Public health planning in most developing countries has focused mainly on the
diagnosis, prevention and control of communicable diseases which were responsible for
most morbidity and mortality. However, with the growing economy and affluence life
style changes have been creeping in the daily lives of people living in these countries
and posing an important threat to developing economies in the form of non
communicable diseases, draining a good chunk of their scanty health budget. It is
predicted that by 2020, these diseases will be causing 7 out of 10 deaths in developing
countries. Developing world is now faced with a dual dilemma of dealing with both
communicable and non-communicable diseases.

Hypertension is described as one of the commonest non communicable disease
affecting mankind. It is still largely ignored as a public health problem in most
developing countries, despite it being a major risk factor for cardiovascular diseases,
stroke, renal failure, and peripheral vascular disease. Nearly 40 million people in India
are hypertensive and majority of them present with no apparent cause and are diagnosed
as essential hypertensive. The burden of morbidity and mortality posed by hypertension
is enormous.

The prevalence of hypertension, mean systolic and diastolic blood pressures
varies from one country to another and between communities in the same country
depending upon the economic development and affluence. In a meta-analysis of 34
epidemiological studies from rural and urban populations of India, it was observed that
hypertension is emerging as a major public health problem in our country and is more
prevalent among urban people compared to those of rural area. These studies also
suggested that predictors of hypertension may be different in various geographical
regions of India.

The prevalence of hypertension in Asian countries varied between 2-24% in
rural and urban areas, respectively. The migration of people from rural to urban areas
increases over time in search for better jobs, education and living conditions. It has both
negative and positive effects on the survival and well-being of peoples. It is expected in
rural-urban migration, the transformation of rural settlements to the cities are the major
determinants of a rapid population growth in urban areas of developing countries
including India in the next thirty years which increases the non-communicable disease due to life style changes. Many studies show that awareness of hypertension in the developing world population is low especially in the rural areas. It is possible that this is an outcome of low level of literacy and education. This lack of awareness is also responsible for delayed treatment thus creating problems for the early and effective management of the disease.

Essential hypertension is undoubtedly a heterogeneous group of disease with a common end result of elevated blood pressure (BP). Therefore, determination of the relative roles of genes and environment in the etiology of high blood pressure is very important. Environmental factors seem to play a significant role in the observed variations in the distribution of BP among different population groups. There is also a correlation between genetic polymorphism(s) and antihypertensive therapy. Antihypertensive drugs lower blood pressure by acting on specific targets. Due to the vast genetic differences among individuals, it is reasonable to expect that variation in BP and response to anti hypertensive drugs could be genetically determined. Diversity in responses to the above mentioned therapy has been well documented. African Americans are reported to be more responsive to diuretics and calcium channel blockers and less responsive to β-blockers and angiotensin converting enzyme (ACE) inhibitors than their Caucasian counterparts. However, it is not simple to select a specific antihypertensive drug in patients within the same ethnical group. The prescription of anti hypertensive drug(s) in a population could well define the response of patients to these drugs. Pharmacogenomics could pave the way to identify a drug or drugs most likely to reduce a patient’s blood pressure, based on the patient’s genetic make-up. While not proven, it seems probable that successful blood pressure control with the initial drug would increase the patient’s likelihood of remaining on their prescribed therapy. Additionally, such a genetic prediction should reduce the number of physician visits needed to achieve blood pressure control and results in shorter periods of uncontrolled hypertension, potentially leading to reduced health care expenditures and improved patient outcomes. The likelihood that such predictive tests will be available in the next decade seems high as there is data linking genetic polymorphism with response to ACE inhibitors, diuretics and β-blockers.
Many studies in India and a few in Haryana have shown that detection rate of hypertension is comparatively low and there is lack of awareness and knowledge about the morbidity, complications and method of control of hypertension. Although the detection and awareness levels of hypertension in urban area is comparatively better than rural area. But it is also true that the prevalence rate of hypertension in urban areas is more than rural areas, because of several risk factors such as tobacco consumption, lack of physical activity, unhealthy diet, and obesity. Till date there are hardly any pharmacoepidemiological and/or pharmacogenomic studies of essential hypertension in rural areas of Haryana. Therefore, a holistic approach has been attempted in this study to:

