From Individualized to Personalized Medicine in Diabetes: An Expert Overview

Viswanathan Mohan¹, Ashok Kumar Das², Jagat Jyoti Mukherjee³, Krishna Seshadri⁴, Sujeet Jha⁵, Sanjay Kalra⁶

Abstract

Personalized medicine is an individualized and stratified approach to the management of a disease. Personalized medicine can reform the prevention, prediction, and management of diabetes. Use of genetic information in polygenic and monogenic forms of diabetes can help to identify genetic variants and reclassify patients into pathophysiological subgroups. Targeted diagnostic, preventive, and therapeutic interventions can be defined for these groups for effective management of diabetes. 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 Maturity Onset Diabetes of the Young (MODY) and Neonatal Diabetes Mellitus [NDM]) than in polygenic, diabetes. The most frequently mutated genes in MODY include HNF1A and HNF3A. The common genes responsible for NDM include KCNJ11 and ABCC8 (SUR) genes. These genes influence various aspects of glucose metabolism such as β-cell K-ATP channel modulation, production of insulin and development of pancreas. The Madras Diabetes Research Foundation has fostered research in personalized medicine for diabetes based upon genetic information and has developed a national registry for neonatal diabetes and other monogenic form of diabetes.

Personalized medicine in type 1 and type 2 diabetes

Genetic mutations and polymorphisms lead to heterogeneity in disease characteristics and response to treatment in both type 1 and type 2 diabetes. Candidate gene analysis and genome wide scanning have identified molecular markers for the risk, development, progression, and treatment response in diabetes. Type 1 diabetes is characterized by an autoimmune response-mediated loss of β cells in the pancreas. Individuals with glutamic acid decarboxylase or islet autoantibodies and those with a family history of type 1 diabetes are at a higher risk of developing type 1 diabetes. More than 40 genetic loci, linked to autoimmunity and β cell survival, have been described for type 1 diabetes. Variants in the HLA class II genes, carrying codes for polymorphic antigen-presenting proteins, account for almost 50% of
the genetic risk of type 1 diabetes. Examples of other genes include INS, PTPN22, ERBB3, CCR5, IL7R, IL2RA, and PRKCQ. Specific HLA class II alleles and haplotypes are associated with progression of disease in type 1 diabetes and describe the acute-onset, fulminant, and slowly progressive variants of the disease. Genetic variants also explain the differential requirements of immuno-suppression in type 1 diabetes.

Insulin secretion and responsiveness in type 2 diabetes are influenced by genetic determinants. Variants in about 23 genes associated with type 2 diabetes can potentially impact diagnostics, therapeutics and prognostics, and treatment decisions. Genes have been identified for reduced β cell mass (HHHEX, CDKN2A/CDKN2B), β cell dysfunction ( KCNJ11, TCF7L2), insulin resistance (PPARG, ADAMTS9), and altered body mass index (FTO). Polymorphisms in the transcription factor 7-like 2 (TCF7L2) gene are associated with an increased risk of type 2 diabetes. Genetic predispositions might also influence the development and progression of macrovascular and microvascular, in diabetes. These can guide personalized decisions in the management of both type 1 and type 2 diabetes.

Protein kinase C-β1 (PRKCB1) gene has been associated with end-stage renal disease in type 2 diabetes. Polymorphisms in the angiotensin I converting enzyme (peptidyl-dipeptidase A) 1 (ACE) gene influence the incidence of diabetes nephropathy and response to ACE inhibitors in person with diabetes. Independent of glycemic control, the ACE II genotype is associated with a lower incidence and the I/D or DD genotypes with a higher incidence of nephropathy in patients with diabetes. When compared to the I/D and DD genotypes, the II genotype has a better antiproteinuric response to ACE inhibitors. While the population impact of genes on the phenotypic expression of diabetes is low, it is expected that at an individual level genetic polymorphism will impact the response to different therapies.

