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Molecular Genetics of Type 2 Diabetes Mellitus

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Abstract
In this chapter, the cellular and molecular genetics of diabetic complications have been discussed. Several mechanisms may be responsible for the potentially damaging overproduction of reactive oxygen species observed with hyperglycemia. Several genes may contribute to the known pathophysiologic features of diabetic complications by a number of mechanisms, including the upregulation of cytokines and growth factors. Diabetic macro vascular disease may arise more from insulin resistance than from hyperglycemia, and the authors speculate that this may reflect a selective loss of insulin-dependent vascular homeostasis.

Keywords: Type 2 Diabetes Mellitus, Insulin Resistance, Molecular Mechanisms, Signalling Pathways in Diabetes

Introduction

Diabetes disease burden is high and rising in every country, spurred by an increase in the prevalence of obesity and unhealthy lifestyles around the world. According to the most recent estimates, the prevalence rate of diabetes in Northern America and the Caribbean was 11.1 percent in 2019, and is anticipated to climb to 13 percent by 2045. Africa has the lowest prevalence rate (4.7 percent), which is anticipated to rise to 5.2 percent by 2045 [1]. Countries in Southeast Asia and South America, in general, have high or intermediate occurrences. According to a study published in 2019 by Saeedi *et al.* [1], there are 463 million individuals living with diabetes globally, representing a 9.3% prevalence rate. This prevalence rate is expected to reach 10.2 percent by 2030, and 10.9 percent by 2045. The diabetes prevalence by region is estimated for numerous countries, resulting in a list of the countries with the highest number of diabetic patients in 2019 [2].

China, with 116 million diabetes patients, has the highest proportion of diabetic patients among these countries. India comes in second with 77 million people, followed by the United States of America with 31 million, indicating that the United States will be one of the most diabetic-prone countries in the following decade. Pakistan, Brazil, and Mexico are expected to have the highest numbers of diabetic patients, with 19 million, 16 million, and 12 million diabetic people, respectively. While

Bangladesh is at the bottom of the list, the country's growing population and lack of well- planned intervention methods mean it is no less at risk of diabetes than the United States [3]. (Figures 1 and 2).

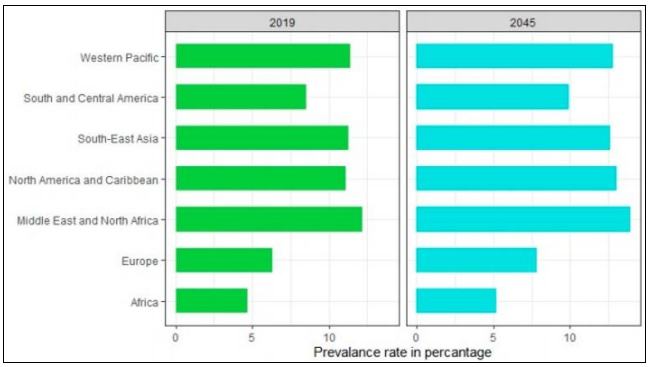

Fig 1: Diabetes prevalence by world regions between 2019 and 2045 (estimated) [3]

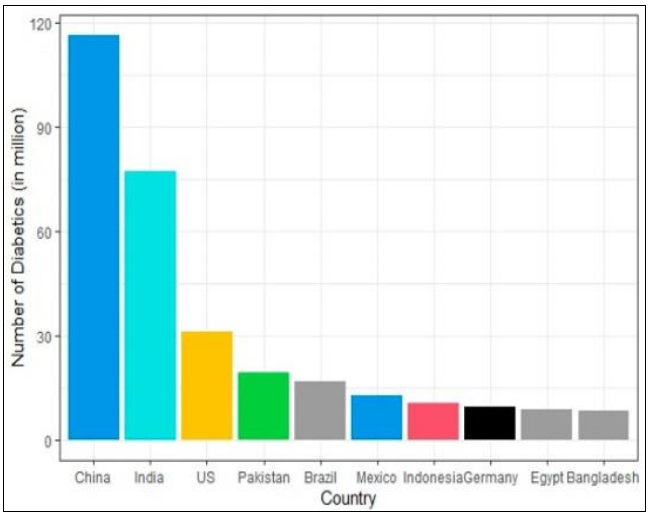

Fig 2: In 2019, the countries with the greatest number of diabetic patients [3]

Type 2 Diabetes Mellitus

Type 2 diabetes (T2DM), often known as adult-onset diabetes, is a type of diabetes marked by high blood sugar, insulin resistance, and insulin deficiency [4, 5]. Beta cells are the primary organ for secreting insulin, maintaining an adequate beta-cell mass in response to diverse alterations is critical. Insulin resistance, which is a key cause of T2DM, causes an increase in beta-cell mass and insulin production to compensate for insulin sensitivity. Chronic elevations in plasma FFA levels disrupt lipid metabolism, resulting in impaired beta-cell activity and lipotoxicity, which promotes T2DM [5].

