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Current pathophysiological understanding of type 2 Diabetes Mellitus

[1,*]Archi Suthar and [2]Guno Sindhu Chakraborthy

[1]Department of Pharmacology,
[2]Department of Pharmacognosy, Parul Institute of Pharmacy and Research, Parul University, P.O. Limda, Waghodia, Vadodara-391760 (India)
*Corresponding Author: archisuthar134@gmail.com

Abstract

Among all the types of diabetes, type 2 diabetes mellitus (T2DM) is the most prevailing type. The pathophysiology of type 2 diabetes is knotty and involve many factors that contribute to the disease progression. Obesity, and the combination of genes along with environmental variables are thought to be the key causes of disease development. Environmental factors include mainly obesity and sedentary lifestyle as main culprits along with other factors such as age and diet playing a role. Genetic factors include various polymorphisms with in certain genes and with environmental factors manifest the phenotype of the disease. In type 2 diabetes mellitus, fluctuating levels of impaired insulin production and its action on targeted organs is seen. The clinical features of the disease rely exclusively on assessments of raised glycemia without a clear understanding of the pathology behind it. As a result, treatment focuses solely on lowering blood glucose levels without the knowledge of the underlying cause. As such, targeting and focusing on the specific etiology responsible for the disease in a particular patient can help achieve targeted blood glucose levels along with reducing the risk of developing the complications related to the disease. The review focuses on the brief outline of various pathologies affecting or playing a part in T2DM progression and hence can furnish insights for a better treatment or prevention for the disease by targeting the specific etiology.

Key words : T2DM risk factors, T2DM genetic disposition, Insulin resistance mechanism, β-cell dysfunction.

Our body uses the metabolic process to turn food into energy. The primary ingredients of the diet are proteins, carbohydrates, and fats. With the aid of chemicals in the body, it is further reduced into sugars and acids to be used as fuel or stored as energy in the bodily tissues for later use. As a result, aberrant chemical interactions interfere with this regular

process and cause metabolic disease. Diabetes is referred to by WHO as a "disease of metabolism involving distinct etiologies defined by perpetual hyperglycemia with alteration in the metabolism of carbohydrate, protein, and lipid due to insufficient production of insulin or its action and or including both"[29]. T2DM among the three primary forms of diabetes, accounts almost 90% of the encountered cases, more frequently than either T1DM or other types of diabetes.

Insufficient beta cell synthesis and release of insulin, together with insulin resistance, are known as primary causes of T2DM[14]. Insulin resistance develop and further leads to 'relative insulin deficiency'. During insulin resistance, the β-cells produce more of insulin to overcome the resistance, but after a time, exhaustion prevails, leading to 'relative insulin deficiency' [6]. There is no single factor causing T2DM progression. It involves the interplay of certain risk factors which together promote the disease progression; insulin resistance and beta cell dysfunction being main metabolic defects in T2DM. The review will discuss the overview of the current information regarding this disease progression.

Role of genetic predisposition :

T2DM disease is an inherited family trait[13]. The likelihood of developing T2DM is hiked twofold when one or both parents have the disease. The interaction of numerous genes dispersed throughout the genome appears to be the cause of the genetic basis of T2D risk instead of a single area of the genome. Candidate gene study, genetic linkage, and genome-wide association studies have revealed a certain number of genes responsible for traits of T2DM, which are detailed below:

Candidate gene study :

The method used most frequently to link human genetic variants to the phenotypes they cause[36]. Genes identified and considered responsible for T2DM by this technique are[2,15]:

1. *PPARG*–Peroxisome proliferator-activated receptor gamma
   When compared to other metabolically active organs, adipose tissue bares the highest PPARγ expression level. By increasing the expression of certain genes playing role in the signaling cascade of insulin, activation of PPARγ in mature adipocytes improves insulin sensitivity[22]. Studies found that when arginine switched out proline at 12th position of gene PPARγ, it resulted in a raised risk of diabetes by 20%.

2. *IRS* – Insulin receptor substrates
   The receptor of insulin and a sophisticated web of intracellular signaling molecules are connected by proteins known as the IRS (insulin receptor substrates). A likely candidate for inherited resistance towards insulin is IRS-1, which is phosphorylated on numerous tyrosine residues during insulin signaling. Polymorphisms in amino acids like Gly972Arg & Ala513Pro are identified and ascribed to the gene IRS-1 [19].

3. *KCNJ11* – Inwardly rectifying potassium channel subfamily J member 11
   Beta cells' ability to secrete insulin is significantly regulated by the Kir 6.2 ATP-

sensitive K^+ channel, which is encoded by the KCNJ11 gene. Numerous studies have linked the Kir6.2 gene's E23K variant to T2DM, and this variant accounts for most of the population T2DM risk[32].

