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Editorial

Precision diabetes: Where do we stand today?

Diagnosis, monitoring and therapy of several diseases have shifted from a 'one size fits all' approach to a more individualized model of care. The term 'precision medicine' has therefore attracted wide attention worldwide, and one of its emerging applications is in the care of individuals with diabetes mellitus.

The concept of 'personalized medicine' is not new; clinicians have been tailoring treatment to individual patient characteristics from time immemorial[1]. Blood grouping and cross-matching before blood transfusion is also an example of precision or personalized medicine. However, today the term 'precision medicine' refers to a narrower aspect of personalized medicine that is backed up by robust scientific evidence. Advances in several wide-ranging fields such as genomics, epigenomics, transcriptomics, proteomics, metabolomics and the understanding of the gut microbiome have enabled the wider application of precision medicine to several diseases, particularly cancer. In diabetes care, the scope of precision diabetes applies both to the more common forms of diabetes such as type 1 and type 2 diabetes (T2D) as well as the relatively rare subtypes of diabetes such as monogenic diabetes. Precision diabetes also finds practical applications in the context of continuous glucose monitoring (CGM). The Table summarizes the current concepts of precision diabetes.

Precision medicine in type 2 diabetes (T2D)

T2D is a heterogeneous disease, and all patients with T2D do not respond equally to commonly used therapeutic modalities. Recent advances have helped to postulate the reasons for this differential response to treatment in various subgroups of patients with T2D.

While T2D has a polygenic inheritance, the *TCF7L2* gene has been shown to confer the greatest susceptibility to T2D in a wide variety of populations. It has now been shown that this gene may also, at least partially, determine the response of patients to various oral antidiabetic agents (OADs). For instance, the rs7903146T allele of the *TCF7L2* gene was more frequent in patients with T2D who failed to respond to sulphonylureas (SU)[2]. Similarly, carriers of the risk allele rs12255372 T/T were less likely to respond to SU than carriers of G/G[3]. Differences were also observed in the response to some dipeptidyl peptidase-4 inhibitors (DPP-4 i)[4]. Variants in the *SLCO1B1* (encoding the hepatic cationic transporter OATP1B1) and *CYP2C8* genes (encoding the drug-metabolizing enzyme CYP450 C8) have been shown to have an impact on the therapeutic response to the thiazolidinedione OAD, rosiglitazone (but not to pioglitazone)[5].

Genomic markers are not the only predictors of response to OADs; in a study from the UK database, the presence of markers of insulin resistance such as higher fasting C-peptide, HOMA2 insulin resistance and higher triglycerides were shown to be associated with attenuated response to DPP-4 inhibitor therapy[6].

Precision medicine can also help predict side-effects of medications. The CYP2C9*2 allele was found to increase the risk of hypoglycaemia in patients treated with SU[7]. The gastrointestinal side effects of metformin have been linked to the interaction between the genes encoding the organic cation transporter 1 and the serotonin reuptake transporter[8].

A recent study from Scandinavia has divided patients with T2D into five novel 'clusters' based on the age of onset, glycated haemoglobin (HbA_{1c}), insulin sensitivity, β cell function and body mass index. These clusters consist of some 'mild', and some 'severe', phenotypes of diabetes[9]. Preliminary analyses indicate that individuals in the severe insulin-deficient diabetes cluster are more prone to retinopathy, and those in the severe insulin-resistant diabetes cluster,

Table. Application of precision diabetes

Polygenic diabetes
Type 2 diabetes:
Prediction of development of diabetes
Response to therapy
Prediction of development of complications
Identifying clusters of type 2 diabetes
Type 1 diabetes:
β cell function- Completely absent/partially preserved
Insulin autoantibodies- Present/absent
Risk of complications- Low/high
Monogenic diabetes:
Maturity onset diabetes of the young (MODY)
Neonatal diabetes (onset of diabetes below six months of age)
Congenital hyperinsulinemic hypoglycaemia
Monitoring and follow up

to nephropathy. However, these clusters may vary in different populations; for example, South Asians have an increased susceptibility to T2D despite being relatively leaner and also get T2D at a much younger age. Hence, their T2D clustering may well be different.

Precision medicine in type 1 diabetes (T1D)

The role of precision medicine in T1D is not well-defined. While patients with T1D vary with respect to their pancreatic autoantibody profile and the rate of β cell destruction, there have, thus far, been no studies linking these differences to implications in diagnosis and treatment of T1D. Moreover, it is well known that there are some individuals (and families) where complications set in early, even with short duration of diabetes. Conversely, there are others who despite poor control of diabetes for decades, seem to be protected from the complications of diabetes. This is another field in precision diabetes research.