Causes of Type 2 Diabetes Mellitus

A mix of lifestyle and genetic factors contribute to the development of type 2 diabetes. While some of these factors, such as diet and obesity, are under one's control, others, such as advancing age, feminine gender, and heredity, are not. In many places of Africa, women are more likely than males to be obese. The mother's nutritional state throughout fetal development may potentially play an effect, with DNA methylation being one hypothesized way. Type 2 diabetes has been linked to the gut bacteria *Prevotella copri* and *Bacteroides vulgates* [6, 7].

More than a trillion germs, mostly bacteria, invade the oral-gastrointestinal tract in humans and live in the intestine's distal section [7, 8]. The gut microbiota plays a role in many of the host's physiological activities, and the host provides a niche and nutrition for these microorganisms to survive [9]. The gut microbiota is responsible for digestion and glucose fermentation, as well as vitamin synthesis, mucosal lymphoid tissue development, epithelial barrier maintenance, and pathobiont colonization prevention [10]. Furthermore, maintaining mucosal immune homeostasis and epithelial barrier integrity requires interaction between the host immune system and the gut microbiota [11]. However, when this healthy connection is disrupted by an imbalance in the normal bacterial ecology in the gut, known as intestinal dysbiosis, metabolic and chronic inflammatory illnesses such as T2D can occur [11].

Bacterial translocation, metabolic endotoxemia, faulty incretin secretion, and reduced butyrate concentrations are some of the processes postulated to explain the impact of the gut microbiota on insulin resistance and T2D [10]. Lipopolysaccharides are endotoxins found in Gram-negative bacteria's cell walls, and they are chiefly responsible for endotoxemia seen in metabolic diseases [12].

Increased intestinal permeability, along with changes in Gram-negative bacteria numbers in the gut, could facilitate LPS escape into the bloodstream and cause systemic inflammation [12]. Insulin resistance is linked to inflammation because proinflammatory cytokines disrupt insulin signaling by reducing insulin receptor phosphorylation. High-fat diets also promote a rise in Gram-negative bacteria in the stomach and enhanced LPS absorption in the intestinal mucosa, according to animal studies [13].

Increased IL-6 plasma concentrations, C-reactive proteins, and intestinal dysbiosis have all been linked to obesity and T2D development in recent studies [12]. Ruminococcus gnavus and Bacteroides spp. have been found to be more abundant in the feces of T2D patients in some investigations [14]. Butyrate-producing bacteria with anti-inflammatory properties, such as Roseburia intestinalis and Faecalibacterium prausnitzii, were shown to be reduced in T2D patients [14].

Life style

Obesity and being overweight (defined as a BMI of greater than 25), lack of physical activity, poor food, stress, and urbanization are all factors that lead to type 2 diabetes development [15, 16]. Excess body fat is linked to 30% of instances in people of Chinese and Japanese ancestry, 60%–80% of cases in people of European and African ancestry, and 100% of cases in Pima Indians and Pacific Islanders [17]. A high waist–hip ratio is common among persons who are not obese [17]. It suggests that smoking raises the risk of type 2 diabetes [18]. Type 2 diabetes has also been connected to a lack of sleep [18]. Short-term sleep deprivation in laboratory studies has been related to alterations in glucose metabolism, nervous system activity, and hormonal variables that may lead to diabetes [19].

Dietary factors can have a role in the development of type 2 diabetes. Excessive consumption of sugar-sweetened beverages has been linked to an elevated risk [20-22]. Dietary fats play a vital role, with saturated and trans-fatty acids increasing risk and polyunsaturated and monounsaturated fats lowering risk [23]. White rice consumption appears to be linked to an increase in risk [24]. About 7 percent of instances

are thought to be caused by a lack of exercise [25]. Organic contaminants that are persistent in the environment may also play an impact [26].

Genetic

Most cases of diabetes are caused by a combination of genes, each of which plays a little role in the development of type 2 diabetes [27, 28]. It is estimated that 72 percent of diabetes cases are hereditary [29]. Researchers discovered more than 36 genes and 80 single nucleotide polymorphisms (SNPs) that influence the risk of type 2 diabetes [30]. Despite this, all of these genes account for barely 10% of the disease's overall heritable component [31]. For example, the TCF7L2 allele raises the risk of diabetes by 1.5 times and is the most dangerous of the prevalent genetic variations [32]. The majority of the genes associated to diabetes are involved in the activity of pancreatic beta cells. Genetic factors are crucial because several genes and their interactions, including as PRKAA2 [33], ABCA1 [34], FTO [35], FADS [36], and TCF7L2, play critical roles in the progression of T2DM [37].