4. *ABCC8*–ATP-binding cassette transporter sub-family C member 8
   Gene ABCC8 encodes for SUR1 (sulfonylurea receptor 1) and along with kir6.2 channel, regulates insulin secretion. The pathogenicity of T2D is influenced by multiple SNPs of gene ABCC8 and their interactions[5].

Genetic linkage study :

Genetic linkage is the propensity for closely spaced DNA sequences on a chromosome to be passed down in simultaneously during the meiosis stage of sexual reproduction[7]. Only two genes are reliably identified as being related to T2D in these studies[24]:

1. *CAPN10* – Calpain 10
   The role of the Calpain-10 gene is been implicated in insulin-stimulated glucose uptake, β-cell functioning, and T2D susceptibility. Diabetes links to polymorphisms of the four CAPN10 gene: InDel (insertion or deletion)-19 (rs3842570), SNP (single nucleotide polymorphism)-43 (rs3792267), SNP-44 (rs2975760) and SNP-63 (rs5030952)[26,27].

2. *TCF7L2* – Transcription factor 7 like 2
   The transcription factor that TCF7L2 gene encodes is known to be active in beta cells and is also involved in the Wnt signaling pathway. Intron 3 of the gene TCF7L2 contains the risk allele which elevated the amount of protein TCF7L2 in β-cells and is linked to flawed insulin secretion, mediation of incretin effects, and an increased rate of glucose production in liver[9].

Genome wide association study :

Numerous genetic variations that are connected to β-cell functioning and insulin resistance have been found by genome-wide association studies (GWAS) conducted on single nucleotide polymorphism (SNPs). Few of these SNPs seem to cause T2DM more likely. More than 40 distinct loci show a correlation with a higher risk of T2DM. The most likely subsets to cause are - TCF7L2, MTNR1B, FADS1, DGKB, GCK, FSADS1, PPARG, KCNJ11, FTO, IGF2BP2, HHEX, SLC30A8, WFS1, CDKN2A/B, IRS, HMGA1, and GIPR [30].

Role of environmental factors in T2dm:

The fact that the diabetes genotype often just results in a propensity for sugar intolerance and that environmental factors determine whether someone eventually acquires the phenotype is crucial[21]. Such environmental factors include obesity, sedentary lifestyle, diet, and age.

Obesity :

The major risk factor for T2DM is obesity, which is defined as excess fat and a person bearing body mass index of ≥ 30 kg/m^2. Obesity is linked to metabolic abnormalities that cause insulin resistance. Due to the fact

that both the amount and the distribution of body fat have a significant impact on insulin sensitivity, central or visceral obesity is the primary cause of insulin resistance[25]. Obesity leads to IR (insulin resistance) in following ways:

1. *Free fatty acids (FFA's) :*
   Adipose tissue is the most ideal site for storing extra fat. Only adipose tissue's fat cells can safely store a huge amount of fat, making them one-of-a-kind. There are no negative metabolic implications (other than being overweight) unless these cells are metabolically healthy. The ability of the fat cells to grow, however, is limited. When the storing capacity of the fat cells is exceeded; it can result in hypoxia, which in turn activates gene HIF-1 and results in JNK & IKK increased expression causing inflammation. The resulting inflammation leads to the maturing of IR within given cell.

   Higher quantities of FFAs may exit fat cells and enter into the bloodstream to be absorbed by the organs like the skeletal muscle and the liver. These organs develop IR due to their incapability of healthily storing such excess fat. Increased fat cell inflammation results in the migration of more M1 macrophages into adipose tissue as well as cytokine release (like TNFα), further elevating IR and lipid breakdown[33].

   Another theory contends that cytoplasmic intermediates like DAG (diacylglycerides), acyl-CoA, or ceramides accumulate as a result of lipid overload and can reduce insulin signaling and transport of glucose[10].

2. *Inflammation :*
   In pancreatic β-cells and macrophages, endogenous accumulation of excessive amounts of DAMPs (danger-associated molecular patterns) like FFAs, glucose, ROS, hypoxia, and ceramides can activate a cytoplasmic multiprotein complex named inflammasome (a crucial metabolic dysregulation sensor which regulates pancreatic beta cell failure and insulin resistance caused by obesity).

   Inflammasome complex is formed by the interaction between domains of proteins such as NLRP3, ASC and Procaspase-1 which leads to the caspase-1 activation and release of IL-1β and IL-18. The nuclear transcription factor-kB is then activated by IL-1β signaling, which causes the production of inflammatory genes. Although lymphocytes are thought to be IL-1β and IL-18 principal targets, receptor for them are widely expressed in a variety of cells and organs, with pancreatic islets having the highest levels of expression[16].