Precision medicine in monogenic diabetes: Now a reality!

The term 'Monogenic diabetes' refers to types of diabetes which are due to a single gene mutation. The monogenic forms of diabetes can be termed the 'poster child' of precision diabetes. While there are several phenotypes of monogenic diabetes, three in particular have demonstrated the utility of a precision approach to diagnosis and management. These are maturity-onset diabetes of the young, neonatal diabetes and congenital hyperinsulinemic hypoglycaemia.

Maturity onset diabetes of the young (MODY)

While there are at least 14 known forms of MODY, HNF 1α and 4 α mutations (MODY 3 and MODY 1) are the most common forms. Patients with these subtypes of MODY are usually diagnosed before the age of 25 yr, they are lean and do not have any features of insulin resistance. They are therefore, often misdiagnosed as T1D and initiated on life-long insulin therapy. However, they have a strong family history of diabetes (across three or more generations) and exhibit preservation of β cell function beyond the honeymoon phase. Diagnosis of the precise mutation by genetic testing enables transitioning of these patients to SU, as they have been found to have good response to even low doses of these drugs[10].

Individuals with glucokinase mutations (MODY 2) exhibit stable fasting hyperglycaemia from birth, with minimal increment in glucose levels after a meal, and relatively low HbA_{1c} levels. These patients are at very low risk of diabetes complications and treatment of the mildly elevated glucose levels is neither warranted nor beneficial. Diagnosis of this mutation can enable the cessation of treatment in these patients, many of whom might have been misclassified as T1D or T2D[10].

There are at least a dozen types of MODY each with its own characteristic phenotype. We have recently described the profile of MODY in south India and also a novel mutation in *NKX6-1* gene which could be a novel form of MODY[11].

Neonatal diabetes mellitus (NDM)

NDM has been defined as autoantibody negative, insulin sensitive hyperglycaemia that is diagnosed within the first six months of life. NDM is predominantly monogenic. There are two types of NDM: transient NDM (TNDM) and permanent NDM (PNDM). In the TNDM variety, the diabetes disappears before the first birthday but may reappear in some in adulthood. In PNDM variety, the diabetes persists throughout life. Therapy of patients with neonatal diabetes offers the most dramatic example of the benefits of precision medicine. Children with NDM have mutations in the genes encoding the ATP-sensitive potassium (K-ATP) channel on the cell membrane of the β cell, which is one of the key players in insulin secretion. These children are typically diagnosed as T1D and initiated on insulin therapy, but the response is often suboptimal. Many of

these children with mutations in genes encoding the Kir 6.2 and SUR subunits of the K-ATP channel can be successfully weaned off insulin and transitioned to SU[12]. While the doses of SU used are often higher (on a per kg basis) than those used in HNF mutations or T2D, the response is excellent and has now been shown, in a large multinational cohort, to be maintained over a period of 10 years[13].

Congenital hyperinsulinemic hypoglycaemia

Congenital hyperinsulinemic hypoglycaemia is, in a sense, the opposite of neonatal diabetes. Here, neonates present with features of persistent hypoglycaemia. While some respond to diazoxide, some may need a subtotal pancreatectomy[14]. Genetic testing helps to accurately diagnose and treat these children.

Precision diabetes: Its role in continuous glucose monitoring (CGM)

The use of CGM systems has been advocated as a useful tool for studying day-to-day glucose variability, thereby providing a personalized snapshot of the patient's glycaemic profile. CGM is perhaps one of the best examples of personalized medicine available today as it enables detection of the patient's blood glucose patterns at a glance and helps the patient and clinician come to a shared decision based on the information obtained[15]. The ambulatory glucose profile (AGP) has become very popular in India[16]. The physicians are now able to make adjustments based on the AGP readings.

In summary, current guidelines for the management of diabetes emphasize an 'individualized approach' to choosing therapy. While these guidelines suggest using patient characteristics such as age, duration of diabetes, HbA_{1c} levels and presence of comorbidities and drug characteristics such as efficacy, side effects and cost to guide therapy, application of the precision approach can help provide a robust scientific basis for such choices. Unfortunately, many of the tools used in precision medicine are still very expensive and unavailable in many parts of the world including India. It is to be hoped that with advances in technology, these modalities will increasingly be made available and affordable to clinicians and patients so that the dream of personalized diabetes care can come to fruition in the near future.

***Conflicts of Interest*:** None.

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