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A Systematic Review of the Type 1 Diabetes Mellitus and Autoimmune Diseases: Personalized Medicine in Diabetes Mellitus

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Abstract

Diabetes mellitus affects approximately 382 million individuals worldwide and is a leading cause of morbidity and mortality. Over 40 and nearly 80 genetic loci influencing susceptibility to type 1 and type 2 diabetes, respectively, have been identified. Additionally, there is emerging evidence that some genetic variants help to predict response to treatment. Other variants confer apparent protection from diabetes or its complications and may lead to development of novel treatment approaches. Currently, there is clear clinical utility to genetic testing to find the at least 1% of diabetic individuals who have monogenic diabetes. Diagnosing many of these currently underdiagnosed types of diabetes enables personalized treatment, resulting in improved and less invasive glucose control, better prediction of prognosis and enhanced familial risk assessment. Efforts to enhance the rate of detection, diagnosis and personalized treatment of individuals with monogenic diabetes should set the stage for effective clinical translation of current genetic, pharmacogenetic and pharmacogenomic research of more complex forms of diabetes.

Keywords: Monogenic diabetes; Type 2 diabetes; Pharmacogenetics; Gene environment interaction; Pharmacogenomics

Introduction

Type 1 Diabetes Mellitus (T1DM) is a chronic disease characterized by the inability of the body to produce insulin due to the autoimmune destruction of the beta cells in the pancreas. Insulin is a key anabolic hormone that has numerous effects on glucose, lipid, protein and mineral metabolisms in addition to growth. T1DM thus presents as a systemic disease characterized by the phenotype of hyperglycemia. Numerous studies have demonstrated that genetic factors contribute significantly to the development of type 1 diabetes [1].

Currently, there is little widespread implementation of personalized medicine in diabetes mellitus treatment. Diabetes mellitus encompasses a range of hyperglycemic conditions, which the American Diabetes Association (ADA) divides into four categories. The first category, Type 1 Diabetes Mellitus (T1DM), is classified as an autoimmune disease with progressive β cell destruction, leading to polyuria, polydipsia, weight loss, and hyperglycemia [2]. Individuals with type 1 diabetes eventually become completely reliant on non-endogenous insulin. In the case of true type 1 diabetes, glucose levels must be closely monitored and insulin levels individualized to maintain glucose homeostasis. It could be said that making a proper diagnosis of type 1 diabetes, including obtaining clear evidence of β cell destruction through the presence of auto islet antibodies and then prescribing endogenous insulin, represents a form of well-established personalized medicine that will not be discussed further in this review. There is also emerging evidence that oral medications including those used to treat type 2 diabetes may be effective adjunct therapies for individuals with insulin requiring type 1 diabetes. Thus, some of the findings discussed in this review may ultimately have relevance for type 1 diabetes. Finally, there are some 40 genes implicated in the complex etiology of type 1 diabetes, with currently unknown practical clinical implications [3].

Literature Review

Most diabetes is classified in the second category, Type 2 Diabetes Mellitus (T2DM), a heterogeneous group of disorders caused by some combination of insulin resistance and impairment of insulin secretion. T2DM has a range of risk factors, etiologies and clinical presentations. Progress has been made in understanding the genetic etiology of T2DM, with nearly 80 susceptibility loci identified, but the use of molecular testing to customize treatment is not yet possible [4]. Other risk factors include obesity, low activity and poor diet, sometimes referred to as lifestyle or environmental risk factors. As the knowledge base increases, the ideal implementation would use genetic testing and variant analysis to help clarify the etiology of T2DM, the appropriate therapy for the patient and possibly, susceptibility testing for at risk relatives and members of the general population. Future genetic testing may help to identify which patients with diabetes and prediabetes may benefit from specific lifestyle interventions and which may need pharmaceutical treatment as an adjunct to a healthy lifestyle [5]. Results of studies examining genetic influences on response to both behavioral and pharmaceutical interventions to prevent, delay or treat diabetes will be examined in this review.

A third category of diabetes encompasses forms with specific known genetic and non-genetic etiologies, including the at least 1% of all diabetes cases which are caused by a defect in a single gene. These varieties of monogenic diabetes are highly penetrant and often have

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similar clinical presentations to T1DM or T2DM. Monogenic forms of diabetes mellitus are the low hanging fruit in which genetic testing has already proven the ability to improve treatment, but they are currently underdiagnosed [6]. Clinical implementations for genetic diagnosis and treatment of monogenic diabetes can provide a template for translating genetic findings of T2DM into clinical practice in the future and will be discussed in that context. The fourth category of diabetes, gestational diabetes, may have etiology in common with other types of diabetes and represent expression of underlying susceptibility enabled by pregnancy induced insulin resistance.

