Precision medicine application in diabetes mellitus 1

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Literature Review

Keywords: Genomics, Insulin, pharmacogenetics, polygenic, beta cells, islet, pancreatic

Abstract:
Type 1 Diabetes mellitus is when your body makes little to no insulin. Insulin is a secreted hormone in the pancreas responsible for glucose management in the bloodstream. Glucose is primarily used for energy in cells; however, it builds up in the bloodstream without insulin. In this literature review, we interpret various studies looking at genetic makeup for preventing and managing type 1 diabetes.

Introduction:
From the beginning of history, 1552 BC, in Egypt, physicians noted the excessive urination of their patients because of an unknown disease. Later on, in the 5th century BC, the famous Indian physician Sushruta identified diabetes, characterized by the sweet-sticky urine in his patients.[1] Moreover, he associated these symptoms with the upper castes due to their excessive consumption of carbs and sugars. Nevertheless, the most accurate description of diabetes mellitus came in the 2nd Century AD when Greek-Roman physician Aretaeus published two works based on the causes and cures for chronic diseases based on the four humors. Eventually, this mystery disease, characterized as siphon honey in Greek and Latin, was named diabetes mellitus.[1]

According to the World Health Organization, diabetes has risen from 108 million in 1980 to 422 million in 2014. In 2019 alone, 2 million people died of diabetes and complications due to diabetes. However, the pathophysiology of diabetes is strikingly intricate as molecular features, pathophysiological processes, risk factors, complications, and comorbidities inflict a unique situation. Clinical trials have moved away from the one-size-fits-all approach to individualized diabetic management. Through this practice, precision medicine will tailor treatment and evaluate the ideal course of action based on each patient's underlying genetic and environmental factors.[2]
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Discussion

Old Models and Discoveries of Diabetes Mellitus 1
Though morbid, before the discovery of insulin in 1921, many patients diagnosed with diabetes

did not live long. Consequently, Frederick Banting and Charles Best's discovery of insulin was incredible. Both of their experiments consisted of Banting and Best working with the pancreas of dogs.[1] Later, they crushed the pancreatic glands of the dogs and then combined them with physiological salt. Finally, they administered that mixture to a dog. Incredibly, that dog's blood sugar fell significantly. Using this discovery, Banting and Best refined their extract and later administered it to humans.[1]

Following the discovery of insulin, George Eisenbarth created a conceptual model that depicts the change in β-cell against age. Genes determine the β-cell number, with environmental conditions decreasing it over time. Nevertheless, though the model is still relevant, it oversimplifies the complexity of diabetes.[3] With the emergence of patient-specific treatment, newer studies look deeper into gene mutation and inhibiting specific variants imposing risks on the patient.

Genetic Factors of Diabetes Mellitus 1

Genetics plays a significant role in the development and expression of diabetes 1. *Diabetes* is a polygenic disease expressed by multiple genes and tied by blood. Identical twin cordance risk of 30-70%, sibling risk of 6-7%, and a 1-9% risk for children of diabetic parents.[3] However, two HLA class 2 haplotypes, *HLA DRB1*0301-DQA1*0501-DQ*B10201* (*DR3*) and *HLA DRB1*0401-DQA1*0301-DQB1*0301 (DR4-DQ8),* are associated with the maximum probability of developing diabetes 1.[3] Still, other studies have shown 60 additional non-HLA genes expressing a risk for type 1 diabetes. Furthermore, these genes aid in the body's immune system responses, such as insulin expression and T cell activation.[3] As a result, mutations inhibit immune system response and exacerbate type 1 diabetes. Furthermore, autoimmune attacks progress as T1D ages with time. The presence and accumulation of islet cell autoantibodies.[4] Nevertheless, studies found evidence that genetics is a factor, but differing factors in different stages of T1D.

Though T1D is prevalent throughout all racial and ethnic groups, the current knowledge of T1D genetics primarily comes from the NHW population, where the disease is most prevalent.[4] However, studies have found racial/ethnic differences in the genetic and clinical characteristics of T1D. For instance, the amount of HLA haplotypes associated

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with T1D differs throughout various racial groups.[4] One study found that high-risk and moderate-risk genotypes were prevalent in Hispanic newborns compared to the NHW population.[4] Other studies have taken perspective differently. Similar haplotype frequencies were found in African American and NHWs but had opposite effects on T1D in both groups. With the progression of precision medicine, studies have to consider the genetic differences in racial groups from the Western to Eastern hemispheres.

