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Personalized Management of Hypertension: The Emerging Role of Omics in Pharmacotherapy of Hypertension

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ABSTRACT

Hypertension is a chronic disease affecting more than a billion people globally and associated with serious long-term consequences. Effective and sustained control of blood pressure over years is of prime importance to prevent complications. Although there are multiple groups of pharmacotherapy options available, still the control achieved is less than 50% globally which is an alarming situation. Hence newer avenues must be explored to understand the pathophysiology of hypertension to formulate effective management guidelines rather than adopting trial and error approach. OMICS sciences including genomics, transcriptomics, proteomics and metabolomics offer a newer approach to better understand not only the pathophysiology of hypertension but also provide us with an opportunity to personalize the management of hypertension.

Keywords: Uncontrolled Hypertension, OMICS sciences, Personalized treatment

INTRODUCTION

Elevated blood pressure or Hypertension is a serious medical condition with a high prevalence affecting more than a billion people globally [1,2]. It is often referred to as the 'silent killer' as it often remains asymptomatic but on long term is associated with development of serious ailments like heart failure, ischaemic heart disease, stroke and kidney disorders [3,4]. It contributes significantly to global mortality with almost ten million deaths annually and loss of disability adjusted life years [3,4]. The American College of Cardiology/American Heart association (ACC/AHA) in their latest guidelines in 2017 defined hypertension as systolic blood pressure of ≥ 130 mmHg and diastolic blood pressure of ≥ 90 mmHg in comparison to higher threshold of ≥ 140/90 mmHg by the earlier guidelines [5]. This has the potential to further increase the prevalence of hypertension as reported by Garies S et al. [6] in their cross-sectional study reporting an increased prevalence of hypertension in Canada from 13.3% to 32% after implementation of the new guidelines.

The two main types of hypertension are primary (essential) which is the predominant form (>90% of cases) and secondary hypertension with an identifiable cause seen in <10% of cases. The pathophysiological determinants of essential hypertension include environmental (Unhealthy diet, increased salt intake, low potassium intake, physical inactivity, overweight/obesity), genetics (multiple risk alleles, epigenetic, gene-gene interactions) and socio-economic factors (age, sex, income, education, occupation, accessibility to healthcare) [7]. Hence the treatment of hypertension often includes non-pharmacological measures including lifestyle modifications (reduction of salt, healthy diet, moderate alcohol consumption, weight reduction, smoking cessation, regular physical activity) and pharmacological treatment [8].

Despite the availability and use of multiple pharmacotherapy

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options still the high prevalence of uncontrolled hypertension in United States (45%), France (51.3%), England (40%), Germany (30%), Italy (28%), Spain (19%), Sweden (21%) and Ethiopia (52.5%) is a big concern [9]. In India, a recent study by Ramakrishnan et al. [4] reported prevalence of hypertension to be 30.8% with 51% of them being aware, 88% were on treatment and only 41% had their blood pressure under control. The postulated major causes for uncontrolled hypertension include lack of adherence to treatment, unhealthy lifestyle, socio-economic factors, duration of hypertension and other co-morbidities [9,10]. Trials have suggested a major reduction in cardiovascular events and all-cause mortality in those whose blood pressure is adequately controlled in comparison to those whose blood pressure remains uncontrolled [10].

Hence there is an urgent need to further explore uncharted territories in understanding the pathophysiology and management of hypertension. As the interplay of genetics and environmental factors play a crucial role in pathogenesis of essential hypertension, capturing all genetic and environmental factors in an individual would greatly help to predict the current status of disease, future progression and associated complication over long term in a particular individual. The 'OMICS' sciences including genomics, transcriptomics, proteomics and metabolomics in reckoning over last two decades might help to identify new molecular features that have potential to regulate blood pressure. Implementation of the same would ultimately lead to personalized management of hypertension and might lead to better control of hypertension in every individual [11].

GENOMICS IN PHARMACOTHERAPY OF HYPERTENSION

The familial correlation to blood pressure was first identified by Pickering and co-workers in their study published in 1954 [12]. The genetic element contributes to almost 30-50% variation in blood pressure, hence identifying genetic variants helps in better understanding of disease. Several approaches have been employed to identify genetic loci predisposing to hypertension including candidate gene approach, genomic-wide scanning (Genome Wide Association Studies-GWAS), intermediate phenotype which represents an early stage towards development of disease (eg: M235T genotype at angiotensinogen locus leads to phenotype with angiotensin II unable to modulate secretion of aldosterone and renal blood flow), comparative genetics (animal data to target genetic locus in humans) and a combination of above methods. The methodologies used to identify the same include linkage analysis, allele-sharing methods (non-parametric method), association analysis and studies using animal models [13].

