Commentary

The Scope of Precision medicine in management of type 2 diabetic patients with hypertension.

Abstract: There is an exponential increase in prevalence of diabetes and hypertension worldwide and more so in India, and despite of numerous state and national awareness programs and evidence-based approach in management of these diseases, the burden of mortality and morbidity, instead of decreasing, has been rapidly climbing upwards. Hence, there is definite need of precision medicine approach, even though the pathway would be challenging, can provide more precise treatment to an individual based on his/her genetic, phenotypic, and metabolic make up.

Key words: Precision Medicine, Diabetes mellitus, Hypertension, Gene.

1. Introduction:

Type 2 diabetes mellitus (DM) and Hypertension (HT) are among the most common chronic noncommunicable diseases and multifactorial disorders affecting both developed and developing countries. [1] As per epidemiological study ICMR- INDIAB, the overall weighted prevalence of diabetes by OGTT was 11·4% (95% CI 10·2–12·5; 10 151 of 107 119 individuals), and the weighted prevalence of hypertension was 35·5% (95% CI 33·8–37·3; 35 172 of 111 439 individuals) in India. [2]According to the data from the National Family Health Survey 2015–16, India, prevalence rate of HT among diabetic individuals was approximately 37 %. [3]

The presence of hypertension in diabetic patients substantially increases the risks of cardiovascular disease, stroke, nephropathy, and retinopathy. When HT coexists with DM, the risk of cardiovascular disease is increased by 75%, which further contributes to the overall morbidity and mortality of already high-risk patients. HT and DM are common, intertwined conditions that share a significant overlap in underlying risk factors like ethnicity, positive family history, dyslipidemia, and lifestyle determinants (food intake, smoking, alcohol, sedentary).The pathophysiologic relationship between diabetes mellitus and hypertension is bidirectional. Long term Diabetes causes damage by resulting in arteriosclerotic changes in the kidneys, which in turn leads to salt and water retention, which raises blood pressure. Also, diabetes damages the small blood vessels, causing the walls of the blood vessels to stiffen and become hard and function improperly, thereby resulting in further increase of blood pressure.

Patients with HT alone often have significant insulin resistance.Approximately 30-50% of patients do not respond to initial treatment for diseases such as diabetes, hypertension, etc. It has been suggested that, in some cases, differences in response to treatment are related to mutations in genes that code for drug-metabolizing enzymes, drug targets, or drug transporters, etc. It is known that humans share 99.9 % of DNA and any two people selected at random would only have 1 in 1500 base pairs as different. But this small difference is sufficient in causing the variation in response of individuals towards a particular modality of treatment. [1, 4, 5]

" To control a disease, why to apply combination therapy (dual/triple/quadruple), why not precision medicine? "Precision medicine (PM) also known as personalized or individualized medicine, is part of the logical evolution of contemporary evidence-based medicine, that tailors the diagnosis and treatment of diseases to the individual based on genotypic, phenotypic, biomarkers or psychosocial characteristics; in simpler words, it is the approach of administering the accurate treatment, to the right patient, at the right time of disease process.PM also focuses on identifying patients who, despite a diagnosis, do not require treatment (or require less than might conventionally be prescribed).[6,7]

2. Precision hypertension medicine:

Despite the availability of various modalities of treatment, hypertension is poorly controlled, with huge lacunae in understanding of hypertension, antihypertensive therapy adoption, and blood pressure target control levels. Over the last half-century, the treatment approaches have remained virtually unchanged, and personalization of treatment has not gone beyond taking African ancestry and serum renin levels into consideration.Furthermore, substantial genetic, molecular, and physiological research discoveries are not being integrated into screening, diagnostic, and management regimens. More than half of patients require multiple clinic/hospital visits at varied intervals to try dose titration, switching, or adding medicines until a satisfactory outcome is obtained, or intolerable side effects develop.Majority cases of hypertension are idiopathic, which is also known as essential hypertension. It has long been demonstrated and confirmed, that an increase in salt intake increases the risk of developing hypertension in most of the population.One of the highlighted and studies factors for the development of essential hypertension is the patient's genetic ability to salt response.[1, 5, 8-10]In the modern era of genomics, hypertension is among the first few diseases to which genotyping has been applied for characterization of subgroups, with a focus on the angiotensin-converting enzyme (ACE) gene indel subtypes which paved the way for a growing number of similar studies resulting in making genetic testing as an established option for different applications in the field of hypertension, for example in phaeochromocytomas and paragangliomas, familial hyperaldosteronism type 1 and other forms of endocrine hypertension and the evidence from monogenic forms of hypertension shows that identification of causative mutations can help to improve therapy.[7, 11, 12]Examples are:

2.1. Glucocorticoid-remediable aldosteronism, also called as familial hyperaldosteronism type 1 (OMIM #103900) is an autosomal dominant syndrome in which high blood pressure is caused by increased aldosterone secretion driven by pituitary adrenocorticotropic hormone (ACTH). Individuals with this mutation respond paradoxically to glucocorticoids, as glucocorticoids suppress pituitary ACTH secretion and thus remove the stimulus for the abnormal aldosterone excretion in these set of patients. [7]

2.2. Mutations in the epithelial Na+ channel gene results in Liddle's syndrome (OMIM #177200), an autosomal dominant condition with high blood pressure being associated with suppressed aldosterone and renin levels. The mutated Na+ channel in this syndrome leads to inability of β and γ subunits to bind neural precursor cell expressed developmentally downregulated 4 (Nedd4) resulting in constitutive expression of Na+channels and prolongation of its half-life. This results in increased rates of Na+ reabsorption, volume expansion and finally, hypertension. Knowing the molecular defect in Liddle's syndrome, treating physician can apply direct disease-targeted treatment with specific inhibitors of the epithelial Na+channel, such as amiloride or triamterene. [7]

2.3. A single nucleotide polymorphism (SNP) in the upstream end of the uromodulin gene (UMOD) has been found to be associated with hypertension. The UMOD gene exclusively expressed in the thick ascending limb (TAL) of the loop of Henle's in the kidney where normally 22-25% of the filtered Na+ is reabsorbed. Follow-up transgenic studies confirmed that UMOD was indeed involved in blood pressure regulation, possibly through interaction with the Na+–K+–2Cl− co-transporter 2 (NKCC2) channel in the TAL. The commonly used diuretic furosemide is an inhibitor of NKCC2, and this medication is not used routinely in hypertension management. Genotype-directed trials are required to determine whether the UMOD risk variant is an effective stratifier for loop diuretic like furosemide treatment in uncontrolled hypertensive patients.[7, 13]

Many proposed genes could to be false positive, hence a deep phenotyping will be required to determine the utility of genetics in the management of hypertension. Physicians need to be careful while considering features and criteria before subjecting individual patient to undergo genetic testing.

2.4. Suggested Criteria for consideration for genetic testing in hypertensive patients[10, 14, 15, 16]**:** Patients can be included or excluded if they had other known causes of secondary hypertension other than monogenic hypertension based on the required levels of precision.

1. Positive family history, especially immediate family members like father or mother.

2. Low plasma renin levels

3. Salt sensitive/Salt resistant type hypertension

4. High serum uric acid levels

5. High urine micro albumin

6. Ratio of aldosterone to plasma renin activity (PRA) - 20 to 30

7. High aldosterone levels

8. High urinary catecholamines and fractionated metanephrines

9. Urinary potassium exceeds 30 mmol/L

10. Ethnic background - African (Caribbean), European

11. Presence of typical syndromic clinical features

12. Drug resistance (rule out poor drug adherence and persistence)

13. Early onset of hypertension: age of onset ≤ 35 years

14. Hypertension with abnormal imaging results: adrenal or abdominal CT scan

Thus, identifying specific drug, prediction of blood pressure response and adverse drug reactions to antihypertensive drugs through the identification of genetic markers is a highly promising field for precision medicine.

3. Precision diabetes medicine:

The main reason for developing type II diabetes is a combination of genetic factors and an unhealthy lifestyle. Analysis of the genetic predisposition to DM, helps to identify the presence of pathological forms of genes and prior identification protocols require prescreening based on clinical features (e.g., positive family history, age at onset of disease, phenotype including syndromic features) and nongenetic testing (islet autoantibodies and C-peptide). This allows the treating physician, to choose precise treatment and methods for preventing the development of type 2 diabetes mellitus.[17, 18]Few examples are:

3.1. CDKAL1 gene: The CDKAL1 gene is an inhibitor of the CDK5 kinase enzyme in pancreatic cells, which plays an essential role in the release of insulin, from pancreas into the bloodstream. There are several regions in the CDKAL1 gene that can influence the development of type II DM. For instance, some mutations in the CDKAL1 gene are associated with reduced insulin production, which increases blood glucose levels.[17]

3.2. CDKN2A and CDKN2B genes: CDKN2A/2B genes (cyclin-dependent kinase inhibitor 2A/2B) encode several proteins. These proteins normally regulate the division of pancreatic cells. Mutations in the CDKN2A/2B genes are usually associated with type 2 DM. Similarly, HHEX

gene, IGF2BP2 gene, and SLC30A8 Gene, are also found to be associated with type 2 diabetes. [17]