These genes' products are linked to the metabolic process that leads to T2DM or excessive blood glucose. G6PC2 encodes a member of the catalytic subunit family of the glocose-6-phosphatase enzyme, which is involved in the final stage of the gluconeogenic and glycogenolytic processes, allowing glucose to enter the bloodstream. GCK's product is in charge of regulating glucose levels and insulin secretion. GCKR products interact non-covalently to form an inactive complex with glucokinase in liver and pancreatic islet cells, inhibiting the enzyme. Many endogenous tiny organic cations, as well as a variety of pharmaceuticals and environmental pollutants, are excreted and transferred via the OCT3, also known as SLC22A3. Figure 2.3 shows Glucose transporters 1 transfer glucose into the hepatic cell (GLUT1). During glycogenolysis, liver glycogen is hydrolyzed and isomerized to glucose-6-phosphatase (G-6-P). Then the catalytic subunit 2 (G6PC2) of glucose-6-phospatase catalyzes the formation of free glucose, which is an important step in gluconeogenesis. The key enzymes that regulate glucose phosphorylation, which is followed by glycolysis and aerobic oxidation in the glucose activation process, are glucokinase (GCK) and glucokinase regulator (GCKR) [38]. (Fig 3).

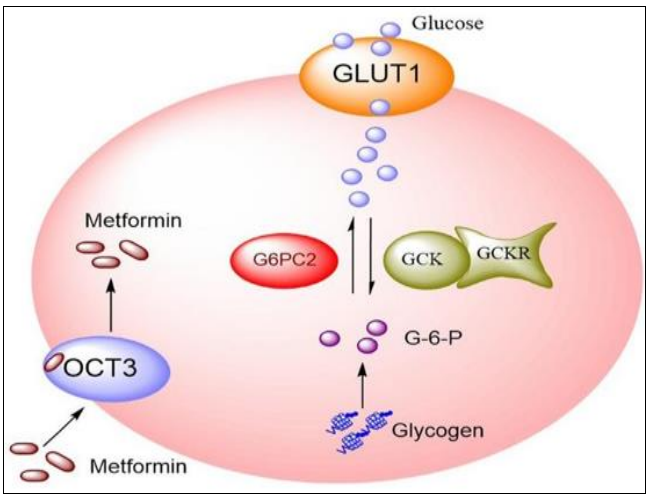

Fig 3: Gene involved in glucose control and related to glucose metabolism [38].

Glucose-6-phosphatase catalytic subunit 2 (G6PCS2) gene

G6PC2 catalyzes the hydrolysis of glucose-6-phosphate, allowing glucose to enter the bloodstream. G6PC2 has four exons and is found on human chromosome 2q31.1. This gene produces a 355-amino-acid protein that acts as a negative regulator of glucose-stimulated insulin release in the absence of glucose. G6PC2 deletion in pancreatic islet beta cells has been shown to lower fasting blood glucose levels [39]. Single nucleotide variants in the G6PC2 gene were linked to differences in fasting blood glucose (FBG) but not fasting plasma insulin, according to GWAS and mice studies [40]. Glucokinase (GCK) gene.

Glucokinase (GCK) is an enzyme that phosphorylates glucose to glucose-6-phosphate. It has an important role in regulating glucose metabolism and insulin production in pancreatic –cells [41, 42]. As a result, it's not surprising that a mutation or polymorphism in the GCK gene can result in pathoglycemia and diabetes mellitus. Mutation of GCK has been linked to Chinese MODY (maturity onset diabetes of the young type) [43]. GCK rs1799831 SNPs were linked to gestational diabetes mellitus (GDM) in the Indian population, according to a meta-analysis [44]. The propensity to T2DM has been linked to a genetic variation in the GCK gene.

Glucokinase Regulator (GCKR) gene

GCKR, also known as GKRP, is a Sugar Isomerase family protein that encodes a member of the GCKR subfamily. GCKR is mostly expressed in the liver. Is a regulatory protein that binds to the glucokinase and inhibits it, inhibiting glycolysis, glycogen deposition, and de novo lipogenesis [45]. T2DM [46], nonalcoholic fatty liver disease (NAFLD) [47], familial combination hyperlipidemia (FCHL) [48], coronary artery disease, ischemic stroke [49], gout [50], and chronic kidney disease [51] have all been found to be linked to GCKR mutations or gene variations. A lot of studies have found a link between the GCKR polymorphism and T2DM in various ethnic groups. GCKR rs780094 is found in the Han Chinese population. A specific allele has been linked to a lower risk of T2DM and obesity. Fasting glucose was discovered to be influenced by a gene-gene interaction between GCKR rs780094 and GCK rs1799884. The study by Qi *et al*. [52], also confirmed the effect of the GCKR rs1260326 polymorphism on T2DM.