Sedentary lifestyle :

In today's society, there are countless opportunities to engage in sedentary behavior, including watching television, car driving, or operating computer. As a result, sedentary habits become a crucial component of the human lifestyle[38]. Lengthy periods of sedentary behavior results in reduced contractile activity of the skeletal muscles, thereby lowering the lipoprotein lipase (LPL) activity in the muscle. Sedentary behavior also lowers basal metabolism which results in increased intake of food and decreased energy output ultimately

leading to gain in weight and elevated levels of glucose; promoting the progression of T2DM [23].

Diet :

The amount of food consumed and the content and quality of one's diet have both been substantially associated with obesity[31]. When a person is genetically and epigenetically predisposed to T2DM, chronic fuel surplus is the main pathogenic event that causes this condition. Certain obese or overweight individuals safely distribute extra fat to SAT (subcutaneous adipose tissue) instead of the skeletal muscle, β cells, liver, and the heart and remain free from acquiring diabetes due to adaptive mechanisms by the body like: adequate beta cell recompense, preservation of nearly healthy blood-nutrient concentrations, minimal induction of insulin resistance, enhanced extension of subcutaneous adipose tissue as compared to visceral adipose tissue (VAT) and minimal rise in the liver fat. Susceptible obese individuals develop T2D due to the inability of these adaptive mechanisms to properly eliminate the fuel surplus safely and instead dispose of excess calories to VAT and other organs like the liver, pancreas, heart, and skeletal muscle which damages them eventually[35].

Abdominal VAT is made up of bigger adipocytes than SAT and secretes more chemicals related to insulin resistance. In addition to having a more robust metabolic activity, VAT also has a more extensive circulatory and nerve system distribution. Large amounts of adipocytokines, FFAs and inflammatory substances are produced during its breakdown, and these substances encourage lipogenesis, glycogen heterogeneity, and insulin resistance.

Age :

A defining hallmark of aging is chronic inflammation. Through the generation of cytokines by ROS & NF-KB; human polynucleotide phosphorylase may have a substantial impact on the pathological alterations associated with aging. Body fat composition increases along with increasing age and concentrates particularly in the abdominal region, increasing the likelihood of central or visceral obesity. Aging also affects metabolism of lipids and causes increased storage of fat leading to elevated levels of FFAs in the blood[37].

Insulin resistance (IR) :

When the target organs develop resistance towards insulin, it is termed as insulin resistance. The primary organs that fail to react towards insulin and develop insulin resistance are the skeletal muscles, the liver, and the adipose tissue. Resistance to insulin results in the following consequences:

- Failed inhibition of gluconeogenesis which leads to increased production of glucose in the liver and high levels of sugar in blood, resulting in elevated fasting glucose level.

- The skeletal muscles fail to uptake glucose and as a result, is unable to synthesize glycogen post a meal resulting in high post-prandial blood sugar level.

- Failure in lipoprotein lipase inhibition in the adipose tissue, which results in excessive levels of the FFAs in the bloodstream, which in turn exacerbates the condition of insulin resistance[20].

In combination with genetic predisposition, obesity and sedentary behavior birth insulin resistance which leads to stress on β-cells and their malfunction which gradually lowers the insulin output. Mechanisms behind insulin resistance are:

Lipid accumulation and insulin receptor substrate proteins :

The phosphorylation of tyrosine is the primary mechanism by which the insulin signal travels from the insulin receptor via the intracellular signaling peptide cascade. Ectopic accumulation of lipids raises DAG (diacylglycerol) levels in tissue, which activates PKCθ in muscle, PKCδ and PKCε in the liver[8]. Insulin resistance results from activation of these PKCs since they phosphorylate serine residues on IRS-1, which may be a mechanism by which the insulin signal is attenuated to normally switch off the insulin response[12].

Dysfunctional mitochondria :

A theory relating mitochondrial dysfunction to insulin resistance is the buildup of reactive oxygen species inside the mitochondria. A dysfunctional electron transport chain (ETC) may cause excessive leaks of electron, which would then cause excessive reactive oxygen species (ROS) production and cellular damage. A surplus of ROS that outpaces the antioxidant capacity of the cell, damages cellular contents and affects viability and function is known as oxidative stress[28].

Additionally, it has been discovered that people with T2DM have downregulated PGC 1α regulated genes which are crucial in oxidative metabolism and mitochondrial biogenesis[39].