The focus of personalized medicine in type 2 diabetes has been gradually shifted from characterizing subgroups based on molecular architecture alone to subgroups based on differential treatment responses. Simple clinical information, such as age, gender, body mass index (BMI), and glomerular filtration rate, can be used to calculate the probability of glycemic response to anti diabetic medication. This may be supplemented with other biomarkers such as C-peptide) or the omics data such as pharmacogenomics to predict response to a particular class of antidiabetic medication or its safety profile. Gender and BMI have been used to stratify response to therapy with thiazolidinediones (obese females) and sulphonylureas (slim males). Novel subgroups of type 2 diabetes have been defined recently by a data-driven cluster analysis with newly diagnosed diabetes (n=8980) based on six variables: age at diagnosis, BMI, HbA1c, homoeostatic model assessment 2 estimates of β-cell function, insulin resistance and glutamate decarboxylase antibodies. Five clusters were defined with different patient characteristics and risk of diabetic complications: Severe autoimmune diabetes (SAID), Severe insulin-deficient diabetes (SIDD), Severe insulin-resistant diabetes (SIRD), Mild obesity-related diabetes (MOD), and Mild age-related diabetes (MARD). These clusters included 65, 18%, 15%, 22%, and 39% patients, respectively in white Caucasians (Europeans). One interesting observation is the identification of lower risk clusters MOD and MARD. It is possible that a less aggressive approach may be warranted in this group if these results are applicable to the general population. However, Personalized medicine in type 1 and type 2 diabetes is still in its infancy and is mostly limited to monogenic forms of diabetes.

### Personalized medicine in monogenic diabetes

Genetic architecture defines specific subgroups with typical phenotypes and treatment response in monogenic diabetes. Neonatal diabetes

Neonatal diabetes mellitus (NDM) has been defined as antibody negative, insulin-sensitive hyperglycemia that is diagnosed within the first six months of life. NDM is predominantly monogenic and is of two types: Transient neonatal diabetes (TNDM) and permanent neonatal diabetes (PNDM). TNDM is characterized with remittance before one-year of age followed by relapse in adolescence and persistence throughout life, whereas PNDM is permanent. About 10% patients with NDM have syndromes and pancreatic aplasia (PTF1A, FOXP3, EIF2AK3, HNF1B, and IFP1). Genes responsible for the development of NDM include KCNJ11 (30%), ABCB8 (20%), IDDM2 (20%), PTF1A, and FOXP3. These genes influence various aspects of glucose metabolism such as β-cell K-ATP channel modulation, production of insulin, pancreatic development, and control of immune response. Genes like GATA4, RFX6 and IER3IP1 are associated with heart defect; gall bladder atresia and microcephaly in NDM. In the experience of the Madras Diabetes Research Foundation (MDRF), the commonest mutations in NDM are, sulphonylureas receptor (SUR or ABCB8) and KCNJ11 genes while rarely they could be in INS genes or other rare mutations.

Patients of NDM with mutations in genes KCNJ11 and ABCB8 show excellent glucose control with high-dose sulfonylureas. These patients have no additional risks of hypoglycemia and may also show an improvement in neurological functions with sulfonylureas therapy. Patients with TNDM with 6q24 methylation defect respond to low-dose sulfonylureas. In a study of genetic screening of NDM in India, carrying the KCNJ11 (Cys42Arg, Arg201Cys) and ABCB8 (Val86Ala, Asp212Tyr) mutations from India reported a fall in fasting plasma glucose and glycated hemoglobin (HbA1c) after switching over from insulin to oral sulfonylurea.

