme activity level is higher in patients with longer duration of hypertension.

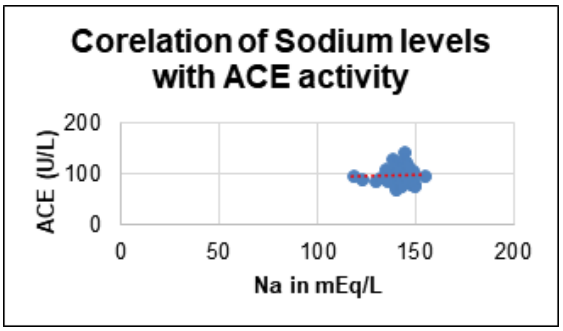

Figure 4: Correlation of serum ACE enzyme activity level and serum Na level in hypertensive cases.

[Figure 4] shows positive correlation of serum sodium level with serum ACE enzyme activity level. ($r=0.742$, $p = <0.01$)

[Figure 5] shows D/D genotype is common in hypertensive cases & I/D genotype is more common in control group.

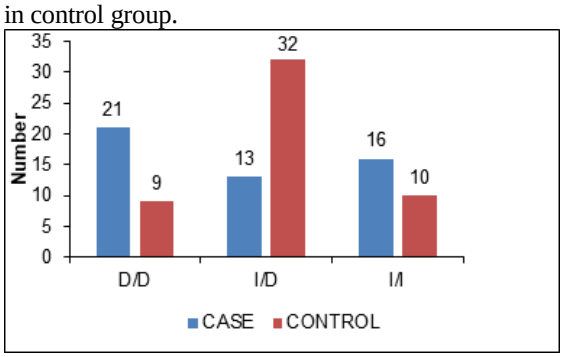

Figure 5: Bar diagram showing ACE gene polymorphism in cases and control

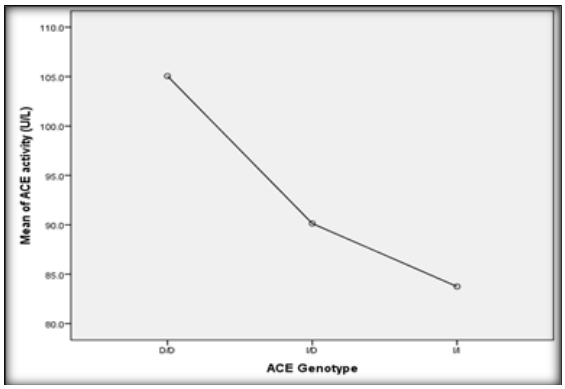

Figure 6: Mean of serum ACE enzyme activity with ACE genotype in cases

[Figure 6] shows D/D genotype has higher serum ACE enzyme activity level.

ACE I/D GENOTYPING BY PCR

Samples from both groups were genotyped by PCR thermo cycler product. After gel illumination by UV illuminator, by100 BP marker ϕ X174 RF DNA Hae III length of PCR products is determined. I: stated for insertion while D stated for deletion polymorphism [Figure 7]. Difference between I and D genotype is about 300 base pair sequence.

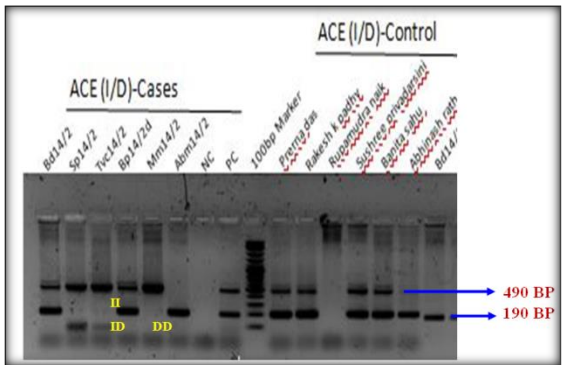

Figure 7: Gel doc image after 2% agarose gel electrophoresis (II/ID/DD)

