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Diabetes Mellitus: A Group of Genetic-Based Metabolic Diseases

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Abstract

Diabetes mellitus (DM) is a disease characterized by defects in action and/or secretion of insulin that results in chronic hyperglycemia and long-term severe vascular complications. The main clinical presentations with the proven genetic base are covered. Type 1 diabetes (DM1) is an autoimmune, heterogeneous, multifactorial, and polygenic-based disease. Selectively destroys 90% of beta cells of the pancreas, mediated by activated T lymphocytes in patients with haplotypes linked to major histocompatibility complex (MHC). Genetic and genomic studies have been carried out in family groups, demonstrating up to 15 affected chromosomal regions. Type 2 diabetes (DM2) presents genes with various polymorphisms which, together with post-genomic and environmental factors, make it more complex to understand the pathogenesis. Monogenic diabetes comprises neonatal diabetes (ND), maturity onset diabetes in young (MODY), an autosomal dominant transmission which is inherited directly in three successive generations, and the very rare mitochondrial diabetes. Latent autoimmune diabetes in adults (LADA) mainly affects patients with normal weight and initially diagnosed as DM2. Its characteristics are low levels of C-peptide in both fasting and post-glucagon tests. They present MHC alleles of susceptibility and positive autoantibodies: Anti-decarboxylase glutamic acid.

Keywords: diabetes mellitus type 1, diabetes mellitus type 2, monogenic diabetes, LADA

1. Introduction

Diabetes mellitus (DM) is a group of metabolic diseases of different etiologies characterized by chronic hyperglycemia resulting from a deficit in both the secretion and the action of insulin hormone. Now-a-days, there is a genetic basis of these clinical manifestations. In this chapter, we describe the most important ones such as diabetes mellitus type 1 (DM1), diabetes mellitus type 2 (DM2), monogenic diabetes, and latent autoimmune diabetes in adults (LADA).

2. Diabetes mellitus type 1

DM1 is characterized by autoimmune destruction of the beta cells of the pancreatic islets, which leads to an extreme insulinopenia. The character of autoimmunity confirm the presence of islet cell antibodies (ICA), insulin auto antibodies (IAA),

glutamic acid decarboxylase auto antibodies (GAD65), protein tyrosine phosphatase 2 (IA-2), and zinc transporter gene ZnT8 [1]. There is an interaction between genetic and environmental factors in the development of DM1 (**Figure 1**).

2.1 Genetic factors of DM1

DM1 is a polygenic disease, with at least 15 associated chromosomal regions. The leading group of genes that predispose to type 1 diabetes is located on human chromosome 6 specifically at 6p21, and this chromosomal region contains a group of genes called major histocompatibility complex (MHC), responsible for the immune response and the antigen presentation of the beta cell to T lymphocytes [2]. The classic histocompatibility genes are extremely polymorphic (amino acid sequence differs among individuals) and include MHC-A, B, and C molecules (class I histocompatibility antigens) and the immune-response genes DP, DQ, and DR (class II histocompatibility antigens). Numbers (DR3, DR4; A1, A2; B1, B8) are given to distinguish different alleles of any given gene. The designation w (workshop) with numbers is given for provisionally named alleles (DQw8, DQw7) [3]. DM1 has been associated mainly with allelic variants of MHC-DR (DR3/DR4). The MHC locus is a genetic factor of great importance in DM1, and it was first shown in an association study that revealed that about 95% of all patients with DM1 were heterozygous for MHC-DR3/DR4. The majority of type 1 diabetics have the MHC-DR3, MHC-DR4 haplotype, or both [4]. Susceptibility to DM type 1 is associated with these linked DQ alleles that are often in linkage disequilibrium with DR. The closest association in DM1 occurs with the haplotypes DQA1*0301, DQB1*0302, DQA1*501, and DQB1*0201. It has been shown that the beta DQ chains of those affected have valine, alanine, or serine at position 57; near the peptide-binding gap, presence of aspartic acid is normal [5] Factors involved in the pathophysiology of DM1 are shown in (**Figures 2 and 3**).

However, there are exceptions to this association, which indicates that amino acids other than Asp57 at position 57 of the beta chain play an essential but not exclusive role in the susceptibility to DM1 [5]. There is an interaction between genetic and environmental factors in the development of DM1.

2.2 Heritage in type 1 DM

The inheritance of DM1 is unknown. Several hypotheses have been suggested, such as that of dominant inheritance, but it is ruled out by the rarity of DM1 in relatives, children, and descendants. The possibility of recessive inheritance was also

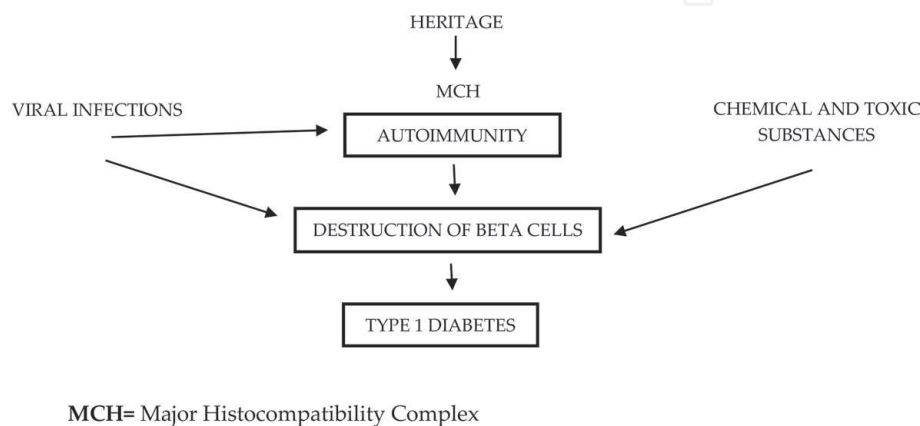


Figure 1.
Pathogenesis of type 1 diabetes.

