Genetic and biochemical risk factors for type 2 diabetes mellitus

Sukumaran Prabhu
Department of Biotechnology, Sri Venkateswara College of Engineering, Pennalur, Irungattukottai 602 117, India

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Diabetes is a chronic disease that occurs due to high sugar levels in the blood. Type 1 and type 2 diabetes occur in a large number of people. World Health Organisation (WHO) has reported that about 172 million people around the world are suffering from diabetes as of year 2000, and has estimated the numbers to increase to 367 million in coming years. India has been reported as the country with the maximum diabetic patients, followed by China, USA, Indonesia and Japan. In addition to the symptoms of tiredness, hunger, thirst and excess urination, it also causes a large number of complications when coupled with other conditions, like difficulties in surgeries. Hence, a good understanding of the genetic and biochemical risk factors for diabetes and how it affects our body can help us to develop a cure or a better treatment method that have maximum potential with less adverse effects. The present review discusses the most common genetic and biochemical risk factors of type 2 diabetes mellitus.

Keywords: KATP channel, lifestyle, oxidative stress, polymorphism, TCF7L2, type 2 diabetes mellitus

Introduction

Glucose is the source of energy for the body and enters the bloodstream from the digested food. The glucose then has to be taken up from the blood so as to enter the muscle, fat and liver cells, where it will be used as a fuel. The uptake of glucose is mediated by the hormone insulin and when the uptake is hampered, it leads to increase in glucose concentration in the blood. This condition of chronic high sugar level in blood is known as diabetes. It occurs when enough insulin is not produced from the pancreas, or the cells do not respond properly to insulin or both.1

Insulin is a hormone central to regulating carbohydrate and fat metabolism in the body, and is secreted by the β-cells of the islets of Langerhans in the pancreas. The β-cells produce proinsulin, which is then acted upon by proteolytic enzymes like prohormone convertases and the exoprotease carboxypeptidase E2. The two chains, A and B, thus produced are joined by a disulphide bond to form functional insulin. Insulin is a protein made up of 51 amino acids having a molecular weight of 5808 Da. It stops the cells from utilising fat as a source of energy by inhibiting the release of glucagon. It then induces the cells to take up glucose and store it as glycogen.

Three types of diabetes are recognised. The first type is type 1 diabetes. It can occur at any age and most often seen in children, teens or young adults. It arises because the β-cells in the pancreas produce little or no insulin. Type 1 diabetes is considered to be an autoimmune disease where the insulin producing β-cells are destroyed. A study indicated that only about 10% of the β-cell mass behave normally after the onset of the disease. Type I diabetes can be caused by combination of a trigger, an antigen or a genetic susceptibility. The first signs of type 1 diabetes are the symptoms of high blood sugar levels like thirst, hunger, tiredness, blurry eyesight, weight loss and frequent urination. Glucose levels can be maintained in the blood by monitoring diet, taking insulin injections and maintaining a healthy lifestyle.

Gestational diabetes is the next type. It is diagnosed in pregnant women who did not have any previous history of diabetes. The disease occurs because the hormones produced during pregnancy block the function of insulin by binding to the insulin receptor and, hence, the concentration of glucose increases in the blood. This type of diabetes is considered as a risk factor for the development of type 2 diabetes. Diet modification and treatment with insulin is sufficient to control glucose levels in this type of diabetes.

The final type is type 2 diabetes mellitus (T2DM). It is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. Insulin resistance in
muscle and fat cells reduces glucose uptake (and also local storage of glucose as glycogen and triglycerides, respectively), whereas insulin resistance in liver cells results in reduction of glycogen synthesis and storage, and a failure to reduce glucose production and release into the blood. It is caused by a combination of lifestyle and genetic factors. The present review discusses the major genetic and biochemical risk factors of T2DM. These factors include several reasons for increased glucose concentration in the blood and decreased glucose uptake by the cells.

Biochemical Risk Factors

When nutrients enter the body, β-cells rapidly release insulin that decreases plasma glucose concentration by inhibiting endogenous glucose production (EGP) and stimulating glucose transport into skeletal muscle, heart, and white adipose tissue (WAT). Insulin resistance and β-cell dysfunction are two major causes of T2DM and they are because of impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT), the risk factors for T2DM. Having impaired IFG increases the incidence rate of T2DM by 11 times. In case of both IFG and baseline glucose tolerance, individuals have 20 times higher incidence rate. If insulin resistance occurs in the liver, insulin loses its capacity to suppress EGP, whereas if it occurs in the peripheral tissues like muscle, glucose uptake via insulin is reduced. β-cell dysfunction on the other hand reduces the production of insulin itself.

Many biochemical risk factors are correlated with the incidences of diabetes. Besides IFG and IFT, they include insulin resistance, low insulin secretion in response to glucose, overweight/obesity, hypertension, and dyslipidemia. The incidence of T2DM has similar pattern in men and women. The incidence, irrespective of men and women, increases significantly with age, with the maximum incidence rate being 11.9/1000 persons/yr in the age group of 60-69 years. The rate of incidence was also found to be 3 times higher in people having the body mass index (BMI) range of 25-30 kg/m² and 10 times higher in obese individuals when compared with those having BMI in the range of 25. When compared with normotensive individuals, the incidence rate was reported to be 2 times higher in hypertensive individuals. It was found to be 1.5 times higher in individuals with dyslipidemia.