DISCUSSION

Hypertension has reached epidemic proportions worldwide, placing a substantial burden on healthcare services. Historically, hypertension was considered a disease confined to developed countries and affluent people. However recent estimates suggest that the prevalence of hypertension is rising globally, particularly in developing countries. The reasons attributed to this shift in disease pattern include: increased life expectancy, rapid population growth, unplanned urbanization, low literacy and increased external debt and resultant cutbacks on national healthcare expenditure. This is called as "Epidemiological transition" Rural to urban migration was also found to be a major risk factor for hypertension and obesity. Increased mechanization of agricultural industry, automation of daily activities, popularization of television and increased computer usage in rural areas are leading to changes in lifestyle with resultant decrease in physical activity. Collectively these related issues have contributed to the emergence of non-communicable disease such as hypertension as a substantial regional health problem.In the present study, we found that lipid profile parameters such as total cholesterol and LDL cholesterol were higher in cases as compared to controls, which is statistically significant. HDL cholesterol was lower in hypertensive compared to healthy controls & Serum triglyceride mean level found to be high in cases than controls but which is not statistically significant.KamrunNaharChoudhury et al, Charles U. Osuji et al in their studies observed a significant increase in TC, TG and LDL cholesterol in cases compared to controls and significant decrease in HDL cholesterol in cases.[8,9] High cholesterol, TG, LDL are the risk factor of hypertension and in term atherosclerosis. The present study is in accordance with all the above studies without any conflictions. Hypertension is known to be associated with alterations in lipid metabolism which gives rise to abnormalities in serum lipid levels. C. M Reza QureshiForhad et al Hypertension and dyslipidaemia can be modified either by proper life style changes or medical management or by the combination of the both.[10] This study suggests that hypertensive patients need measurement of blood pressure and lipid profile at regular interval to prevent heart diseases and stroke.

Serum electrolytes

In present study serum sodium and potassium level were higher limit in cases as compared to controls which were found to be statistically significant. Priyanka D et al found that Serum sodium level was significantly more among hypertensives& was correlated positively with the blood pressure, similar to present study.[11]FengJ.He et al observed those individuals who develop a rise in blood

pressure have a reduced ability to excrete sodium.[12] which is responsible for the tendency for an increase in extracellular volume. Experimental increases in plasma and CSF sodium concentrations greater than 5 meq/L can increase the blood pressure independent of the extracellular volume. Lu Xi et al observed that baseline serum potassium level was high in hypertension.[13] Serum potassium level was positively related to the risk of hypertension in the Chinese population.

Serum urea and creatinine

We observed the serum urea (37.70 ± 23.52 mg/dl)and creatinine (1.01 ± 0.22 mg/dl)in cases and (23.5±8.4 mg/dl, 0.91 ± 0.24 mg/dl) in controls respectively , higher in cases compared to controls is statistically significant (P < 0.001).Pooja et al observed that serum creatinine in relation to hypertension have been found to be higher in hypertensive cases than normal healthy controls i.e. 1.13± 0.54 mg/dl vs 0.78 ± 0.12 mg/dl,(p < 0.000) was found statistically significant.[14] Similar findings were obtained in hypertensive patients that showed increase in serum creatinine by Nagah et al in Sudan.[15]RakheeYadav et al found two parameter (serum urea, creatinine) were markers of renal function, serum urea was show the renal status in hypertensive.[16]Serum urea and Creatinine was high in hypertensive.

Angiotensin converting enzyme (ACE)