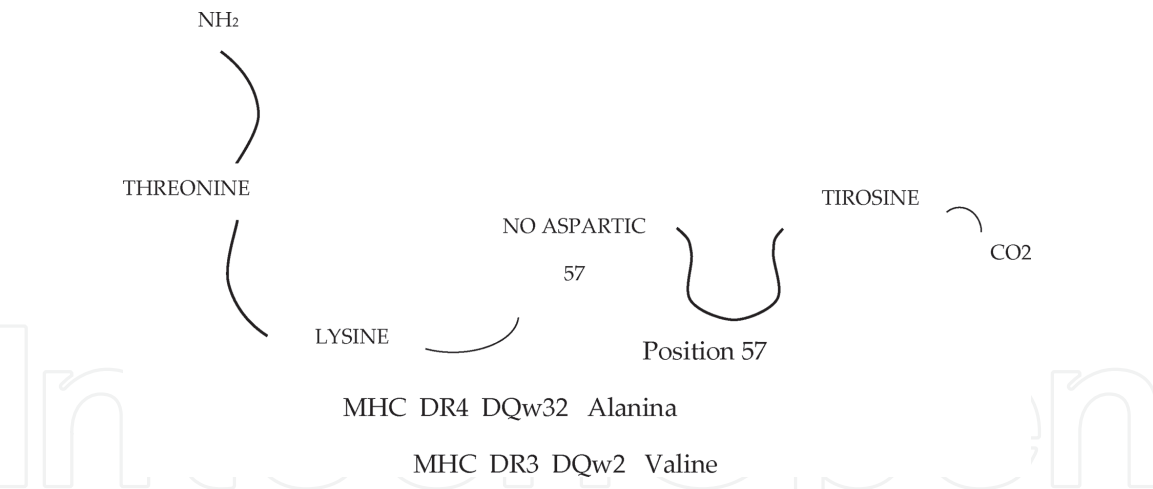


Figure 2.
Etiology of type 1 diabetes. MHC-DQ B antigen amino acid sequence.

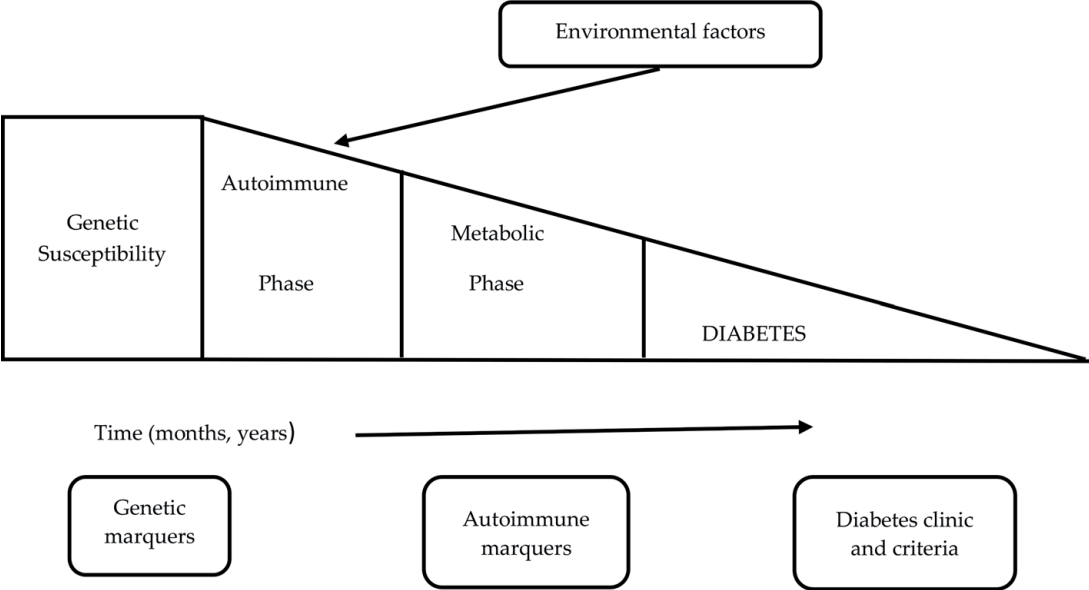


Figure 3.
Pathophysiology of type 1 diabetes.

considered, however, invalidated because in homozygotes for the DR3 or DR4 alleles, the susceptibility to the disease is not increased. The observation that heterozygosis DR3/DR4 increases the risk for diabetes, compared with that presented by homozygotes from other high-risk alleles, suggests a polygenic way of inheritance. The diabetogenic MHC haplotype is necessary for the susceptibility to DM1, but must be positively or negatively influenced by genes not linked to MHC, such as the gene located close to the repeated DNA sequence minisatellite, in the promoter region of the gene of the insulin (chromosome 11p15); one gene on chromosome 11q and another on chromosome 6q [6]. Some genes seem to confer protection against the development of the disease. For example, the DQA1*0102 and DQB1*0602 haplotypes are present in 20% of the United States population but is extremely rare in individuals with DM1 (<1%). This situation indicates that several genes are interacting to determine the DM1 phenotype, so this disease presents genetic heterogeneity (**Figure 4**).

DM1 is uncommon in Chile and usually does not occur in native Chilean families. A study of a family with an affected female child was carried out in a Mapuche community in the Southern (VIII region). This case is a unique and sporadic DM1 case with Mapuche heritage. Genetic analysis by PCR was done

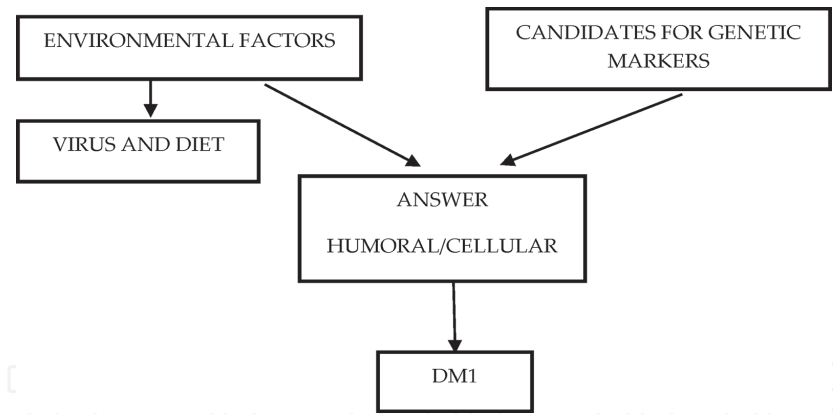


Figure 4.
Interaction of genetic and environmental factors about the immune response in type 1 diabetes.

to detect class I and II HLA genes by reverse dot blot. The proband, her mother, and sister had positive islet cell antibodies (ICA). Her father and brother were negative. All the family was positive for anti-glutamic decarboxylase antibodies (GAD65). All subjects had HLA-DRB1 0407/0407 and HLA-DQB1 0302/0302 alleles. The index case and her father were homozygotes for the HLA-A1: A*68012/A*68012 allele. No evidence of viral infections such as rubella, mumps, or measles was found in this family. All genotypes were compared with the European population, where the diabetogenic combination DR4/DQB1*0302 is the most prevalent [5]. Finally, despite of the high relative risk of DM1 in subjects with certain MHC class II alleles, it does not develop in the majority of people who inherit these alleles, which also suggests that environmental factors influence development of the disease [1] (**Figure 4**).

