Diabetes and cardiovascular diseases (I)

Diagnosis, Classification and Pathogenesis of Diabetes Mellitus

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Diabetes mellitus (DM) is a metabolic disorder characterized by the presence of chronic hyperglycemia accompanied by greater or lesser impairment in the metabolism of carbohydrates, lipids and proteins. The origin and etiology of DM can vary greatly but always include defects in either insulin secretion or response or in both at some point in the course of disease. When characteristic symptoms of DM are clearly present and blood glucose levels are high enough, the diagnosis is usually unequivocal. However, it is important to remember that the diagnosis is made in asymptomatic patients in most cases, based on the results of routine tests. The prevalence of DM, its specific complications and the presence of other diseases that often accompany DM make this disease one of today's main social and public health problems.

The great increase in information available on the etiology and pathophysiology of DM and its chronic complications has led necessarily to the revision of diagnostic criteria and reclassification of the processes involved. Revised diagnostic criteria and classifications were agreed upon in 1997 and 1998 by the American Diabetes Association and the World Health Organization, respectively, and new recommendations were published. Thanks to cross-representation on the committees, the conclusions and final recommendations are, in general, very similar, although a few minor differences are present.

Clarification of diagnostic criteria and better classification of patients suffering from DM should allow us to make better choices among the various treatment options available and to improve prognosis.

Key words: *Diabetes mellitus. Classification. Diagnosis. Pathogenesis.*

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Diagnóstico, clasificación y patogenia de la diabetes mellitus

La diabetes mellitus (DM) es una alteración metabólica caracterizada por la presencia de hiperglucemia crónica que se acompaña, en mayor o menor medida, de alteraciones en el metabolismo de los hidratos de carbono, de las proteínas y de los lípidos. El origen y la etiología de la DM pueden ser muy diversos, pero conllevan inexorablemente la existencia de alteraciones en la secreción de insulina, de la sensibilidad a la acción de la hormona, o de ambas en algún momento de su historia natural. En aquellos casos en que los síntomas son floridos, persistentes y las cifras de glucemia suficientemente elevadas, el diagnóstico es obvio en la mayoría de ocasiones. Pero no debemos olvidar que, en muchos casos, el diagnóstico se realiza en sujetos asintomáticos y a través de una exploración analítica de rutina. La prevalencia de la DM, sus complicaciones específicas y la presencia de otras entidades que suelen acompañarla hacen de la enfermedad uno de los principales problemas sociosanitarios en la actualidad.

El crecimiento exponencial de la información disponible sobre la historia natural de la DM, de su etiología y del conocimiento de la fisiopatología de sus complicaciones crónicas ha obligado a que, en los últimos años, se revisaran los criterios diagnósticos de esta entidad y se reclasificaran los diferentes procesos que en ella se incluyen. La revisión de los criterios diagnósticos y de la clasificación de la enfermedad se llevó a cabo en 1997 y 1998 en sendos documentos consensuados por los comités de expertos de la American Diabetes Association y de la Organización Mundial de la Salud. El hecho de que algunos participantes de ambos comités fueran comunes hace que las recomendaciones finales y las conclusiones de ambos grupos sean, aunque con pequeños matices, muy similares.

La clarificación de los criterios diagnósticos y la mejor clasificación de cada una de las personas afectadas por la DM debe permitirnos en el futuro elegir mejor entre las diferentes opciones de tratamiento y mejorar el pronóstico de la enfermedad.