- Assess the prevalence and risk factors for causing essential hypertension,
- Ascertain prevalent drug therapy and its outcome, and
- Understand the contributions of candidate genes (ACE, β-1 ADR and ADD1) in antihypertensive therapy

To achieve the objectives, a hospital based retrospective and prospective study was conducted at M M Institute of Medical Science and Research, Mullana, Haryana. The retrospective study was conducted during the period June 2003 to September 2006 wherein data on patients visiting the Outdoor Patient Department (OPD) of the hospital was collected. A total of 2295 (1446 males and 849 females) patient visited the OPD, of which 876 were essential hypertensive. Our retrospective data suggested that sufficient number of essential hypertensive patients were available and were chosen for further prospective study to identify various risk factors involved in its etiology. The prospective study was carried out from December 2006 to June 2007 and January 2010 to July 2011 during which various anthropogenetic variables were investigated in a case control study.

In case of hypertension, many types of antihypertensive drugs are available; besides controlling blood pressure, correct use of these drugs contributes to longevity and reduced patient mortality rates. The type and correct combination of antihypertensive drugs are central to achieving better control rates. The prescriptions of antihypertensive drug therapy at different times from June 2003-September 2006 and
January 2010 to July 2011 was investigated to evaluate any trends or shift in the prescription patterns in the treatment of essential hypertension in the same place, where the earlier audit was conducted. Prescription records were used to identify antihypertensive regimen, single and/or combination therapy, given to the patients during the defined study period.

For pharmacogenomics studies, the blood samples of 106 essential hypertensive patients and 110 normotensive random age and sex matched controls were studied. Additional blood samples were also collected during January 2010-July 2011 period for ascertaining the relationship between the genetic profile of patients and their response to various anti hypertensive therapy. The obtained blood samples were processed for the isolation of genomic DNA by modified inorganic method and quantified using spectrophotometric analysis. The patients and control samples were then screened for ACE gene polymorphism for the presence or absence of an Alu sequence of 287 base pairs in intron 16 of the ACE gene. The PCR product of 490-bp and/or 190-bp denoted the presence or absence of the Alu sequence. ADD1 gene polymorphism located at nucleotide position 614 of exon 10 was analyzed for G→T substitution for 460th amino acid residue using amplification refractory mutation system (ARMS-PCR) methodology. β-1 ADR gene polymorphism responsible for serine to glycine substitution due to A→G change at codon 145 of exon 10 was studied using standard PCR followed by restriction fragment length polymorphism. The genotypic and allelic distribution of ACE, ADD1 and β-1 ADR gene polymorphisms among the cases and controls were compared and analyzed using appropriate statistical methods.

**SALIENT RESULTS**

- Our hospital based study reported that of the total OPD cases 38.2% were essential hypertensive patients comprising of 59.16 % males and 40.83% females.
- Prospective study based upon, age and sex matched, essential hypertensive versus normotensives Haryanvi Jat population revealed that body mass index, hip circumference, systolic blood pressure and diastolic blood pressure showed highly significant difference (p<0.0001) between the two studied populations. Waist
circumference (p=0.0028) and waist hip ratio (p=0.0345) were also found to be statistically significant.

- All anthropometric variables were highly significant except weight and waist hip ratio in Essential hypertensive females versus normotensives females.

- Multi-logistic regression analyses revealed body mass index and smoking as strong risk predictors of essential hypertension.

- Pharmacoepidemiology data showed that monotherapy prescription of antihypertensive drugs were more common than combination therapy from both the surveyed conducted during 2003-2006 (retrospective study) and January 2010 to July 2011 (prospective study).

- Among monotherapy category, the prescriptions of β1 blocker were highest during (2003-2006) and ACE inhibitors were the most prevalent drug during (2010-2011). Followed by diuretics and calcium channel blockers. In case of combination therapy ACE inhibitors with β1 blockers was the predominant prescribed combination. During 2003-2006 and 2010-2011 periods, the prescription of diuretic therapy alone decreased from 21 to 12% whereas the prescription of ACE inhibitors increased from 27 to 40%.