2.3 Clinical manifestations of type 1 diabetes

The onset of DM1 is usually abrupt, with severe symptoms attributable to hyperglycemia maintained for days or weeks, such as polyuria, polydipsia, polyphagia, asthenia, and progressive weight loss, and manifests as diabetic ketoacidosis. Two pathophysiological situations must be present to establish this condition: extreme insulinopenia and increase of counterregulatory hormones, principally glucagon. DM1 is observed mainly in children, adolescents, and young adults, generally under 30 years, although it can also appear in individuals of more advanced ages.

3. Diabetes mellitus type 2

DM2 has an important genetic component in its pathogenesis. There are multiple genes involved in different metabolic pathways that contribute to the pathogenesis of the disease, in addition to environmental factors such as obesity, an unhealthy diet, and a sedentary lifestyle. These genes have various polymorphisms, which added to post-genomic factors related to their expression and inhibition are responsible for this complex disease, as seen in **Figure 5**.

3.1 Heritage in type 2 diabetes

The genetic nature of DM2 has been based on high heritability, estimated at 30–70% and high prevalence in some ethnic groups; 39% of patients with DM2 have at least one relative with the disease. There are 1.5–3 times higher risk of presenting

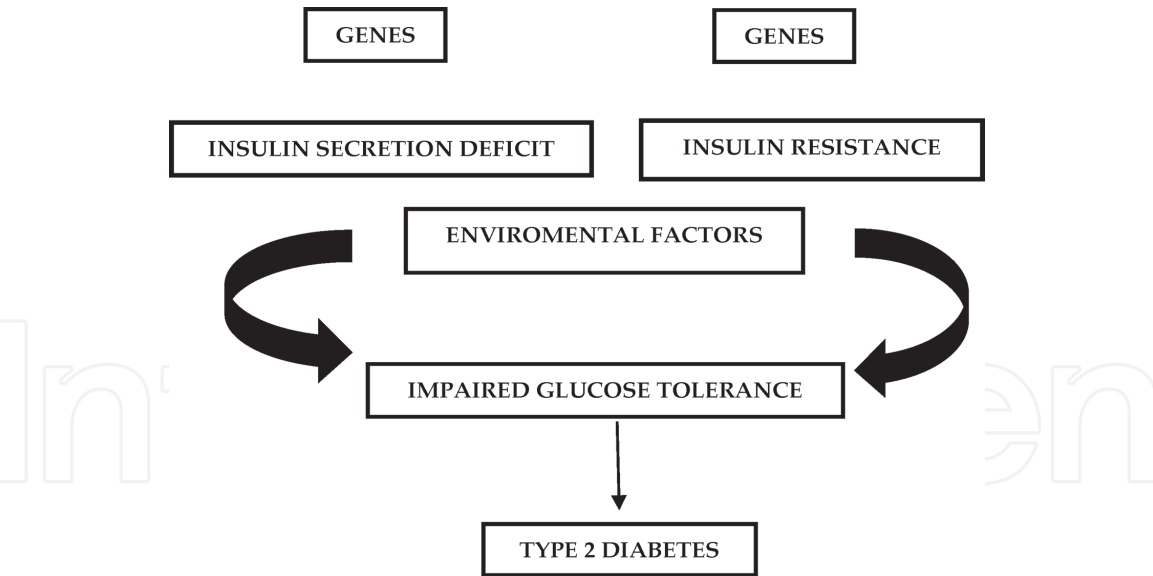


Figure 5.
Pathogenesis of type 2 diabetes.

DM2 if there is a history of the disease in the family; if the affected one is the mother or the brother, the risk is of 2 and 3 times greater, respectively. The heritability described is mainly in middle-aged people (35–60 years) decreasing markedly in larger groups [6]. First-degree relatives of people with DM2 show early defects in insulin withdrawal and action [7]. If other factors such as obesity and impaired fasting glycemia are added to the family history, the risk of presenting the disease is 16 times higher. The presentation of DM2 involves genes that code for proteins or related enzymes in the process of pancreatic formation, synthesis, sectioning, and insulin action. Genome-wide association studies (GWAS) have shown more than 100 locus susceptible to DM2, most related to insulin sequestration, suggesting that this alteration, essential for the presentation of the disease, is more strongly determined by genetic factors.

The genetic susceptibility given by the presence of risk variants is responsible for about 10% of the family aggregation of the disease. There is a considerable percentage of “missing heritability” that could be explained by: frequent variants of low power, others of low frequency but powerful effect, interaction between gene–gene, gene–environment interaction, epigenetic factors, and others.

3.2 Genetic defects in the action of insulin

The genetic variants associated with the action of insulin and DM2 are related to the transcription of the intracellular signal of insulin. Due directly to protein mutations of the signaling cascade intracellularly or indirectly due to mutations in genes associated with metabolic syndrome, such as those related to obesity and lipid metabolism. Yaghootkar et al. evolved cluster of 17 genetic variables associated with insulin resistance related to the development of DM2 [8]. Some of the genes that are most related to DM2 appear in **Table 1** [9].

3.2.1 *Insulin receptor substrate-1 gene (IRS-1)*

Located on chromosome 2, it encodes peptides related to the insulin signaling cascade. Arg972Gly mutation, a common variant of IRS-1, is more prevalent in Caucasian DM2 than in non DM2, and in obese adults, it has been associated with increased insulin resistance.

Insulin resistance genes
• Insulin receptor substrate gene-1 (IRS-1)
• Peroxisome proliferator-activating receptor gene (PPAR γ)
• Protein tyrosine phosphatase receptor type D (PTPRD)
• β -3 adrenergic receptor gene
• Adiponectin gene
• Leptin gene

Table 1.
Candidate genes of DM2 for insulin resistance.

3.2.2 *Peroxisome proliferator-activated receptor gamma 2 gene (PPARG)*

Located on chromosome 3, it codes for the peroxisome proliferator-activated receptor. It has a key role in adipocyte differentiation. The presence of a type of polymorphism is associated with 1.25 odds ratio (OR) for DM2.