### Maturity onset diabetes in the young

Maturity onset diabetes in the young (MODY) accounts for about 5% of all person with diabetes. MODY has an early age at onset (<25 years) and an autosomal dominant inheritance. MODY may be controllable without insulin for at least 5 years after which patients need insulin therapy. The major phenotype is impaired insulin secretion due to an autoimmune response to beta cells. Obesity and insulin resistance are usually not seen. MODY is predominantly monogenic. The most common MODY genes include those encoding glucokinase (GCK), hepatic nuclear factor 1 alpha (HNF1A) and hepatic nuclear factor 4 alpha (HNF4A). These genes explain the variations in clinical course of MODY. GCK-MODY is associated with a stable and high fasting glucose whereas the genes HNF1A, HNF4A and HNF1B show progressive deterioration of glucose over time.
but respond to low dose sulfonylurea agents\(^5\) HNF1B-MODY is associated with \(\beta\) cell development defect, exocrine pancreatic insufficiency, and developmental defects in other organs especially in the kidney. Patients with this gene architecture require insulin for treatment. HNF1A-MODY and HNF4A-MODY are associated with glycosuria and neonatal hypoglycemia, respectively. GCK –MODY could explain 5% of the gestational Diabetes Mellitus (GDM) cases in various population. it is imperative to identify pregnant female harboring GCK mutation,since it has major clinical implication and its management is different The Madras Diabetes Research Foundation has been leading the research in MODY in India and has been reporting on the genetics of all forms of MODY for last 20 years including HNF1A (MODY 3),\(^25\) HNF4A (MODY 1),\(^26\) GC-MODY (MODY 2),\(^27\) HNF1B (MODY 5).\(^28\) The group has Recently reported the largest and more comprehensive report on all the 14 MODY subtypes and has shown that except MODY 10 (INS Gene) all other MODY subtypes are present among Indians. They have also reported on a possible novel MODY subtype with a mutation in the NKX6-1 gene in addition to possible other novel MODY genes.\(^22\) Christian Medical College, Vellore has also studied patients with MODY in India and have reported NEUROD1, PDX1, PAX 4, INS and BLK mutations along with the common mutations identified among early onset diabetes patients and pregnant women.\(^7\),\(^30\)

In a genomic analysis of 152 clinically diagnosed cases of MODY at the Madras Diabetes Research Foundation, HNF1A (7.2%) and ABCC8 (3.3%) were the most frequently mutated MODY genes. In addition, variants were identified in RFX6, WFS1, AKT2, NKX6–1.\(^22\) The Christian Medical College, Vellore has developed a cost-effective and accurate Next-Generation Sequencing (NGS)-based strategy to screen for MODY mutations.\(^31\) Specifically studying GCK gene in women diagnosed with GDM, at Max Healthcare reported a novel pathogenic variant.\(^32\) In collaboration with Madras Diabetes Research Foundation, this group further compared GCK variants in women affected with GDM with the healthy controls and found no association.\(^33\)

The MDRF has developed a national registry for neonatal diabetes and other monogenic form of diabetes (www.neonataldiabetes.in).

**Personalized medicine in blood glucose management**

Response to treatment in diabetes is determined by the genetic architecture of patients. Pharmacogenetic studies aim to define biomarkers for predicting response to treatment in diabetes. Genetic variants with single nucleotide polymorphisms (SNPs) can explain the variations in the pharmacokinetics and pharmacodynamics of various drugs in different patient populations.

Variants of genes that code the drug targets, transporters, and metabolizing enzymes for various oral hypoglycemic agents can influence the response to these therapies (Table 1). An understanding of these genetic compositions and their impact on the drug metabolism can help to tailor treatment for high efficacy and safety. Better response to sulfonylureas is seen in patients who are K-allele carriers. Similarly, the carriers of CC genotype of ABCC8 show better response to sulphonylureas when compared to CT and TT genotype patients.\(^34\) Metformin dose needs to be increased in people with diabetes with SLC22A1 gene and decreased in those with SLC22A2 gene. Diabetic patients with SLC47A1 gene may have decreased glucose lowering effect of metformin.\(^35\) DPP4 inhibitors are more effective in patients with KCNJ11 gene polymorphisms and less effective in patients with TCF7L2 gene polymorphisms. The CTRB1 and CTRB2 genes produce chymotrypsin that reduces the efficacy of incretin therapy.\(^36\) Glucose-lowering effect of pioglitazone is partly ascribed to the polymorphisms associated with PPAR\(\gamma\) gene. Rosiglitazone shows a markedly increased effect in patients with the AA genotype of leptin G-2548A.\(^37\)

**Personalized medicine in glucose monitoring and follow-up**

Continuous glucose monitoring (CGM) for glucose values, glycated hemoglobin (HbA1c), and hypoglycemic episode can provide a more personalized approach to optimizing the management of diabetes.\(^38\) Small, accurate, easy to use systems, for example, the flash glucose monitoring system, Free Style\(^5\) Libre\(^\text{TM}\) (Abbott Diabetes Care, Alameda, CA), allow real time monitoring of blood glucose values. It has become easier to identify glucose variability.\(^39\)-\(^41\)