Lifestyle

The lifestyle, whether sedentary or active, also plays an important role. At least half an hour of exercise each day is required to maintain a healthy life. Sedentary lifestyle accumulates HDL and increases risk of obesity, which is another major risk factor for T2DM. A study was conducted by the Diabetes Prevention Program Research Group, in which T2DM patients were subjected to one of the following treatment methods for a year: intensive lifestyle intervention with a goal of ≥150 min/wk of exercise and ≥7% loss of body wt, and metformin treatment at 850 mg twice a day or placebo. When the patients were examined after a year, the intensive lifestyle group showed a 58% decrease in the risk of developing T2DM. The metformin treated groups showed a 31% decrease and the placebo treated group showed no change. The reason for decrease in the intensive lifestyle and metformin treated groups were found to be an increase in insulin sensitivity and an improvement in the β-cell preservation. There was a significant decrease in the fasting and 120 min glucose values in the lifestyle group, whereas only fasting and 120 min glucose values decreased in the metformin treated group. The placebo treated group showed an increase in the 30 min and decrease in the 120 min glucose values. After the first year, however, the 120 min glucose values did not differ in the placebo and metformin treated groups but were significantly greater in the lifestyle group.

Polymorphism of K\textsubscript{ATP} Channel

Polymorphism of the ATP-sensitive K⁺ channel (K\textsubscript{ATP} channel) is considered to be another cause of late onset of diabetes. The metabolic changes in the pancreatic β-cell are detected by the channel and the metabolism is coupled to electrical activity and finally insulin secretion. When K\textsubscript{ATP} channel opens, the β-cells get hyperpolarized and insulin secretion is suppressed. When there is an E23K polymorphism (glutamate converted to lysine at position 23) in KCNJ11, the activity of K\textsubscript{ATP} channel increases due to reduction in sensitivity to intracellular ATP. This occurs due to one of the two reasons: reduction in ATP affinity or increase in intrinsic open state stability. Such occurrences cause an alteration in the sensitivity of K\textsubscript{ATP} channel to metabolites, metabolic signal or number of active K\textsubscript{ATP} channels. Any of these alterations can disrupt electrical signaling in the β-cell and ultimately alter insulin release. The K\textsubscript{ATP} channel polymorphism that increase channel activity,
could act in combination to other genetic and environmental factors and can contribute to impaired β-cell function. This leads to decreased production of insulin and hence T2DM.

**Oxidative Stress**

Obesity caused by increased intake and reduced physical activity induces a state of insulin resistance. The tissues affected most by insulin resistance are the muscle and adipose tissue. When the energy uptake is more than its use, there is an increase in the citric acid cycle because of the excess substrate. As a result, increased quantities of mitochondrial NADH (mNADH) and reactive oxygen species (ROS) are generated. ROS is, as such, harmful to the cell and the cell tries to reduce ROS formation or to enhance ROS removal. If the cell tries to decrease ROS formation, it has to decrease the nutrient uptake (energy containing molecules like pyruvate and fatty acids into the mitochondria). In consequence, the blood sugar level increases. When the β-cells are unable to produce enough insulin to overcome the insulin resistance, IGT is observed.

Unlike the mitochondrial cells, the β-cells and endothelial cells are not dependent on insulin but on facilitative diffusion to take in glucose. Therefore, when there is increased concentration of circulating insulin, such cells cannot prevent the entry of sugar. Due to the prolonged exposure to high glucose levels or high free fatty acids (FFA) levels or both, β-cell dysfunction may occur. Repeated exposure may lead to irreversible β-cell conditions. As the β-cells are low in enzymes that target ROS, such as, catalase, glutathione peroxidase and superoxide dismutase, they are more prone to damage caused due to ROS. In such situation, insulin secretion reduces significantly. Sakai et al. have reported that a 15 min exposure to high glucose increases the intracellular ROS and this in turn reduces the glucose-induced insulin secretion. An increase in ROS production and oxidative stress can be caused by an increase in insulin, FFA and glucose levels. This in turn deteriorates both insulin action and secretion, which further accelerates the progression to T2DM.

**Genetic Risk Factor**

**Polymorphisms in TCF7L2 Gene**

Transcription factor 7-like 2 (TCF7L2), a gene located in chromosome 10q25, is responsible for cell proliferation and differentiation. Polymorphism in this gene is associated with T2DM. Coleen et al., in this region of the chromosome, have identified a microsatellite marker in intron 3 (DG10S478) and five correlated single nucleotide polymorphisms (SNPs) in Icelandic individuals that show strong association with T2DM. The study has focused on four of these SNPs (rs7901695, rs7903146, rs11196205 & rs12255372) and observed that rs7903146 increases the effect on insulin sensitivity. It has been shown that SNPs cause a decrease in insulin sensitivity and a defect in insulin secretion in β-cells. As there is now an inability to compensate for insulin resistance, it causes T2DM. Grant et al. hypothesized that differential transcriptional regulation of the insulinotropic hormone glucagon-like peptide-1 (GLP1) influences T2DM susceptibility. This peptide encoded by GCG is expressed in the brain and gut and is involved in glucose homeostasis and satiety.

**Conclusion**

The present review emphasises the role of various risk factors in type 2 diabetes mellitus. Understanding the mechanism of these biochemical and genetic risk factors could be helpful to determine an appropriate mode of treatment for T2DM. Sedentary lifestyle, the polymorphisms in K<sub>ATP</sub> channel and TCF7L2 gene together may act with other environmental factors that can lead to decreased production of insulin, which in turn causes T2DM. Treatment of diabetes ultimately involves the reduction of any increase in the concentration of blood sugar without any abnormal decrease in sugar level during treatment. Medications for T2DM are to be designed in such a way that they increase the production of insulin by the pancreas, decrease the release of glucose from the liver, increase the insulin sensitivity, decrease the carbohydrate absorption from the intestine, and delay the carbohydrates presentation for digestion and absorption in the small intestine. At least half an hour of exercise each day is required to avoid sedentary lifestyle in T2DM. When these measures fail to control the blood sugar level, oral medications are to be used. If oral medications are still insufficient, only then insulin injections are to be used as the final mode of treatment.

**References**