3.2.3 *Protein tyrosine phosphatase receptor type D gene (PTPRD)*

Located on chromosome 9, it is encoded for PTPRD. Its overexpression in the skeletal muscle generates insulin resistance. Diabetes-related polymorphism has been evidenced in Chinese with an OR 1.57.

3.2.4 *β -3 adrenergic receptor gene*

It regulates lipolysis of visceral fat and is related to thermogenesis. It is associated with risk of obesity and early presentation of DM2.

3.2.5 *Adiponectin gene*

It is located in chromosome 3q27. Low levels of adiponectin have a role in the pathogenesis of insulin resistance and obesity. Insulin sensitivity is a consistent and independent predictor factor of DM2. Variants in the genes that code for adiponectin receptor have proven to be a risk factor for presenting DM2 in some populations.

3.2.6 *Leptin gene*

Mutations related to this gene are involved with the pathogenesis of obesity and glucose metabolism, thereby decreasing insulin sensitivity and inhibiting the expression of the pre-proinsulin gene in the pancreatic β -cells. Recent evidence suggests that high circulating levels of leptin probably independent of adiposity are associated with an increased risk of type 2 diabetes in men.

3.3 Genetic defects in insulin secretion

There are multiple loci associated with this defect that have been found in GWAS studies. Among them most relevant are those presented in **Table 2** [9].

3.3.1 *Calpain 10 gene (CAPN10)*

Encodes a family of calpain enzymes, it was one of the first to study in linkage, but it is currently known that the risk of this association is low OR 1.17 [10].

Insulin secretion genes
• Calpain 10 gene (CAPN10)
• Transcription factor 7-like 2 (TCF7L2)
• Potassium voltage gated channel subfamily
• Q member 1 (KCNQ1)
• J member 11 (KCNJ11)

Table 2.
Candidate genes of DM2 for insulin secretion.

3.3.2 *Transcription factor 7-like 2 gene (TCF7L2)*

It has appeared to be more relevant in the genetic susceptibility to DM2, since a polymorphism of this gene has been found in several ethnic groups of DM2 patients. The increased expression of the gene in the pancreatic beta cell causes secretion alteration due to a decrease in the incretin effect. In liver and adipose tissue, it generates insulin resistance. The risk of DM is consistent with an OR up to 2.5 for homozygous variable [11].

3.3.3 *Potassium voltage-gated channel subfamily*

Q member 1 (KCNQ1) located on chromosome 11, it codes for the same name channel present in the cell membrane. There are four variants associated with DM2 in various populations. Studies suggest that the effect linked to DM2 is related to epigenetic modifications. J Member 11 (KCNJ11): code for Kir6.2 ATP-sensitive potassium channel. Variant E23K increases the risk of DM2 by 1.2 times associated with decreased insulin sequestration [12].

3.4 **Epigenetics in DM2**

Epigenetics or genetic modifications not associated to nucleotide mutations that influence the expression of a gene play a key role in the pathogenesis and T2DM complications. There are prenatal factors that induce epigenetic changes that increase the risk of T2DM by altering the secretion and sensitivity of insulin, hepatic glucose production, and the release of hormones involved in glucose metabolism.

The sustained activation of inflammatory-related genes in T2DM patients by epigenetic mechanisms contribute to the progression of vascular complications, arteriosclerosis, and retinopathy.

Types of epigenetic modifications and relation to DM2 are shown in **Figure 6**.

3.4.1 *Methylation and histone-modification*

These are the epigenetic modifications most associated to vascular complications related to DM2. Both hypomethylations and hypermethylations generate persistent activation of proaterogenic genes such as NF-kB-dependent oxidative and inflammatory signaling pathway.

3.4.2 *Non-coding RNAs (ncRNAs) and chromatin remodeling*

Non-coding nRNAs play an essential role in post-transcriptional regulation of gene expression.

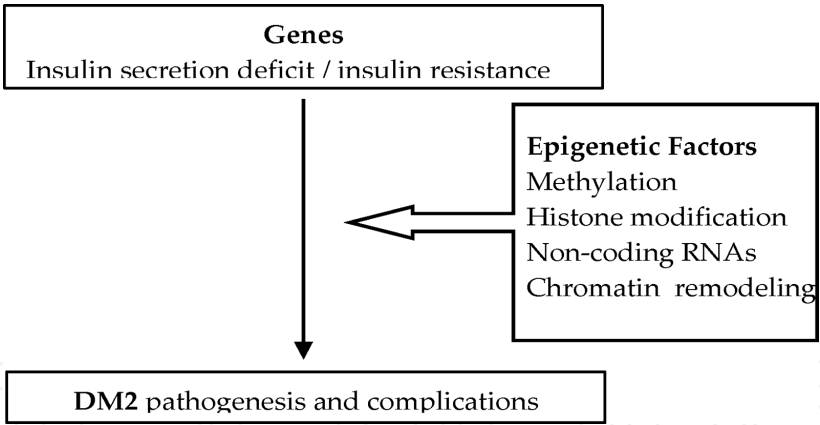


Figure 6.
DM2 epigenetic factors.

The most extensively studied are short nucleotide sequences (18–25) called MicroRNA (miRNA) and represent the principal epigenetic regulators of gene expression.

Deregulation in epithelial cells is correlated to the risk of developing vascular complications in DM2.

There are miRNAs associated with inflammation; for example, miR-155, which is associated to the progression of kidney disease in DM2 patients and miR-126, that when inhibited in pre-diabetes patients is correlated with the increase of activation of the NF-kb pathway in endothelial cells.

Long non-coding RNAs (lncRNAs) have been associated with pancreatic B cell damage, increase of inflammatory processes, alterations in the immune response, and insulin resistance in TSDM. Chromatin remodeling that regulates gene expression, such as p66Shc, has been linked with insulin resistance, increase of vascular risk in DM2, and obesity [13].

DM2 is a polygenic disease, of high heritability, which involves genes related to insulin and action, in addition to those that code for the components of the metabolic syndrome. What has been discovered so far is broad but only accounts for a part of the complex relationship of genetics and its phenotypic expression in DM2. The study of epigenetics in DM2 has opened the possibility to find pathogenetic markers at the onset of the disease and during the development of chronic complications, which will allow early screening and individualized treatment in the near future.

4. Monogenic diabetes

It is caused by one or more defects in a single gene. The disease can be inherited within a family by the genetic transmission of a dominant or recessive nature and not Mendelian. It can also be presented as a spontaneous case due to a de novo mutation [14]. Monogenic diabetes includes neonatal diabetes, maturity onset diabetes young (MODY), and mitochondrial diabetes (**Figure 7**).