- β1 blockers therapy (Metoprolol) alone was found to be the most effective way of controlling systolic blood pressure. After treatment with β1 blockers, the average systolic blood pressure of essential hypertensive patients reduced significantly from 146.55±11.03 to 125.76±7.17 and showed highly significantly result (p<0.0001) at 4th week. In case of ACE inhibitor (Ramipril) and diuretic (Hydrochlorothiazide), the blood pressure decreased and found to be slightly significant.

- In case of average diastolic blood pressure of essential hypertensive patients treated with ACE inhibitor (Ramipril) and β1 blocker (Metoprolol) showed highly significantly reduction (p<0.0001) compared with baseline blood pressure at 4th week. In case of diuretic (Hydrochlorothiazide), slightly significant (p<0.05) results were observed.

- The Gly allele frequency of codon 49 of β-1 ADR polymorphism showed significant increase among the hypertensive population compared to the normotensive controls.
However, the distribution of Ser/Ser, Ser/Gly and Gly/Gly genotypes were statistically non significant between the two populations.

- About 10% of the essential hypertensive patients with Gly allele treated with 50mg β1 blocker showed non responding effect while 50.5% patients responded to the same dose of the drug and they all had Ser allele.

- The insertion/deletion polymorphism in ACE gene was not very informative. The distribution of I and D alleles among the two groups were very similar and differences were statistically non significant (p = 0.694).

- The frequency of I/D heterozygote as compared to homozygote was higher both in the patients and control group. It was observed that the DD genotype was slightly higher than II genotype in patients as compared to control.

- Distribution of responder and non responder among hypertensive population to antihypertensive therapy of ACE inhibitor indicated statistically non significant differences based on the presence of D allele versus I allele.

- Allelic and genotypic distribution of ADD1 polymorphisms in essential hypertensive versus control population was found to be non-significant

- Gene-gene interaction showed the statistical non significant association between three genes (ACE/β-1ADR/ADD1) in normotensive and hypertensive population.

- Gene-drug interaction analysis revealed statistically non significant association of pharmacological response with their respective polymorphic alleles for all the drugs (Ramipril, Hydrochlorothiazide & Metoprolol) in the population under study.

**Conclusion**

- This is the first investigation that attempts to study prevalence rates, prescription of antihypertensive treatment and role of candidate gene polymorphisms in essential hypertensive population from a rural region of Haryana.

- Male and female essential hypertensive patients showed variable association with anthropometrics parameters and susceptibility to essential hypertension.

- Body mass index and smoking are strong predictors of essential hypertension in our study population.
The prescription pattern of anti hypertensive regimens changed considerably between 2003-2006 and 2010-2011 periods. A clear increase was observed in the prescription of ACE inhibitor and calcium channel blockers while usage of diuretics decreased, whereas not much change was observed in the usage of β1 blockers.

The distribution of Gly49 allele of the β-1 ADR differed statistically among the essential hypertensive patients from the controls. Two third of the patients with Gly allele failed to respond to 50mg of the β1 blocker.

ACE insertion/deletion polymorphism of 287 base pairs in intron 16 of ACE gene can be a good parameter to decide the dosage to be prescribed to essential hypertensive patients. DD genotype individuals would have the highest serum concentrations of ACE enzyme and hence would require higher doses as compared to patients with genotype II.

ADD1 gene polymorphism failed to reveal any meaningful association with the essential hypertensive population.

Finally the data obtained clearly suggests that the response to anti hypertensive treatment is in part genetically determined and the efficacy of these drugs among the non responders will improve if the genetic profile of the patients is taken in consideration. To fully appreciate the interaction between various candidate genes in dictating susceptibility to hypertension and response to antihypertensive therapy, a much larger study is warranted. Such an approach will go a long way in guiding clinicians in prescribing individualized antihypertensive drugs for their patients.