Adipokines :

Adipose tissue changes physically as its size changes (fat cells become larger or more numerous). As a result, adipocytes and other cells in the tissue start producing TNFα, which promotes the synthesis of monocyte chemoattractant protein-1 (MCP-1) in various adipose tissue cell types and can be the primary element luring macrophages from the bloodstream to fat tissue. Also, changes in the secretion of leptin & adiponectin brought on by TNFα may encourage macrophage migration to adipose tissue resulting in an increased local production of the inflammatory cytokines, which could change adipocyte function and its production[3].

Unfolded protein response (UPR) :

The primary organelle in charge of secretory protein production, it's folding, and trafficking is endoplasmic reticulum. When the capacity and the demand of the endoplasmic reticulum outmatches, or there is an increased protein production or disruption in its process; it leads to endoplasmic reticulum stress and activates UPR. This response is an adaptive mechanism to retain the homeostasis of the endoplasmic reticulum. In case of failure to restore the balance, UPR signaling ultimately leads to death of the cell[4]. Misfolded or

unfolded proteins in the ER lumen activates the UPR.

The three unique sensors which are responsible for carrying out the unfolded protein response are: PKR-like ER kinase (PERK), Inositol-requiring protein 1 (IRE1α), and Activating transcription factor 6 (ATF6). PERK attenuates translation of the protein and activates the transcriptional process regulated by transcription factors like ATF3, ATF4, and CHOP by phosphorylating eIF2α (Eukaryotic Initiation Factor 2)[34]. While undergoing kinase activation, protein IRE1α splices mRNA which encodes for XBP1 to activate certain transcription factors, which drives ER chaperons and foldases, expansion in the size of endoplasmic reticulum, and ERAD (endoplasmic reticulum-associated degradation). ATF6 protein is cleaved by S1P (site 1 protease) & S2P (site 2 protease) upon its arrival to Golgi complex in response to unfolded or misfolded protein accumulation. The cytosolic region of ATF6 then translocates to the nucleus behaving as a transcriptional factor which carry outs ER chaperones' transcription.

Molecularly, JNK activation by IRE1α is hypothesized to be the mechanism through which the UPR causes insulin resistance[18].

Declining β cell function :

The time by which the disease is diagnosed, there is already a 40-50% loss in the function of beta cells. Further, a 4-5% loss in function is anticipated yearly after diagnosis. Multiple reasons such as aging, mitochondria dysfunction, genetic abnormalities, glucotoxicity, lipotoxicity, glucolipotoxicity, amyloid deposition, ER stress, obesity (by activating inflammatory response), and insulin resistance can be reasons behind the β-cell failure. Initially, three major defects contributing to beta cell failure are[40]:

Decline in β cell mass :

Dysfunction in beta cells is usually linked to beta cell death which can lead to around 60% loss in beta cell mass. Apoptosis is the primary reason behind the declining beta cell mass which is usually due to glucotoxicity. Chronic hyperglycemia results in IL-1β production within the beta cells which upregulates Fas receptors leading to caspase-8 activation[11]. Normally caspase-8 is inhibited by protein FLIP (FLICE inhibitory protein) which along with Fas mediates proliferation, but in T2DM there is decreased FLIP level and upregulated Fas receptor levels resulting in apoptosis and fragmentation of DNA[17].

Exhausted β cells :

As discussed earlier, metabolic stress such as insulin resistance results in beta cell exhaustion due to increased insulin demand. Mechanisms like insulin resistance and lipotoxicity can place severe stress on beta cells leading to ER stress. Increased ER stress whilst a load of proinsulin processing exhaust beta cells and leads in the accumulation of unfolded or misfolded insulin activating UPR[41].

Dedifferentiation of β cells :

Lineage tracing studies revealed that instead of apoptosis, dedifferentiation is the

primary factor behind beta cell deficit[42]. The differentiated cells then share similar phenotyping such as other islet cells of the pancreas. Such a fact states that there is beta cell dysfunction without apoptosis in such case[1,40].

T2DM is a progressive metabolic disorder that, when left undetected or untreated for a long time proves to be fatal. Also, poor control over the disease results in micro and macrovascular complications. There is an increasing rate of disease prevalence among the younger age group which is worrisome. A single factor is not sufficient to cause type 2 diabetes mellitus, multiple factors act in concert to develop the disease. The individuals are started on anti-diabetic therapies without knowing the pathology manifesting it and hence results in poor control of the disease. In order to treat or prevent T2DM there is a need to target multiple pathologies in order to achieve proper glycemic control along with aiming to reduce the cardiovascular risk associated with the disease. Currently proposed theories provide good insight into disease development, however, some still have gaps that need to be filled. In order to specifically target the problem and individualize the therapy for better disease control, there is still more research needed in the field of pathologies regarding the disease development.

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