4.1 Neonatal diabetes

It is defined as diabetes that appears before 6 months of age and is subdivided into transitory (TNDM) and permanent (PNDM). TNDM develops in the first weeks of life and resolves within a few months, but 50% have a relapse in adolescence or adulthood. TNDM is most frequently caused by abnormalities

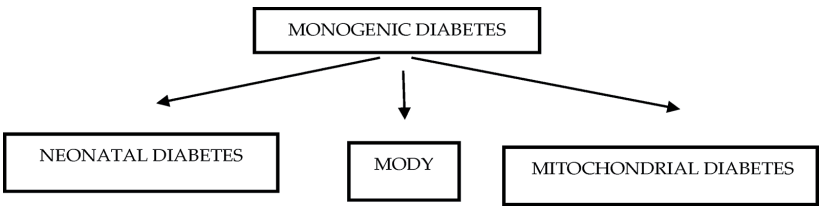


Figure 7.
Subtypes of monogenic diabetes.

in the imprinted region of chromosome 6q24 (spanning two candidate genes *PLAGL1* and *HYMAI*), thereby leading to overexpression of paternally derived genes. Activating mutations in either the *KCNJ11* or *ABCC8* genes encoding the two subunits (Kir6.2 and SUR1, respectively) of the adenosine triphosphate-sensitive potassium channel on the beta-cell membrane prevent insulin secretion in response to hyperglycemia and can cause both PNDM and TNDM. Diabetes caused by mutations in *KCNJ11* and *ABCC8* often responds to sulfonylureas. Mutations in other genes critical to beta-cell function and regulation, and in the insulin gene itself, also cause PNDM. Heterozygous coding mutations in the pre-proinsulin gene (*INS*) are the second common cause of PNDM after K_{ATP} channel mutations [15, 16].

4.2 MODY

Described in 1975 by Tattersall and named in 1976 by Fajans, MODY is recognized as a form of mild-presenting family diabetes that is diagnosed during adolescence or early adulthood. Currently, other types are identified with a less classic presentation [4, 5]. It is estimated that its prevalence is underestimated, and it would correspond about 5% of DM2 and a similar percentage in DM1.

It is presented in 3.6% of the population with diabetes under 30 years [4]. MODY is a heterogeneous group of disorders caused by mutations in genes essential for beta-cell development, function and regulation, glucose sensing, and in the insulin gene itself. Although at least 14 genes are associated with MODY, we describe the four most frequent types (**Table 3**). Mutations in *HNF-1 α* , *HNF-4 α* , *HNF-1 β* , and *GCK* genes account for over 80% of all known MODY cases.

Heterozygous mutations in three of them are responsible for the majority of cases of this type of diabetes: glucokinase gene (*GCK*); two genes encoding hepatocyte nuclear factor (HNF) transcription factors *HNF-1 α* and *HNF-4 α* . Most MODY-causative genes, except *GCK*, encode transcription factors expressed in pancreatic beta-cells (**Table 4**). The majority of patients with MODY exhibit isolated diabetes or stable mild fasting hyperglycemia, but some MODY subtypes have additional features, such as renal abnormalities (MODY 5) and pancreatic exocrine dysfunction (MODY 6) [17–20].

4.2.1 MODY 2 (*GCK*)

GCK, a glucose sensor expressed in pancreatic beta-cells, is a key enzyme in glucose metabolism that catalyzes the conversion of glucose to glucose-6-phosphate and thus controls glucose-mediated insulin secretion. As such, *GCK* serves to facilitate insulin release that is both appropriate and proportional to the blood glucose concentration. Heterozygous inactivating mutations in *GCK* (MODY 2) increase the set point for insulin secretion in response to increased blood sugar, thereby causing stable, mild fasting hyperglycemia. More than 600 mutations have been

	Gene	Frequency %	Physiopathology
MODY 2	GCK	15–20	Glucose sensing defect
MODY 3	HNF-1α	30–50	Insulin secretion deficit
MODY 1	HNF-4α	5	Insulin secretion deficit
MODY 5	HNF-1β	5	Beta cell dysfunction

GCK, glucokinase; HNF, hepatocyte nuclear factor.

Table 3.
Frequent types of MODY and its pathophysiological alteration.

MODY subtypes	Age at the onset of diabetes (years)	Hyperglycemia	Other clinical features	Possible treatment
1	17 (5–18)	High	Neonatal diabetes, neonatal hyperinsulinemic hypoglycemia, low triglycerides	Sensitive to sulphonylureas
2	10 (0–18)	Mild	Mild fasting long-term stability asymptomatic	Diet no medication
3	4 (4–18)	High	Glycosuria—very low C-reactive protein of <0.5 mg/dl	Sensitive to sulphonylureas
5	<25	Variable	Renal malformations, genital anomalies, pancreatic hypoplasia, low birth weight	Insulin

Table 4.
Clinical characteristics of most common MODY subtypes.

reported. Patients with MODY 2 are usually asymptomatic, and they do not require treatment. In pregnancy, insulin may be required to prevent fetal complications, such as high birth weight and neonatal hypoglycemia. These neonatal complications are dependent on whether the mutation is inherited.

In 2018, a MODY family study was published in Chile [21]. The case is about a 17-year-old woman with DM, fasting blood glucose 130 mg/dl, without ketosis or weight loss, and BMI 18 kg/m². No signs of insulin resistance were seen, C-peptide 2.3 ng/ml (normal) and negative DM1 autoantibodies. In a family study, diabetic father and brother with impaired fasting blood glucose (**Figure 8**). The genetic-molecular analysis of the GKC gene, the patient, the father, and the brother presented a mutation at position 1343 of exon 10 corresponding to a heterozygous exchange of guanine for adenine (1343 G > A). The change is not synonymous and determines that at position 448 of the GKC enzyme, the amino acid glycine is substituted by aspartic acid. Diagnosis of MODY 2 was confirmed, and it was established that the mutation was by paternal line.

4.2.2 MODY 3 (HNF-1α)

The transcription factor HNF-1α is expressed in the liver, kidney, intestine, and pancreatic beta-cells. Heterozygous HNF-1α mutations result in progressive beta-cell dysfunction that leads to diabetes in early adult life.