There is still a great deal of progress to be made in the field of personalized diabetes mellitus therapy. This review will focus on the current opportunities for implementations of genetically personalized medicine in diabetes mellitus, specifically monogenic diabetes, as well as the state of current research and potential prospects for future implementation in T2DM.

In addition, T3 promotes the proliferation of pancreatic islet cells. Thyroid hormones increase hepatic glucose production by increasing hepatic expression of the glucose transporter GLUT 2 and stimulate endogenous glucose production by increasing gluconeogenesis and glycogenolysis processes. This decreases the insulin sensitivity of hepatocytes. Both lipogenesis and lipolysis are stimulated by T3 and T4. Lipolysis is largely mediated through the increase in the number of hepatic receptors for Low molecular Density Lipoproteins (LDL) and accelerating LDL clearance. Therefore, thyroid dysfunction can increase cardiovascular risk due to the interaction between dyslipidemia, increased peripheral resistance to insulin and vascular dysfunction. Hyperthyroidismis characterized by a hypermetabolic state with increased energy consumption, decreased cholesterol levels, increased lipolysis and enhanced gluconeogenesis. Patients with hyperthyroidism may be at increased risk of severe hyperglycemia and pre-existing diabetes is exacerbated by hyperthyroidism. Hyperthyroidism is a promoter of the hyperglycemic state. Due to an accelerated rate of degradation and a significant release of physiologically inactive insulin precursors, hyperthyroidism reduces the half-life of insulin. In uncontrolled Graves' disease, proinsulin levels in response to food intake are elevated.

Another mechanism that explains the relationship between hyperthyroidism and hyperglycemia is the increased intestinal absorption of glucose mediated by the excess of thyroid hormones. Thyroid hormone increases GLUT2 concentrations in the plasma membrane of hepatocytes. In addition, an increase in lipolysis is observed in hyperthyroidism. Diabetic patients with hyperthyroidism experience worsened glycemic control. Thyrotoxicosis precipitating ketoacidosis has been demonstrated. Patients with Basedow-Graves' disease who have Graves' ophthalmopathy and diabetes have a higher risk of optic neuropathy, which can lead to blindness. The treatment of hyperthyroidism with synthetic antithyroid drugs does not directly affect the blood glucose level. Corticosteroids are occasionally used for the treatment of Graves' ophthalmopathy and due to the negative effects on metabolic control; they should be administered with caution to diabetic patients with Graves' disease. Patients with diabetes who develop hyperthyroidism should be considered for a modification of their insulin therapy. Patients experiencing symptoms and clinical evidence of ketoacidosis should have their thyroid function assessed. Hypothyroidism is characterized by decreased intestinal absorption of glucose and reduced hepatic and muscular gluconeogenesis and glycogenolysis. The dysregulation of leptin action at the hypothalamus level, impairment of GLUT4 translocation, and elevation of free fatty acids are some known contributing factors to the pathogenetic process that underlies insulin resistance in hypothyroidism. Hypothyroidism in diabetic patients is successfully treated by levothyroxine monotherapy. Excessive levothyroxine therapy induced TSH suppression should be avoided because it can induce iatrogenic hyperthyroidism and cause an additional deterioration of glycemic metabolism. In individuals with hypothyroidism, LT4 replacement treatment largely normalizes the lipid profile but combination therapy with statins is frequently required to achieve improved lipid profile management.

Discussion

Pharmacogenetics of oral T2DM medications

Individuals with type 2 diabetes make up by far the greatest proportion of the population with diabetes mellitus. The first-line medication for T2DM is metformin, a biguanide medication that functions by decreasing gluconeogenesis in the liver. Secondary oral medications include sulfonylureas, meglitinides, thiazolidinediones, Glucose Like Peptide-1 (GLP-1) analogs and Dipeptidyl Peptidase-4 (DPP4) inhibitors. Each of these medication classes has a different mechanism of action and different molecular interactions and consequently, different genetic variants that affect function. Studies of the genetic variants that can alter response to oral diabetes medications have generally shown modest effects, some of which are contradictory. Regardless, these studies represent findings that could provide information about future pharmacogenetic recommendations for oral T2DM medications. The etiology specific treatment recommendations for monogenic diabetes provide a current model of genetic diagnosis to pharmacological treatment that can be used for future implementation of pharmacogenetic findings into clinical recommendations. However, before any of these genetic associations can be implemented into clinical practice, further studies need to be performed to analyze the effectiveness of a priori genetic testing on the patient outcomes.