Currently there are more than 30 genes whose mutations are linked to regulation of blood pressure. Most of the identified monogenic forms of hypertension include those altering aldosterone and renin levels inherited either as autosomal dominant (E.g.: Glucocorticoid remediable aldosteronism, Liddle's syndrome, Gordon syndrome) or autosomal recessive (E.g.: Apparent mineralocorticoid excess, congenital adrenal hyperplasia, 11β hydroxylase deficiency and others). Identification of the same helps to start appropriate pharmacotherapy which often includes mineralocorticoid receptor antagonists (Spironolactone), epithelial sodium channel inhibitors (Amiloride, Triamterene), thiazide diuretics or glucocorticoids [14-16].

In GWAS the entire genome is scanned to generate a hypothesis linking variation in genome (Single nucleotide polymorphisms-SNPs) to phenotype (alteration in blood pressure). Although initial studies were negative, latest GWAS have identified 1477 SNPs which could explain around 27% of the heritable variation in blood pressure, thereby supporting the theory of a multifactorial polygenic basis for regulation of blood pressure [16,17]. The most important drawback is identifying the candidate gene affected by SNPs and some SNPs are linked to more than one disease, hence there is a need of large sample size to generate any meaningful data. Over time it has been realized that GWAS signals can be used to explore variation at population level rather than for personalized therapy [14-17].

The most significant development in GWAS is the identification of SNP in uromodulin gene (UMOD) expressed in thick ascending Loop of Henle in kidneys. It has been postulated to be associated with progression to chronic kidney disease. This is the basis for a multicenter cohort study under trial to evaluate the role of loop diuretics responsiveness in those possessing this SNP (rs13333226). The GWAS signals are also being evaluated to reposition the drugs for use in essential hypertension including endothelin receptor antagonist (interacts with GWAS loci EDNRA), Riociguat (GUCY1A2), Valproic acid (HDAC9, SCN2A, SCN10A) and Nesiritide (NPR3) [15-17].

Hypertension has been linked to epigenetic phenomenon in which there is a heritable change in gene expression without alterations in DNA sequences and is influenced by reversible environmental, nutritional, pharmaceutical and fetal factors. These epigenetic modifications include DNA methylation (e.g.: Low levels of 5-methylcytosine methylation in smokers correspond to higher levels of hypertension), posttranslational modifications of histone proteins (E.g.: Animal studies suggest prenatal ascorbic acid induced reversal of lipopolysaccharide induced histone H3 acetylation in the promoter region of Angiotensin convertase enzyme 1 gene) and non-coding RNAs (E.g.: small 22 nucleotide length hsa-miR-663 interferes with translation of mRNA of renin and apolipoprotein E). These epigenetic modifications could be a potential target to evaluate and develop newer antihypertensive drugs and also might help in personalizing the treatment of hypertension [16,17].

The utilization of genomic data to guide the choice of antihypertensive or its dosing is often referred to as hypertension Pharmacogenomics [15-17]. The clinical pharmacogenetics implementation consortium (CPIC) established in 2009 was tasked with the formulation of guidelines from pharmacogenetic data for clinical use. CPIC has published 23 guidelines which cover 19 genes and 43 drugs (Warfarin, Tacrolimus, Simvastatin, Azathioprine, Atazanavir, Carbamazepine and others) but none of the anti-hypertensives figure in the list [17,18]. The published antihypertensive pharmacogenomic data that is reproducible often involves β-blockers (SNPs associated with ADRB1 is associated with greater response for Metoprolol and a greater reduction in diastolic blood pressure for carvedilol) and thiazide diuretics (SNPs of NEDD4L associated with greater reduction in systolic & diastolic blood pressure and SNPs of YEATS4 associated with greater reduction in diastolic blood pressure) [15-18].

TRANSCRIPTOMICS IN PHARMACOTHERAPY OF HYPERTENSION

The study of the transcriptome which is the sum total of all the RNA transcripts (including messenger RNA and non-coding RNA) obtained from DNA in an organism is known as transcriptomics, first used in 1990s. RNA transcripts reflect the integration amongst various genetic variants in different tissues at particular time points and can serve as an indicator of state of diseases or drug response [19,20]. Various techniques employed to evaluate the same includes microarrays (involves hybridization of transcripts to array of complementary probes) and RNA seq (sequences of complementary DNA transcripts obtained from RNA) [19,20].