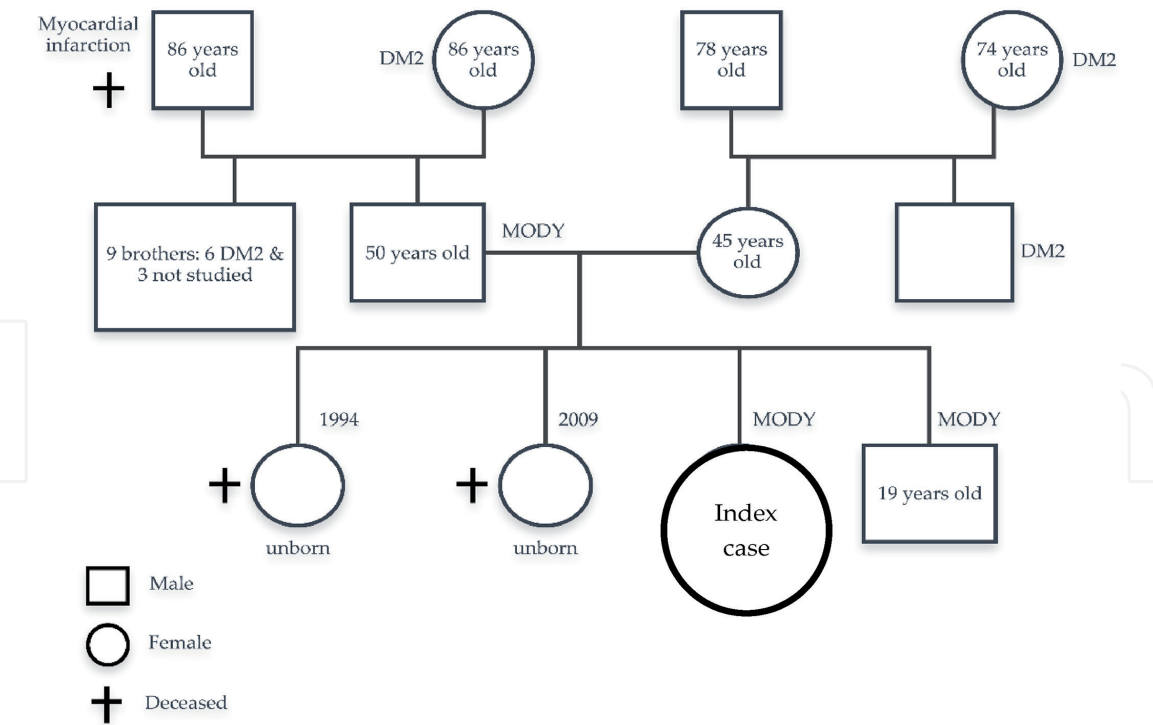


Figure 8.
Chilean family inheritance pattern MODY 2.

According to studies, a total of 414 different HNF-1 α mutations were identified in 1200 families, where a mutation (P291fsinsC) in exon 4 was the most common. Hyperglycemia associated with MODY 3 may be severe, and the risk of microvascular and macrovascular complications is similar to DM1 and DM2. Because of this, patients require strict glycemic control and close monitoring of possible complications. There is a defect in the renal resorption of glucose, characterized by a decreased glucose threshold for glycosuria and reduced tubular reabsorption of glucose. Patients are sensitive to sulfonylurea therapy, but most of them eventually progress to insulin treatment. This subtype of MODY is the most frequent in Europe and the US.

4.2.3 MODY 1 (HNF-4 α)

This MODY was the first described. The transcription factor HNF-4 α is expressed in the liver, kidney, and pancreatic beta-cells. HNF-4 α gene encodes a transcription factor important for pancreatic development and beta-cell differentiation and function. Heterozygous HNF-4 α mutations cause a similar clinical phenotype observed in MODY 3. Most patients have a progressive insulin deficiency, diabetes onset before age 25 years, and a response to relative low-dose sulfonylurea therapy. Fetal HNF-4 α heterozygosity results in macrosomia due to hyperinsulinemia in utero and subsequent neonatal hyperinsulinemic hypoglycemia, which is responsive to diazoxide. MODY 1 is associated with triglyceride metabolism, and mutation carriers may exhibit reduced levels of apoproteins (apoAII, apoCIII, and apoB).

4.2.4 MODY 5 (HNF-1 β)

The transcription factor HNF-1 β is involved in the organogenesis of the kidney, genitourinary tract, liver, lungs, gut, and pancreas. Patients with heterozygous

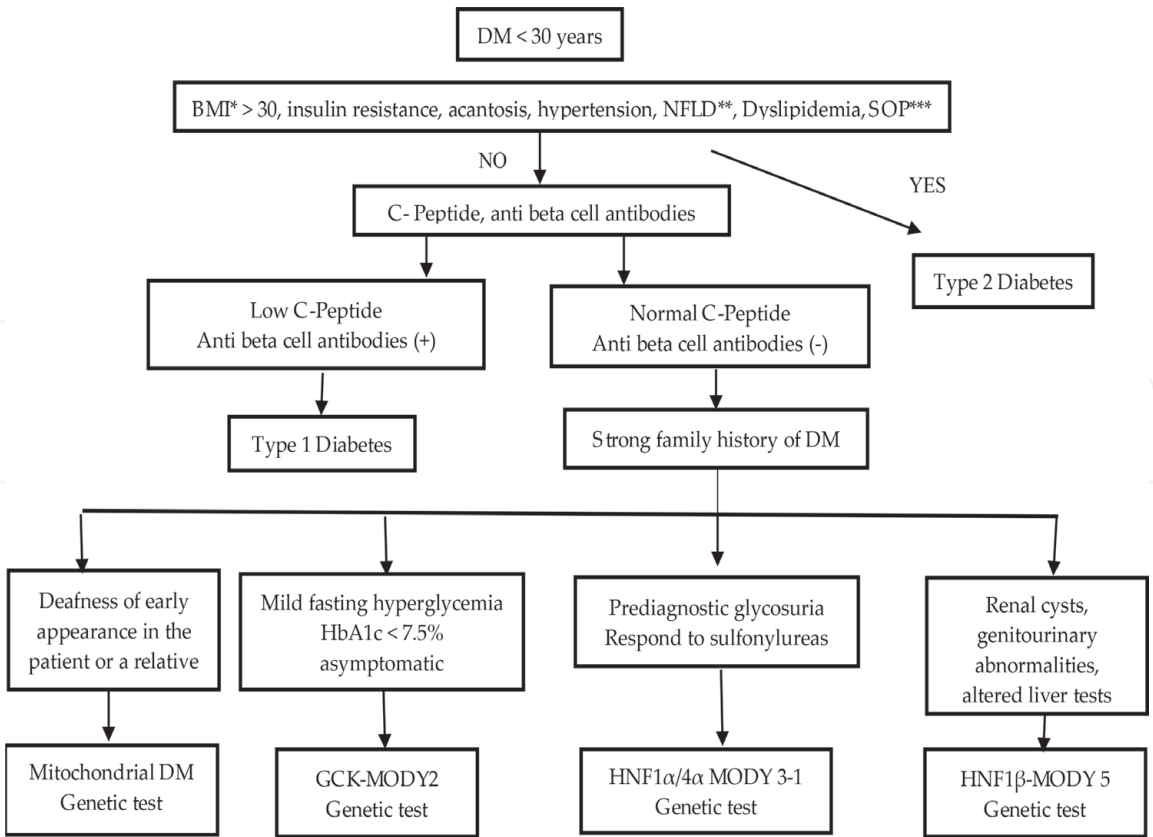
mutations in HNF-1 β rarely present with isolated diabetes. By contrast, patients usually have renal disorders (especially renal cyst and renal dysplasia). Urogenital tract abnormalities and atrophy of pancreas may also occur. The sensitivity to sulphonylureas is absent, and early insulin therapy is required. At least 50% of HNF-1 β MODY cases are due to microdeletion of chromosome 17 (17q12) involving between 15 and 29 genes, including HNF1 β . De novo mutations are frequent (up to 50% of cases) and hence family may be absent.

