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Short Communication

Precision Diabetes - Genes Lead the Way!

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Diabetes, the sugary health challenge, is growing fast in 21st century by almost tripling its count over the past 20 years [1,2]. Diagnosis, monitoring and therapy of several diseases, including diabetes, have transitioned to individualized models of care shifting away from typical 'one size fits all' approach. Consequently, precision medicine grabs limelight globally, with a promising role in diabetes care [3,4].

Precision medicine in diabetes assures a reduction in uncertainty through effective therapies that are less burdensome with a fewer adverse outcomes. Subsequently, there is an improvement in the quality of life and a reduction in the risk of premature death [5].

According to Dr.Mohan's Diabetes Specialities Centre, precision proposes customization of health care tailored to the individual level, as diagnosis and treatment modalities are selected not only on the basis of generic symptoms and health history but also considering specific risk factor profile obtained from genetic assessment.

The following perspectives help us understand the need for precision medicine in diabetes.

Interindividual differences in response to hypoglycaemic drugs

Type 2 diabetes/T2D is a heterogeneous disease where there is subjective response to therapeutic modalities. Recent advances have helped to postulate valid reasons for such differential responses to treatment amongst subgroups with T2D. Vital biological pathways of diabetes such as β-cell dysfunction and lipodystrophy might respond differently to their target drugs including glucagon-like peptide 1 receptor agonist (GLP-1RA), sulfonylureas/SU, Dipeptidyl peptidase-4 inhibitors (DPP4i), and thiazolidinediones [5].

Though type 2 diabetes shows polygenic inheritance, its greatest susceptibility in varied populations is conferred by the TCF7L2 gene. The TCF7L2 gene encodes an active transcription factor of beta cells which belongs to the Wnt signaling pathway. This gene has been implicated in determining the response to several oral antidiabetic agents (OADs). For example, the T allele of rs7903146 (single nucleotide polymorphism/SNP) in the TCF7L2 gene showed higher frequency amongst type 2 diabetics who poorly responded to sulphonylureas (SU)[23]. Similarly, carriers of the risk allele rs12255372 T/T were less likely to respond to SU than carriers of G/G [6,7].

Genes such as pore-forming (Kir6.2, KCNJ11) and regulatory (SUR1, ABCC8) subunits of the K_{ATP} channel influence various aspects of glucose metabolism such as β-cell K-ATP channel modulation, insulin production and pancreas development. Scientific evidence supports the role of risk variant (E23K/S119A) in the KCNJ11/ABCC8 gene in increasing the glycemic response to sulfonylureas; in contrast, the TCF7L2 diabetes risk variant reduces glycemic response to sulfonylureas [5,8,9].

PPARγ (peroxisome proliferator-activated receptor gamma) activation induces the expression of genes involved in the insulin signaling cascade. This gene also finds importance in adipocyte and lipid metabolism.The PPARG Pro12Ala diabetes risk variant has been associated with reduced glycemic response to thiazolidinediones [10,11].

Interpreting HbA_{1c} in Diagnosis and Monitoring

The HbA_{1c} reading depends on factors that impact the hemoglobin levels, red blood cell stability and average glucose values. Genetic testing can reveal unsuspected variants that alter HbA_{1c} [5]. For instance,

- 8% of the white population carrying two loss-of-function variants in the cytochrome P450 family 2 subfamily C member 9 (CYP2C9) gene exhibit a 3.4 times higher likelihood of achieving HbA_{1c} target due to reduced sulfonylurea metabolism and its increased serum concentrations. In genes such as SLCO1B1 and CYP2C8, their genotypes which affect the hepatic uptake and metabolism of rosiglitazone can alter glycemic response (HbA_{1c}) by as much as 0.7% [5,12,13].
- Glucose transporter 2 or the solute carrier family 2, member 2 (SLC2A2) refers to the transmembrane carrier protein which enables protein-facilitated glucose movement across the cellular membrane. In the SLC2A2 gene, a noncoding variant (rs8192675) reduces the expression of its transporter in the liver, intestine and kidneys. The 'C' allele of this variant increases the response to metformin. Additionally, obese individuals carrying two copies of the C allele had an approximate 1.55% reduction in the HbA_{1c} levels compared to a reduction of nearly 1.1% in those without the C allele. Though this looks just a meagre difference, the genotype effect confers a difference of approximately 550 mg in the metformin dosage or an equivalent of about half the average effect of starting a DPP4i [14,15].

Precision medicine can also help predict side-effects of medications

The CYP2C9*2 allele was found to elevate hypoglycaemia risk amongst patients treated with sulfonylurea[26]. The gastrointestinal side effects of metformin relate to its interaction with the genes encoding the organic cation transporter 1 and the serotonin reuptake transporter [16,17].

Genetic testing is crucial in Neonatal Diabetes/ND

Sulfonylurea treatment in potassium channel-linked ND significantly impact the insulin secretion endogenously and is currently the preferred treatment. Early treatment of neonatal diabetes which are responsive to sulfonylurea may improve neurological outcomes. In a new born, it's a prime mandate to differentiate ND from other hyperglycemia causes such as infection, stress or insufficient insulin production (especially in preterm infants). Hyperglycemia (insulin-dependent) persisting for more than a week should raise suspicion for neonatal diabetes mellitus and prompt genetic testing [18].

Monogenic diabetes- precision medicine provides scope to ward off misdiagnosis

Most cases of monogenic diabetes remain misdiagnosed. However, a strong case scenario of precision medicine in diabetes is elucidated through the sustained glycemic response of sulfonylureas efficiently targeting the β-cell potassium channel in insulin-dependent neonatal diabetes.

In pancreas, Glucokinase/GCK enzyme plays a role in glucose-stimulated insulin secretion. Hepatic GCK is vital for glucose uptake and conversion to glycogen. A variation in this gene can cause a type of Maturity Onset Diabetes of Young (MODY2). GCK mutations cause a mild non-progressive hyperglycemia since birth. Mostly characterized as asymptomatic, and stable fasting hyperglycemia usually requiring no specific oral medication or treatment.

Other forms of MODY diagnosed based on gene variants such as HNF1A (MODY3), HNF4A (MODY1) and ABCC8 (MODY12) are acutely sensitive to the glucose-lowering effects of sulfonylureas. The HNF-1A protein regulates the gene activity which is crucial for the growth and development of pancreatic beta cells that produce and release insulin. In pancreatic beta cells HNF4A directly activates insulin gene expression.

However, unless the diagnosis is precise, these therapeutic benefits are lost [5].

Diabetes is regarded as one of the most serious public health challenges of the 21st century. Response to hypoglycemic therapy may actually be related to one's genotype. Thus, understanding relevant genes may help in identifying individuals at-risk of developing a disease alongside guiding in suitable treatment regimens. Pharmacogenetics combines genotypic and phenotypic factors to develop personalized care in various pathophysiological subgroups of persons with diabetes. Personalized medicine finds wider utility in monogenic (especially MODY and Neonatal Diabetes) than in polygenic, diabetes.

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