Organic cation transporter 3 (OCT3) gene

OCT3, also known as SLC22A3, is a 15-exon gene found on human chromosome 6q25.3. OCT3 is a multifunctional organic cation transporter found mostly in the liver, kidney, and gut. Many endogenous small compounds, medicines, and environmental poisons are transferred through OCT3 [53]. As a result, mutations and variations in OCT3 will have an impact on the development of numerous diseases as well as the efficacy of a variety of medications. Lipoprotein.

(a) concentration, cardiovascular disease [53], colorectal cancer [54], metformin pharmacokinetics, esophageal cancer [55], pancreatic cancer [56], and T2DM [57] are just a few of the illnesses linked to SNPs in OCT3.

Medical conditions

A variety of drugs and other health issues can put you at risk for diabetes. Glucocorticoids, thiazides, beta blockers, atypical antipsychotics, and statins are among the drugs [58]. Those who have had gestational diabetes before are more likely to develop type 2 diabetes. Acromegaly, Cushing's disease, hyperthyroidism, pheochromocytoma, and certain

malignancies such as glucagonomas are all linked to this condition [59]. If a person has cancer and simultaneously has diabetes, they may be at a higher risk of dying [60]. Type 2 diabetes has been linked to testosterone insufficiency [61].

Pathophysiology of Type 2 Diabetes Mellitus

In the context of insulin resistance, type 2 diabetes is caused by insufficient insulin production from beta cells [62, 63]. Insulin resistance occurs primarily in the muscles, liver, and fat tissue, and is defined as the inability of cells to respond adequately to normal levels of insulin [64, 65]. Insulin normally inhibits glucose release in the liver. In the case of insulin resistance, however, the liver releases glucose into the bloodstream in an inappropriate manner [66]. Individuals differ in the proportion of insulin resistance to beta cell malfunction, with some having largely insulin resistance and only a little fault in insulin secretion, while others have slight insulin resistance and primarily a lack of insulin secretion [67].

Increased lipid breakdown within fat cells, resistance to and lack of incretin, high glucagon levels in the blood, increased salt and water retention by the kidneys, and inappropriate metabolism regulation by the central nervous system are all potential mechanisms linked to type 2 diabetes and insulin resistance [67]. However, not everyone with insulin resistance develops diabetes since insulin secretion by pancreatic beta cells must be impaired as well. The mass of beta cells expands in the early stages of insulin resistance, boosting insulin output to compensate for the insulin insensitivity [68]. However, by the time type 2 diabetes manifests, a type 2 diabetic will have lost almost half of their beta cells [68]. FOXO1 is activated by fatty acids in beta cells, resulting in beta cell death [68]. (Figures 4 and 5).

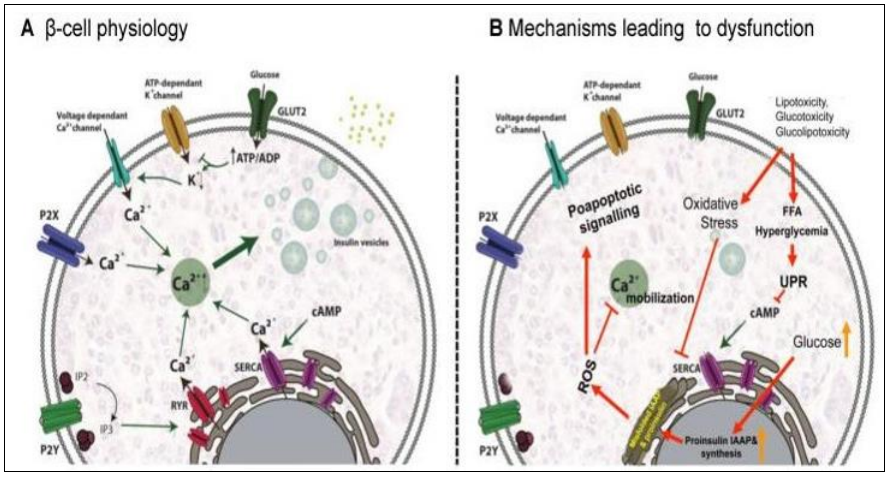

Fig 4: (A) In physiological settings, signaling pathways involved in insulin secretion in –cells, (B) mechanisms that result in malfunction [5].