We found out serum ACE enzyme level (table-4) showed 80.3±14.63 U/L in cases and 58.1±12.37 U/L in controls, when compared it was found to be statistically significant (P < 0.001).Studies done by IpsitaChoudhary et alJung Kyun Oh et al also shows serum ACE enzyme level to be significantly increased in cases when compared to controls.[17,18] Terrence Forrester et al observed in his study that serum ACE enzyme activity was more in hypertensive Jamaican population.[19] In present study we correlated the serum ACE enzyme level and the serum sodium level which shows that ACE enzyme level was positively correlated to sodium level. Serum ACE enzyme stimulated the RAAS system so it increased the excess sodium absorption via aldosterone mechanism and compensatory more water absorption from kidney can lead to hypertension. Kenneth E et al showed that the renal ACE enzyme level was involve severe sodium transporter which leads to sodium and water retention causing hypertension Then we also correlate the serum ACE level with the four category of hypertension.[20] We categorized hypertension in four group according to severity of systolic and diastolic blood pressure. We found that serum ACE enzyme level was positively correlated with the severity of hypertension level.Abraham WT et al showed, serum ACE enzyme formed AngitensinII which was potent vasoconstrictor it can lead to severity of hypertension.[21]Duru K et al concluded that ACE enzyme was high in severe case of hypertension.[22] Severe hypertension can lead to cardiomyopathy and left ventricular hypertension. In present study we also correlated serum ACE enzyme with the duration of blood pressure and the serum ACE enzyme level. Graph -5 showed the longer the duration of blood pressure, serum ACE enzyme level was high. In present study we found that serum ACE enzyme level was high in cases but after starting the treatment in 5 – 10 years in diagnosed cases the serum ACE enzyme level declined compared to newly diagnosed cases. But hypertensive cases > 10 years of treatment shows higher serum ACE enzyme level in comparison to newly diagnosed cases. After starting the treatment initially ACE enzyme was lower in cases in comparison to newly diagnosed cases. Long term treated cases in spite of treatment ACE enzyme was high. Other study also shows same finding.GouveaSAet al this study after the treatment of vasodilator (L- arginine) in renovascular hypertension.[23] The serum ACE enzyme level was low in comparison to base line after the treatment.Masami NiwaAnita Israel et al indicated that the treatment reduced the ACE maximal velocity or the number of available ACE molecules.[24] In vitro studies showed that pindolol had no direct effects on the activity of plasma ACE. A decrease in soluble ACE activity was observed in the lung of young hypertensive patient treated with pindolol. The results suggest that pindolol affects the site of origin of plasma ACE.Huskic J et al concluded in his study that Serum angiotensin converting enzyme (ACE) activity in high in patients with untreated essential arterial hypertension.[25]

ACE genotype and hypertension

In our study (Graph- 9-11) distribution of ACE genotype among the hypertensives cases and controls were shown in the three genotypes, I/I, I/D and D/D was analyzed. D/D, I/I genotype were more in cases than controls which is statistically significant. I /D genotype were low in cases than controls which was also statistically significant.On genotype analysis the percentage of(D/D, I/D and I/I) polymorphism among non-hypertensive's (controls) were 18%, 64% and 18.0% and percentage among hypertensive's (cases) were 42%, 26% and 32% respectively. Our study showed that the South coastal Odisha population, with (D/D) genotypes are more prone for the development of hypertension.We also correlated serum ACE enzyme with ACE genotype. We found that D/D genotype has more serum ACE enzyme when compared to I/D& I/I genotype.In present study the 95% CI was found to be 2.3–8.6. The result was confirmed to be statistically significant. On comparison of the individual percentage of the three genotypes it was found that D/D genotypes were more (D/D vs I/I) and 4.12 (D/D vs I/D). This high association

between D/D polymorphism and hypertension can be explained by the fact that (D/D) genotype is associated with high ACE levels.MorshedMahboob et al concluded a significant association of ACE(D/D) genotype with hypertension among Africans, Americans, Chinese and Japanese population.[26] Jimenez PM et al showed a significant association with ACE (D/D) genotype and diastolic hypertension.[27]Rigat et al observed Deletion polymorphism of ACE gene increases serum ACE enzyme level in hypertension.[28] However other studies have failed to show a positive association. It has been suggested that these inconsistencies may be due to the difference in background of the population characteristics. The heterogeneity in association of ACE I/D polymorphism with hypertension may be due to varied ethnicity or the various other genetic and environmental factors implicated in the regulation of blood pressure. Alaatin Y et al observed that I allele is associated with hypertension in the Pakistani population.[29]Ramalingam Krishnan a et al 30concluded that the study proves the relation between I/D genotype of ACE gene and essential hypertension in south Indian population.

In our study the LDL cholesterol was correlated with ACE genotypes,which shows a negative correlated with ACE genotype(D/D,I/D,I/I) respectively. LDL cholesterol was high in D/D genotype. This may lead to dyslipidaemia,a risk factor for hypertension.

CONCLUSION

We found a significant association between subjects of D/D genotype and hypertension, throwing out light to the fact that D/D genotype people are more prone for the development of hypertension. However, more knowledge about the genetics of hypertension can be obtained by performing the study over a wider population in various geographical regions of India and abroad. The serum ACE levels can be analyzed along with ACE genotyping and the relationships were correlated by the treatment with ACE inhibitor medicines.Some more studies may require to find relation between ACE inhibitor medicine treatment and ACE enzyme, so high risk groups like ACE (D/D) genotype cases and control may be counselled properly to change their life style and salt intake. This study can be extended to their family member to know the predisposition and risk of hypertension.

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