4.3 Mitochondrial diabetes

This disease is a mitochondrial disorder characterized by maternally transmitted diabetes and sensorineural deafness. The most common form is caused by an exchange between an adenine for guanine (3243A/G) in DNA. This mutation also causes a severe neuromuscular disease syndrome called MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke). Diabetes onset is usually insidious, but 20% of patients have an acute presentation, even in diabetic ketoacidosis. It usually occurs in the third to fourth decades of life in non-obese individuals [14].

5. Diagnostic algorithm of diabetes in young adult

Figure 9 shows a diagnostic algorithm for diabetes in patients under 30 years of age.



*BMI= Body mass index (kg/m²), **NFLD= Non-alcoholic fatty liver disease, ***POS= polycystic ovary syndrome

Figure 9. Diagnostic algorithm of diabetes in young adult.

6. LADA: Latent autoimmune diabetes adult

Diabetes is a complex disease, which makes its classification difficult. DM1 is caused by autoimmune destruction of the beta cell, which leads to absolute insulin deficiency. DM2 is secondary to the progressive loss of insulin secretion by the beta cell, in the context of insulin resistance. Other types of diabetes are gestational diabetes, MODY, post-transplant, and exocrine, among others [22]. DM1 is a heterogeneous disease, the incidence of which is higher in children and adolescents, characterized by the presence of specific immunological markers. However, no less than a percentage of adults experience the disease; so, the term latent adult diabetes (LADA) has been coined. In this case, the disease is even more heterogeneous, since there is a variable proportion of destruction of the beta cell, with the presence of immunological markers, but zero or deficient initial insulin requirements, so they can initially be misclassified as DM2 [23]. These patients probably have pathophysiological processes similar to DM1, but with differences in genetic penetrance and immune factors. The term LADA was introduced in the 90s, to define a subgroup of patients with diabetes initially not requiring insulin, but with immunological markers of DM1 detectable in the serum [24]. In 2015, the Immunology of Diabetes Society proposed three diagnostic criteria for LADA: age of onset > 30 years, presence of any DM1 marker antibody, and lack of need for insulin treatment for at least 6 months from diagnosis [25].

Currently, the American Association of Diabetes (ADA) does not recognize this entity, but instead classifies it within the group of patients with DM1, but every day there is more information about its clinical and pathophysiological characteristics, which keep the debate open.

6.1 Epidemiology

The available data show that the prevalence of LADA is higher than previously recognized. About 40% of cases of DM1 occur in adults over 30 years [26]. Scandinavian studies show that 7.5–10% of the population with apparent DM2 have circulating antibodies against the beta cell (ICA or GAD 65) [27]. The Action LADA study, conducted in Europe, which evaluated 6000 adults attended in primary and secondary care centers, reported a frequency of 9.7% of LADA [28]. A Chinese study, LADA China study reported a 5.9% positive antibody in adults previously diagnosed with DM2 [29]. The prevalence of LADA is, therefore generally underestimated, due to the lack of study with antibodies in adult patients; so, the level of clinical suspicion should be high.

6.2 Pathophysiology

6.2.1 Genetics

In genotype analysis, patients with LADA have been shown to share genetic characteristics with DM1 (HLA, INS VNTR, CTLA4, and PTPN22) and DM2 (TCF7L2) [30], which might suggest that LADA is a spectrum of insulin deficiency between DM1 and DM2. The HLA-DRB1*04-DQB1*0302 and HLA-DRB1*0301DQB1*0201 haplotypes, which confer high susceptibility to DM1, and decrease progressively with increasing age, have been further diminished in elderly DM1 patients and have been described less frequently even in patients with LADA [31].

6.3 Autoimmunity

DM1 is a known autoimmune disease, mediated by cells. The presence of T lymphocytes that are reactive to islet cells, in LADA, gives us some evidence that there is a cell-mediated immune response as well [32]. Adult autoimmune diabetes has a “lower genetic load,” characterized by lower circulating antibodies than early-onset DM1 in childhood or adolescence, which correlates with less intense beta cell destruction and lower HLA genetic susceptibility. Many studies have compared circulating antibodies in early DM1 in childhood with LADA, finding ICA, AAI, IA-2, and anti ZnT8 more frequently in children than in adults, while anti GAD and IA-2 were found with similar frequency in both ages [33]. Anti-GAD is the antibody most frequently found in patients with LADA, up to 90% positive, also being the most persistent over time. The beta cell function in early DM1 in childhood and adolescence is severely compromised since diagnosis, a difference in LADA in that the deficit is less severe. It has also been found that there is a correlation between age of diagnosis and fasting C-peptide levels, which is related to the latest age of LADA. To explain the later and less aggressive presentation compared to DM1, several theories are postulated, among others: intermittent crisis of autoimmune aggression (**Figure 10**) or greater capacity to regenerate beta cells and protection against the apoptotic process.