Monogenic forms of diabetes mellitus diagnosis are closest to meeting all criteria for a perfect diagnostic test as it defines a discrete subgroup giving insights into etiology, prognosis, and precise treatment response. In GCK-MODY (MODY2), it is established that patients do not require, or respond to, oral medication. Other MODY diagnoses (HNF1A [MODY3], HNF4A [MODY1] and ABCC8 [MODY12]), are sensitive to the glucose-lowering effects of sulfonylureas.The criteria apply to the proband (i.e. the 1st member of a family with diabetes mellitus to be tested). Once a genetic diagnosis of monogenic diabetes has been confirmed in the proband, other family members can be eligible for testing of the familial variant. [18, 19,20]

3.3. The following features suggest a diagnosis of a GCK (glucokinase) mutation[20, 21, 22]:

A) The fasting hyperglycemia is ≥5.5 mmol/l (98% patients), persistent (at least three separate occasions) and stable over a period of months or years.

B) HbA1c is typically just above the upper limit of normal and rarely exceeds 7.5%.

C) In an OGTT (oral glucose tolerance test) the increment [(2-hour glucose) − (fasting sugar or glucose)] is small (<3 mmol/l). An increment of 4.6 mmol/l is often used to prioritize testing and corresponds to the 90th centile.

D) Parents may have type 2 diabetes mellitus with no complications or may not be diabetic. On testing, one parent will usually have a mildly raised fasting blood sugar (range of 5.5–8 mmol/l) unless the mutation has arisen de novo. Testing of apparently unaffected parents' fasting sugar is essential when considering a diagnosis of a glucokinase mutation.

3.4. The following criteria identify when GCK (glucokinase) testing is appropriate [21, 22, 23]:

A) Persistently raised fasting blood sugar in the range of 5.5–8 mmol/l before, during and after pregnancy.

B) An increment of <4.6 mmol/l on at least one OGTT (either during or after pregnancy).

C) A parent may have mild type 2 diabetes but often this has not been detected and so the absence of family history should not exclude the diagnosis.

3.5. The clinical characteristics of patients with HNF1A mutations include[22-26]:

A) Young-onset diabetes (typically before 25 years of age in at least one family member).

B) Non-insulin-dependent outside the normal honeymoon period (3 years), like, not developing ketoacidosis in the absence of insulin, good glycemic control on less than the usual replacement dose of insulin, or detectable C-peptide measured when on insulin with glucose >8 mmol/l.

C) Family history of diabetes (at least two generations). This may be insulin treated and considered to be type 1 diabetes or type 2 diabetes mellitus. At least two individuals within the family would typically be diagnosed in their 20s or 30s. There may also be an affected grandparent, although often these are diagnosed after 45 years. OGTTs (oral glucose tolerance test) in early stages tend to show a very large glucose increment, usually >5 mmol/l. Some individuals may have a normal fasting level but a value within the diabetic range at 2 hours.

D) The absence of pancreatic islet cell autoantibodies.

E) Glycosuria at blood sugar levels <10 mmol/l is often seen, as these patients have a low renal sugar threshold.

F) High sensitivity to sulfonylureas resulting in hypoglycemia despite poor glycemic control before starting sulfonylureas.

G) Several features suggesting monogenic diabetes rather than a diagnosis of young-onset type 2 diabetes should be considered like, no marked obesity or features of insulin resistance in diabetic family members, absence of acanthosis nigricans and whether the family is from an ethnic background with a low prevalence of type 2 diabetes mellitus like of European descent.

The cost of performing molecular genetic testing is high and universal testing is not cost-effective for type 2 diabetes, especially in developing countries with huge prevalence rates. It is thus, necessary to limit testing to those most likely fulfill the diagnostic criteria.

4. Precision nutrition and exercise for DM and HT:

Even though dietary advice and lifestyle changes like regular practice of yoga, pranayama and meditation, and exercise, are generally prescribed as first line of mainstay therapies to diabetic and hypertensive patients, we need to apply precision methodology in certain set of patients considering nutrition genetics and exercise genetics to achieve accurate target goals. However, currently not much scientific data is available regarding nutrition and exercise genetics.[27-30]

5. Conclusion:

Precision medicine in diabetes and hypertension management can be useful because more information about an individual allows us to be more precise in our approach. Currently, precision medicine can be applied as patient centric, individualized and cafeteria approach in healthcare system. However, we need to use precision data pertinently for patient benefit because still there is need for universal standards for clinical readiness, including consideration of cost-effectiveness, health equity, predictive accuracy, liability, and accessibility.

Ethical clearance: As this is a commentary/Opinion article, and no human/animals are experimented, hence, ethical clearance is not required.

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