Precision medicine in diabetes

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Abstract

This review presents the dynamic and fast growing concept of precision medicine in a simple and succinct manner. It describes the potential of precision medicine in diabetes praxis, under three headings: diagnosis of type of diabetes, choice of pharmacotherapy for glucose lowering, and management of complications of diabetes. This review should make the scope of precision medicine easy to understand for the practicing physician.

Keywords: Genes, metformin, monogenic diabetes, repaglinide, sulfonylureas, incretins.

Introduction

Diabetes is a multifaceted and multifactorial disease. In spite of multipronged means of treatment, the syndrome still defies management and control.

Multilayered strategies have been utilized to improve outcomes in diabetes care. These include concepts such as the glucophenotype and other objective matrices, which help objectify choice of glucose lowering therapy. There is a limit, however, to the utility of such phenotypic or glucometric decision making. This is reflected in the poor rates of glycaemic control that we are able to achieve for our patients.

Precision medicine

Precision medicine is one way of improving the diagnosis and treatment of diabetes.[1] Precision medicine incorporates information about the genetic makeup of an individual, while planning screening and therapeutic interventions for management of diabetes and its complications.[2,3] Thus, it becomes part of the overarching concept of personalized or individualized medicine. Personalized or individualized medicine focuses, apart from genetics-based precision medicine, on the psychosocial and dietary components of management as well.[4]

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Pharmacogenomics

Precision medicine has received a fillip in recent years because of advances in the field of pharmacogenetics and pharmacogenomics. Pharmacogenetics and pharmacogenetics are two terms which are used interchangeably. However, genetics aim to find a genetic explanation for the inter-individual variation in response to drugs, as well as susceptibility to adverse drug reactions. Genomics, on the other hand, uses genome wide association studies in order to assess infinite genetic polymorphisms. This approach aims to discover biomarkers for application of precision based therapy.[5]

Scope of precision medicine in diabetes

We discuss the scope of precision medicine in diabetes under three headings, as follows:

Diagnosis of type of diabetes

Not all adulthood diabetes is type 2 diabetes. Neither is all childhood diabetes type 1 diabetes. Precision medicine has facilitated the discovery of various monogenic anomalies which cause various forms of monogenic diabetes. These include different types of MODY (maturity onset diabetes of young) and neonatal diabetes mellitus (NDM). Most infants with onset of diabetes at an age <6 months have NDM.

It is important to diagnose the type of diabetes, because this has a direct bearing on choice of treatment. Some forms of MODY can be managed with lifestyle modification, and sulfonylureas, while NDM due to the KCNJ11 gene defect can be treated with low doses of glibenclamide.[6]

Choice of glucose lowering therapy

Various drugs are metabolized by specific pathways, such as the cytochrome P450 (CYP) 2C9 pathways. Gain-of-function and loss-of-function mutations in a metabolizing pathway can hasten and reduce the metabolism of drugs which depend upon that particular pathway. This is seen in most secretagogues, and may explain why there is 'primary failure' of some sulfonylureas in type 2 diabetes.[7,8]

Repaglinide is metabolized by CYP2C8 and CYP3A4,[9,10]

while most other secretagogues (glimepiride, gliclazide, nateglinide) are metabolized by CYP2C9. This implies that a person who does not respond to modern sulfonylureas may benefit from a therapeutic trial with repaglinide, and vice versa. Loss-of-function mutations in these pathways may predispose the individual to hypoglycaemia. Precision medicine can facilitate optimization of glucose lowering by helping choose appropriate treatment and dose titration. Genetic influence on insulin secretion also interacts with free fatty acids, as evidenced by data on rs1573611 in FFAR1.[11]

A similar situation occurs with metformin. The pharmacokinetics of metformin depends upon transport proteins as well as metabolizing pathways. Any change in the function of these, including organic cation transporter 1 (OCT1) influences the response to metformin therapy.[12,13] Precision medicine, therefore, may determine whether metformin should be propagated as first treatment, in all, or only in "genetically appropriate" persons with type 2 diabetes.

Newer medications for diabetes also follow the same rules. With respect to incretin-based therapy, persons with diabetes are classified as responders and non-responders. The function of the strongest common diabetes risk variant, the single nucleotide polymorphism (SNP) rs7903146 in TCF7L2, confers resistance against the incretin effect. Individuals with the TCF7L2 gene do not respond to GLP1.[11] However, they exhibit a response (though attenuated), to linagliptin.[4] This aspect of precision medicine needs more study.

Inter-individual and intra-individual variability in the response to insulin is an unwelcome, but unavoidable hurdle of diabetes care. Though modern insulin analogues are associated with lower rates of variability,[15] these are still far from optimal. Precision medicine may offer insight in to genetic factors which influence insulin action and variability.

Management of complications

Diabetes management includes the management of its complications as well. One such chronic complication is painful neuropathy Oxcarbazepine, commonly used for the relief of painful sensory neuropathic symptoms, is associated with a significant chance of Steven-Johnson syndrome and toxic epidermal necrolysis. Both of these have a real risk of mortality. It has been found that the risk of these complications is limited to individuals with the gene HLA-B*1502.[16] Thus, precision medicine can help in identifying persons at high risk of adverse events, and in matching therapy to patient.

Another exemplar of patient centric precision medicine relates to choice of 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 and 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 thus allows appropriate choice of therapy, and optimization of outcomes.

Summary

Precision medicine is a much-talked about development in current literature. Lack of understandings creates confusion regarding the relevance and feasibility of precision medicine in diabetes. This communication explains the scope of the field in a simple, yet comprehensive manner.

It describes the potential role of genetics in diagnosing the type of diabetes, choosing initial therapy, deciding drug dosage and intensity of glycaemic monitoring, and planning treatment for complications of diabetes. Though it may not be a reality in diabetes clinics today, precision medicine should soon become a routine feature of decision making in diabetes care.

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