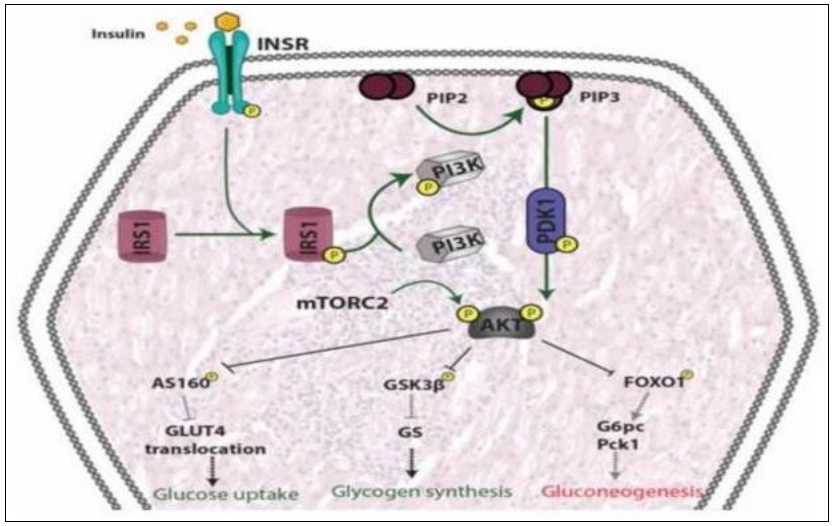

Fig 5: In hepatocytes, signaling pathways implicated in insulin signaling. When insulin binds to INSR, IRSs are recruited and phosphorylated [5].

Signs and Symptoms Type 2 Diabetes Mellitus

Diabetic symptoms include polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased appetite), and weight loss. (Vijan, 2010; Mokashi and Young, 2018) [69, 70]. A history of impaired vision, itching, peripheral neuropathy, recurrent vaginal infections, and exhaustion are all prevalent symptoms at the time of diagnosis (Gardner and Shoback, 2011) [71]. Other signs and symptoms include a loss of taste. However, many persons have no symptoms for the first several years and are diagnosed as a result of normal testing (Gardner and Shoback, 2011) [71]. Hyperosmolar hyperglycemia affects a tiny percentage of patients with type 2 diabetes (a condition of very high blood sugar associated with a decreased level of consciousness and low blood pressure) (Gardner and Shoback, 2011) [71]. (Fig 6).

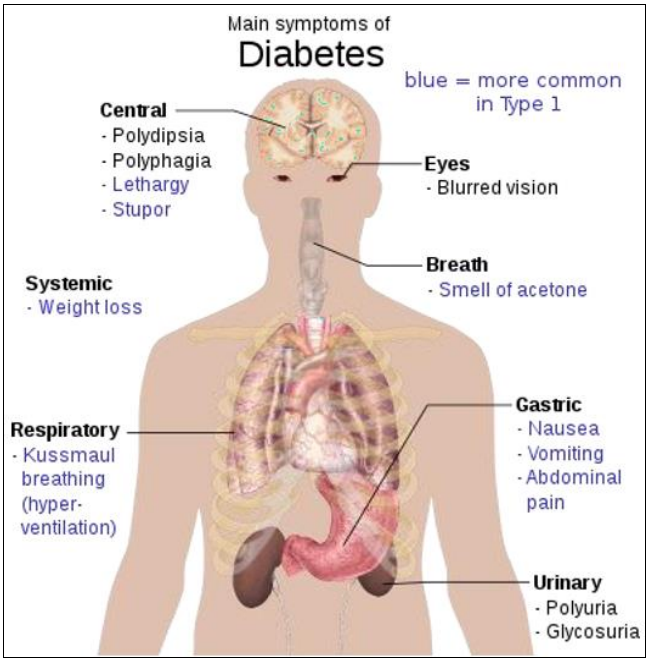

Fig 6: The signs and symptoms of Type 2 DM (Gardner and Shoback, 2011) [71].

Conclusion

The progress in understanding the metabolic staging of diabetes over the past few years has led to significant advances in the regimen of treatment of this devastating disease. Improvements in the treatment or prevention of the disease will depend on understanding the underlying molecular pathophysiology in more detail. Indeed, advances in genetics, signal transduction, and the neurobiology of energy intake and metabolism should permit a more precise and perhaps individualized approach to therapy, allowing us to focus the attack where the problem lies. This alone is reason for optimism.

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