Although it is tissue and cell specific the chief drawbacks are it needs more careful handling of sample as RNA is less stable than DNA, data obtained is more complex compared to genomics and requires validation from real-time quantitative polymerase chain reaction. Studies suggest that a few transcripts (CRIP1, MYADM, TIPARP, TSC22D3, CEBPA, F12, LMNA, and TPPP3) could account for 13% of variability in blood pressure. The strongest association for reduction in blood pressure on pharmacotherapy was established with CRIP1. Hence future studies are needed to consider and evaluate the same while developing newer anti-hypertensive drugs [21].

PROTEOMICS IN PHARMACOTHERAPY OF HYPERTENSION

Human genome with more than two lakh genes after subjected to different splicing and post translational modifications can result in proteins whose numbers are ten times that of genes and all of them determine various cellular functions. The term Proteomics coined in 1994 by Marc Wilkins is the study of proteome (i.e. Snapshot of all the proteins translated from genome) in an organism at a given time. It can predict the exact disease process in an individual at a point of time in comparison to genomic studies which can predict one's susceptibility to the disease [22,23]. The platforms developed to analyze proteome include two-dimensional gel electrophoresis, Liquid chromatography-Mass Spectrometry (LC-MS), Surface enhanced laser desorption/ ionization-MS (SELDI), Capillary electrophoresis-MS (CE-MS), selected reaction monitoring and protein microarrays [23].

Most of the proteomic studies are based on experimental models of hypertension and cardiovascular cell culture models. Angiotensin II infusion model of hypertension and end organ damage in mice and rats have detected increased phosphorylation of isoform of protein kinase-C, glycogen synthase kinase and decreased phosphorylation of protein kinase-C sigma & cyclic adenosine monophosphate [22]. 2D CE-MS studies have reported an increased expression of 13 proteins (alpha-enolase, lactate dehydrogenase B and others) by left ventricular myocardium in spontaneously hypertensive rats [23].

Few of the human studies conducted include study of ageing on vasculature by analysis of urine of individuals aged 2-72 years by CE-MS. The study demonstrated age related changes in 325 peptides out of the total 5000 examined urinary peptides. Relatively more studies have been conducted to determine proteome variations in pre-eclampsia and pulmonary artery hypertension. As of now we have little understanding about the effect of various factors like age, gender and ethnicity on proteome hence it becomes difficult to make specific predictions. Hence with recent advances in the analytical techniques, proteomics can play a crucial role in understanding the pathophysiology, early detection of end organ damage and personalized treatment of hypertension [22,23].

METABOLOMICS IN PHARMACOTHERAPY OF HYPERTENSION

Metabolomics is the comprehensive analysis of the whole metabolome, which enlists profile of all the low molecular weight metabolites (<1500 Da) participating in metabolic process within an organism. Metabolites can be either endogenous (products of activity of genes and proteins) or exogenous (products of microbiota in human intestines) [24]. Biological samples are analyzed to derive metabolome using various analytical techniques including nuclear magnetic resonance (NMR) spectroscopy and Mass Spectrometry along with separation techniques like gas and liquid chromatography [25].

Hypertension being a part of metabolic syndrome is often associated with altered glucose and lipid metabolism; hence metabolomics approach can potentially reveal new pathophysiological mechanisms and newer drug targets [25]. The metabolomic approach, which is still in its infancy, has been employed by studies linking low levels of long chain-

acyl-carnitine in individuals on treatment with amlodipine, bisoprolol and Losartan [26]. After administration of amlodipine those responding to treatment have demonstrated low levels of plasma hexadecanedioate and administration of hydrochlorothiazide associated with increased uric acid levels in plasma [27,28].

CONCLUSION

Although research into the field of hypertension goes back decades still, we have not fully understood the exact pathophysiological mechanisms of hypertension, leaving glaring gaps in the treatment of hypertension. As the genetic and environmental factors play a complex role in the pathophysiology, assessing the effects of environmental factors which are not constant is almost an impossible task, but the constant component of genetics can be fully elucidated for better understanding of disease. The success achieved in mapping of human genome has given a new hope in this direction with major research being concentrated in this arena. Although research may bring in data, the application of the same to clinical practice is the next mile we all have to walk through. The OMICS sciences are flourishing in this direction with research targeting many chronic disorders but no significant progress has been achieved in the field of hypertension. Hence a greater effort is the need of the hour to fully elucidate the pathophysiological mechanisms and realize our dream of personalized management of hypertension.

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