**Personalized medicine in the management of complications**

Diabetes management includes the management of its complications as well. One such chronic complication is painful neuropathy Carbamazepine commonly used for the relief of painful sensory neuropathic symptoms, is associated with hypersensitivity reaction including Steven-Johnson syndrome and toxic epidermal necrolysis. Both carry a mortality risk as high as 30%. It has been found that the risk of these life threatening complications is limited to individuals with HLA allele B1502.\(^16\) Thus, precision medicine can help in identifying persons at high risk of adverse events, and in matching therapy to patient.

Another example of patient centric precision medicine relates to the choice of an anti-platelet medication after acute coronary syndromes. Based upon the function of CYP2C19* 2 and PYR1 gene variants, all individuals can be classified as ultrafast, fast, intermediate or slow metabolizers of clopidogrel.\(^17\) Slow and intermediate metabolizers respond well to this drug, and benefit from its use after acute coronary syndromes. Fast and ultrafast metabolizers, however, do not respond to clopidogrel, and are better treated with newer platelet aggregation inhibitors like prasugrel. Precision medicine not only allows appropriate choice of therapy but also, optimization of outcomes.

After 40 years of research, MDRF has brought Precision Diabetes to India.\(^4\),\(^20\)-\(^24,26\),\(^39\)-\(^42\) Mohan and colleagues have summarized the current role and place of precision diabetes (Table 2).

**Barriers to Personalized Medicine in Diabetes**

Despite all the potential advantages of personalized medicine (precision diabetes), there are several challenges that need to be addressed.\(^5\)

1. A lot remains unknown in the field of type 1 and type 2 diabetes regarding pathophysiology, genetic variation and pharmacogenetics. As such personalized medicine in diabetes is still in its infancy

2. The cost of genetic analysis for currently known variants is high. Unless this cost comes down, it
3. Careful clinical phenotyping is necessary before selecting patient for genetic testing for monogenic diabetes to make it cost effective. For example, if MODY is suspected in a person with diabetes, genetic testing can be considered if the auto-antibodies are negative and the C-peptide shows partially preserved beta cell function and there is a family history of diabetes. In the case of neonatal diabetes, it is easier, because all children with age at onset of diabetes below 6 months can be considered for genetic testing.

4. Awareness about monogenic diabetes is still very low

Summary

Personalized medicine is a revolutionary transformation in medicine with emphasis shifting from ‘one size fits all’ to personalized treatment. Advances in personalized medicine will help to predict susceptibility of the drug, improve disease detection, preempt disease progression and also preventing adverse effects of drugs which occur because of genetic variations. In the field of diabetes, currently personalized medicine is mainly applied in the treatment of monogenic forms of diabetes like MODY and neonatal diabetes. However, in the years to come, this may well extend to type 2 diabetes and type 1 diabetes as well.

It can help to reduce the time, cost, and failure rate of pharmaceutical trials in clinical research. The application of molecular genetic approaches to research in diabetes will provide new opportunities for progressively more targeted, and hopefully, more effective treatments. In routine clinical practice, application of personalized medicine can lead to effective drug therapy with better patient adherence.

Acknowledgments

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for
Table 2: Application of precision diabetes

2. Genotype of type 2 diabetes
3. Treatment:
   - Mild nonprogressive fasting hyperglycemia (GCK MODY) - Can stop all antiandrogen medications and treat with diet and exercise alone.
   - Familial diabetes with affected parent (HNF 1A or HNF 4B MODY) - Respond to low dose sulfonylurea
   - Neonatal diabetes (KCNJ11 or ABCC8 mutation) - Respond to high dose of sulfonylurea.
4. Monitoring:
   - Use of continuous glucose monitoring (CGMS) and ambulatory glucose profile (AGP) to study glycemic variability and response to therapy.

References


authorship for this manuscript, take responsibility for the integrity of the work, and have given final approval for the version to be published.

Medical writing and editorial support in the preparation of this article was provided by Mediception Science Pvt. Ltd. Support for this assistance was funded by Novo Nordisk.