Metformin

Metformin is the first line medication for T2DM because of its safety profile as an insulin sensitizing agent. However, it has a high variability of efficacy between patients, and it often needs to be supplemented with secondary agents. Metformin's mechanism of action has not been well defined and therefore its target molecules have not been analyzed for important pharmacogenetic variants. However, a large scale Genome Wide Association Study (GWAS) discovered that Single Nucleotide Polymorphism (SNP) rs11212617 near the ATM locus was associated with reduction in HbA1c in response to metformin. 38 ATM encodes the ataxia telangiectasia mutated gene, a member of the phosphatidylinositol 3-kinase family important for cell cycle control and DNA repair. In a meta-analysis replication of this study, the association was confirmed, although one of the three cohorts showed no association. Finally, the Diabetes Prevention Program (DPP) found that there was no association between rs11212617 and progression from impaired glucose tolerance to diabetes. This SNP needs further confirmation and exploration for validation and future studies into metformin's mechanism of action.

On the other hand, metformin's transport between cell types has been well characterized. Metformin is actively transported between tissues, but it is not metabolized before excretion. It is absorbed into the intestinal epithelium through the plasma membrane monoamine transporter and the organic cation transporter 2. Organic Cation

Transporter 1 (OCT1) transports the metformin through the basolateral membrane of the epithelium to the bloodstream and OCT1 is also responsible for uptake into hepatocytes. Metformin is transported from the bloodstream into the renal epithelium through organic cation transporter 2. From there, metformin is excreted into the urine through the multidrug and toxin extrusion proteins 1 and 2. These transporters have provided targets for genetic analysis.

Sulfonylureas

Sulfonylureas are insulin secretagogues that act by binding the SUR1 subunit (encoded by ABCC8) to close the ATP sensitive potassium inward rectifying channel, causing membrane depolarization followed by calcium influx and insulin secretion. This haplotype has been shown to be less sensitive to sulfonylurea inhibition through patch clamp analysis. 50 separately; both the E23K and S1369A polymorphisms have disputed associations with T2DM and sulfonylurea efficacy. Other genes have also been associated with response to sulfonylureas. *TCF7L2*, the gene with the strongest association with T2DM, encodes transcription factor Tcf-4, which plays a role in cell proliferation through the Wnt signaling pathway. Likewise, carriers of the common rs1801278 variant in Insulin Receptor Substrate-1 (IRS-1) have an increased rate of secondary failure to sulfonylureas in addition to the general increased risk of T2DM associated with the polymorphism. These genetic variations could affect the pharmacological regimens for individuals known to be carriers.

Meglitinides

Meglitinides are another class of insulin secretagogues that also act by inhibiting the KATP channel to induce depolarization and insulin secretion. However, these medications act in a much shorter timeframe than sulfonylureas and consequently confer less risk of hypoglycemia. Meglitinides are rapidly metabolized by the liver. Another gene, KCNQ1, contains intronic variant rs2237892 associated with repaglinide response. The individuals carrying a TT phenotype showed improved HOMA-IR and 2-hour glucose response to 48 weeks repaglinide therapy, although this effect was lost when accounting for age, gender and body mass index. Meglitinide metabolism differs between repaglinide and nateglinide. Although genetic variants in these metabolizing enzymes may alter pharmacokinetics of the medications, it does not appear to have major effects on the glucose levels of patients.

Thiazolidinediones

Thiazolidinediones (TZDs) are PPAR (Peroxisome Proliferator Activating Receptor) activators that act by improving insulin sensitivity and decreasing hyperglycemia by decreasing circulating free fatty acids. Troglitazone was withdrawn from the market due to hepatotoxicity, but pioglitazone and rosiglitazone are still available. However, these medications have associated drug specific increased risks of fluid retention, heart failure, or bladder cancer, indicating they should be prescribed with caution and careful examination of the risk/benefit ratio. Individual genotype information may be of great benefit for this examination and genetic variants that predispose individuals to these side effects have already been discovered.

Conclusion

The incidence and prevalence of the diabetes mellitus epidemic around the world are currently at all-time highs. Despite medical advances, many people still suffer high rates of complications. Through pharmacogenetics, it is possible to usher personalized medicine into the field of diabetes. Certain types of monogenic diabetes already present an excellent opportunity to practice personalized medicine. Proper genetic diagnosis and appropriate pharmacological treatment of these patients often prevent unnecessary insulin therapy, simplify and increase efficacy of treatment and create opportunities for prediction and personalized treatment of diabetes in family members. Current epidemiological studies are also pushing forward the field of pharmacogenetics of more genetically complex forms of T2DM. Although more work needs to be performed, there are already promising examples, such as zinc supplementation for rs13266634 risk allele carriers in *SLC30A8.* Pharmacogenomic discoveries, like the *SLC30A8* and *APOC3* loss of function mutations, are providing physiological models that can be mimicked in the drug discovery process. Finally, the emerging field of gene environment interactions will progress to provide information about how individuals can tailor their environment to either complement or subvert their genetic predispositions. Many of these exciting developments in the field of personalized medicine for diabetes will likely translate into clinical practices to individualize therapy that will improve the patient experience and public health.

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