Environmental Factors Diabetes mellitus 1

The most prominent precursor for type 1 diabetes is viral infections. Noted from early ecological reports, seroepidemiological studies, and case reports, numerous viruses are tied to pancreatic islet cells and patients with type 1 diabetes. [5]Furthermore, one study noted persistent viral infections reduced the islet cells from becoming β cells.[5] Consequently, reducing the production of insulin due to autoimmunity.[5]

Another potential determinant for type 1 diabetes is dietary factors. For instance, multiple studies have demonstrated that breastfeeding from birth reduces the risk of islet autoimmunity.[5]

Cow's milk has also been noted as a confusing and controversial element in dietary factors. Studies show conflicting evidence on whether cow's milk raises the risk of type 1 diabetes and islet autoimmunity.[5] They speculated the evidence of cow's milk's higher fatty acid content, which could increase the chances of type 1 diabetes.[5]

Precision Medicine Approach

Precision medicine offers individualized treatment for a primarily genetic disorder. Potential from precision medicine comes from the speculation that genetic therapy can inhibit the autoimmunity of islet cells and provide a unique approach to each patient. Monogenic diabetes accurately diagnoses various subtypes of diabetes by classifying different genetic mutations. Evidently, it is seen as some mutations represented in *the HNF1A* transcript of a dozen plus genes known for nuclear β cell transcription, while *KIR6.2* encodes the potassium-sensitive channel in the β cell.[6] Consequently, these varying genetic mutations can outright differ in treatment. In the former, the patient will need low-dose sulfonylurea therapy, and in the latter, respond to high-dose sulfonylurea therapy.[6] However, type 1 diabetes is a spectrum because of the vast array of genetic combinations that can determine a unique kind. Consequently, that is the reason monogenic diabetes is initially diagnosed as type 1 or 2. Later on, the diagnosis mutates uniquely for each patient.[7]

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One variation of precision medicine comes in pharmacogenetics. Pharmacogenetics comes to fruition by determining the best drug, dependent on the genetic variations of each patient. For instance, the glycemic, cardiovascular, and side effects are all dependent.[6] One way is to classify genetic markers associated with adverse drug effects and determine the most effective drug for each patient.[6] Traditionally precision medicine, though innovative, is set on outdated classifications such as the severity of islet cell autoimmunity, insulin resistance, and antibodies. Furthermore, there are various biomarkers dependent on exercise, dietary intake, family history,

medications, and overall lifestyle.[6] The current classifications are two-dimensional and lack the underlying understanding of type 1 diabetes. Studies have proven that genomics, epigenomics, transcriptomics, proteomics, metabolomics, and metagenomes are essential precursors for type 1 diabetes.[6] Furthermore, adding these dimensions can expand our understanding of diabetes and classify patients into varying levels. Later on, by connecting with pharmacogenetics, the patient can then be treated with the best drug. Understanding the multitude of factors in diabetes can then be used to create risk scores and accurately predict patient drug responses.[6]Adding layers to already established biomarkers can further simplify each patient's situation. Precision medicine requires a collection of accurate genomic libraries of data. Each patient would take a test determining their unique genetic makeup. For instance, monogenic diabetes, a condition diagnosed in the 6 months of life, is already taking these genetic tests in patients. Consequently, patients can then be adjusted to the most appropriate drug therapy depending on the subtype.

Challenges with Precision Medicine

There are numerous obstacles to truly providing precision medicine globally and effectively. Pharmacogenetics is still in its infancy because of the deep understanding of genetic data. Many institutions, such as the Nordic Precision Medicine Initiative, are helping to build the broad data set. Nevertheless, an important issue comes to light as racial differences become prevalent in genetics.[7] The data become incredibly biased, as European data is most common, while other racial groups are rare. Subsequently, precision medicine becomes overshadowed as European data becomes most prevalent. This requires a deep understanding internationally to proceed with research. Well, our understanding of genetics must be combined with environmental biomarkers. For instance, beta cell productivity and duration become important markers to predict diabetes accurately.[7]

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Will it work? Using various data sets and biomarkers to predict diabetes progression does not always mean better clinical outcomes. Therefore, research, clinical trials, and predictions must align and be seen commercially. However, the data is privatized in the pharmaceutical industry.[7] Thus, biobanks have arisen globally to collectivize information freely for studies.[7]

Of course, the most obvious but often overlooked factor is cost-effectiveness. Genomic technologies, currently, are exorbitantly expensive and require complicated instruments for each test.[7] Consequently, exorbitant costs further exacerbate the economic disparities in healthcare.[7]Nevertheless, monogenic diabetes is reasonably cost-effective and could become the standard for patients.[7]

Conclusion:

Nevertheless, though the discovery of diabetes has been endless throughout history, a clear collective solution has not been found yet. Even until relatively recently, we did not discover insulin. However, now we learned about the multi-dimensional field of diabetes research. Research is constantly changing how we understand and manage diabetes. Studies continue to discover how to protect against autoimmunity and keep pancreatic beta cells intact.

Nevertheless, genomics research continues to dive deeper. Globally, organizations have worked to classify genotypes and their subtypes further precisely. Research continues to progress as precision medicine takes one step closer and closer to offering more accurate procedures. With advancements in pharmacogenetics and international collaboration, patient care evolves to treat better and manage diabetes.

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