6.4 Clinical characteristics

Patients with LADA are a heterogeneous group, with antibody titers and body mass index (BMI). In general, the appearance of the condition is 35 years later, with cases described since the age of 25. Patients with LADA tend to have a BMI higher than DM1, but less than DM2. The existence of other autoimmune comorbidity or their family history is common, mainly thyroid disease. A higher frequency of anti-peroxidase antibodies (TPO) has been seen, in up to 27% of patients, compared to those with anti-GAD negative, which makes it necessary to monitor thyroid function and perform screening for other autoimmune diseases. The initial response to oral therapy is satisfactory, progressing in varying degrees to insulin requirements, from 6 months to several years, depending mainly on antibody titers (**Table 5**).

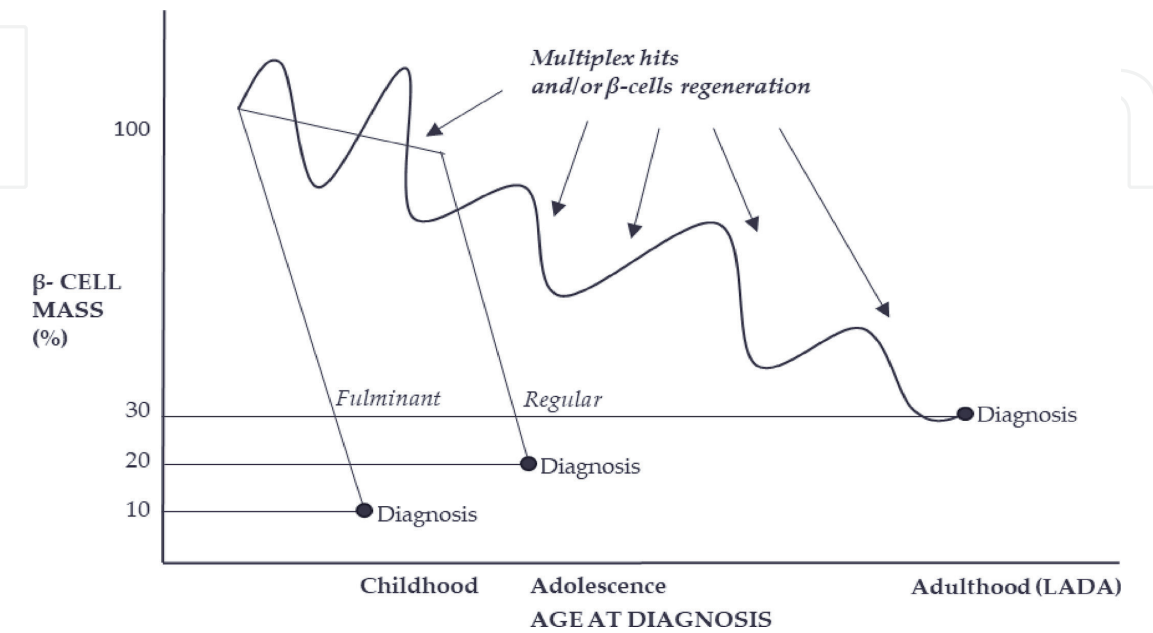


Figure 10. The destruction of beta cell and the appearance of DM1 according to the age of onset and the putative pathogenetic mechanisms.

Clinical features	DM1	LADA	DM2
Age at diagnosis	Childhood and adolescence rare adulthood	>30 years	Adulthood, rare childhood, and adolescence
Start	Acute	Rare acute	Slow
Autoimmunity	Greatly increased	Increased	No modifications
Ketosis	Frequently	Rare	Rare
Insulin resistance	No modifications	Increased or without changes	Severely increased
Beta cell function	Very reduced	Reduced	Increased or unchanged
Insulin requirements	From the diagnostic	>6 months from the diagnostic	Years from the diagnostic
Body mass index	Low or normal	Normal or overweight	Overweight or obesity
MHC susceptibility	Severely increased	Increased	No changes

Adapted to [35].

Table 5.
LADA, DM1, and DM2 clinical features.

High titers of anti-GAD compared to low ones, have lower BMI, less endogenous insulin secretion, and faster progression to insulin-dependence. The presence of anti-GAD antibodies (or ICA) may be useful to identify patients with a previous diagnosis of DM2, who respond partially to treatment with oral antidiabetics and who quickly require insulin therapy. Regarding the metabolic profile, patients with LADA have advantages regarding DM2 with a better profile, that is, lower triglyceride levels, higher levels of HDL, lower BMI, and lower waist circumference. There are no specific guidelines for the treatment of patients with LADA. However, the metabolic goals are the same as for DM1 and DM2 patients, so you should try to achieve HbA1c <7%. The diet and exercise recommendations do not show differences with the classic presentations. Despite the extensive use of oral antidiabetics in DM2, especially metformin, there are no studies of this drug in patients with LADA. Glibenclamide and insulin were compared in LADA patients, finding that the group that used GBC had worse metabolic control and faster deterioration of CP secretion at a follow-up of 30 months. Therefore, the use of sulfonylureas as a first-line drug in this type of diabetes is not recommended. TZD combined with insulin show preservation of beta cell function in a small group of Chinese patients. The use of other agents such as insulin sensitizers could be used in combination with insulin in patients who share characteristics with DM2, that is, BMI >30 kg/m² and signs of insulin resistance. The role of the iDPP4 is not established. Patients with LADA treated with insulin glargine, the effect of adding sitagliptin or placebo was compared, the group with sitagliptin had a minimal decrease in C-peptide at one-year follow-up, compared to placebo. However, more studies support this evidence. We should keep in mind, like DM1 and DM2, patients.

Today, evidence indicates that early insulin therapy, along with changes in lifestyle, is the therapy of choice in patients with LADA when metabolic control is impaired primarily in young patients with elevated antibody titers since this treatment slows the deterioration of beta cell function, controls hyperglycemia, and prevents glucotoxicity [34]. TZD combined with insulin shows preservation of beta cell function in a small group of Chinese patients. The use of other agents such as insulin sensitizers could be used in combination with insulin in patients who share

characteristics with DM2, that is, BMI >30 kg/m² and signs of insulin resistance. The role of the iDPP4 is not established. Patients with LADA treated with insulin glargine, the effect of adding sitagliptin or placebo was compared, the group with sitagliptin had a minimal decrease in C-peptide at one-year follow-up, compared to placebo. However, more studies support this evidence. We should keep in mind, like DM1 and DM2, patients with LADA require a multidisciplinary approach to proper treatment.

6.5 Clinical features of DM1, LADA, and DM2

This Table summarizes major clinical features of DM1, LADA, and DM2.

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