Palabras clave: *Diabetes mellitus. Clasificación. Diagnóstico. Patogenia.*

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INTRODUCTION AND MAGNITUDE OF THE PROBLEM

Given the numbers for diabetes mellitus (DM) in general and diabetes mellitus type 2 (DM2) in particular (the more frequently occurring form), diabetes is a health and socioeconomic problem of the first magnitude. If we take into account the connotation of diabetes type 1 (DM1), its trearment peculiarities, the impact caused by the diagnosis of this disease, and the fact that more the 50% of new cases occur in children, it is easy to understand that although DM1 only occurs in 1 of every 10 cases of diabetes, its actual importance is much greater than the numbers represent. In the case of DM2, the numbers speak for themselves. It is estimated that in the USA the prevalence of DM2 is 6.6% among individuals between 20 and 74 years of age, and this number will probably increase to 10% in the next decade.[1] In Cataluña, in a study recently carried out on subjects between the ages of 30 and 89 years, this number reached 10%, and 40% of the patients diagnosed during the study were unaware of their diabetic condition.[2] In Aragón, this number is approximately 6.1%.[3] In absolute terms we can say that in our country DM2 affects approximately 2 millions people. It must be said that the most optimistic view is that these numbers will increase exponentially during this century will not only affect the western world, but in the year 2010 will reach 215 million individuals worldwide. In the same manner, we know that 50% of people with DM2 have arterial hypertension and a similar percentage have dyslipidemia, both recognized cardiovascular risk factors. On the other hand, at the time of diagnosis, 40% of patients present with some type of macroangiopathy which is already established. In the same context, 35% of patients present with established micro- or macroalbuminuria and 15% with retinopathy; that is to say, some form of microvascular illness characteristic of DM.[4] Regarding economic cost, the numbers are even more eloquent. The North American health system dedicates 14% of its annual proposed budget to the treatment of DM2 and its late complications. The treatment of DM2 and its complications costs Canada 7 to 20 billion dollars annually. In the European Union, the direct annual medical cost of patients with DM2 is 29 000 million euros; of this amount, only 3.5% is destined for hypoglycemic medication. The presence of micro– and macrovascular complications doubles health costs and the coexistence of both triples them.

All this data, and the direct consequences of the illness for the patients, makes DM, without any doubt, one of the principal current social health problems.

Diagnosis of diabetes mellitus and other types of changes in glucose tolerance

Until the World Health Organization (WHO) and the National Diabetes Data Group (NDDG) decided to clarify the diagnostic criteria of DM and other changes in the hydro carbohydrate metabolism at the end of the 1970s, the situation could be called uncertain, not only in terms of diagnostic criteria, but also with respect to the use of the nomenclature.[5,6] After 1985, and various adaptations, the situation was clarified and unified with respect to the cut-off points for glycemia that were chosen, both in baseline situations and after an oral glucose overload.[17] Nevertheless, during the 1980s and 1990s there was an exponential growth in the information available on the natural history of DM, including the different etiologies and the pathophysiology of its chronic complications. This required a new review of the diagnostic criteria and a reclassification of the different processes involved, incorporating its etiological bases. This comprehensive review of the diagnostic criteria and the classification of DM was performed in 1997 and 1998 and generated consensual documents from expert committees of the ADA (American Diabetes Association) and WHO.[8,9] Fortunately, the fact that some participants were involved in both committees resulted in similar final recommendations and conclusions from both groups, with some small differences.

Definition

DM is understood to be that metabolic change characterized by the presence of chronic hyperglycemia accompanied, in a greater or lesser degree, by modifications in the metabolism of carbohydrate, protein, and lipids. The origin and etiology of DM may be diverse, but they share the inexorable existence of changes in the secretion of insulin or in insulin hormone sensitivity, or both, at some moment in its natural history.

Diagnosis

Keeping in mind the consequences that DM can have for the affected individual, the clinician must be certain when establishing a diagnosis of DM. In the

TABLA 1. Diagnostic values of diabetes mellitus and other categories of hyperglycemia

	Fasting plasma glycemia (mmol/L [mg/dL])	2 hours after 75 mg overload (mmol/L [mg/dL])	Cut-off points for plasma glycemia with the risk of illness
DM	≥7.0 [126]	≥11.1 [200]	Retinopathy, nephropathy, neuropathy, CVD
DGT	<7.0 [126]	7.8-11.0 [140-199]	Diabetes and CVD
FGC	6.1-6.9 [110-125]	—	Diabetes and CVD (not well studied)

DM indicates diabetes mellitus; TDG, decreased glucose tolerance; FGC, fasting glycemia change; CVD, cardiovascular disease.

case of florid and persistent symptoms and the presence of sufficiently elevated glycemia numbers, the diagnosis will be obvious in the majority of cases. However, it must not be forgotten that in a great many cases the diagnosis is made in asymptomatic persons following a routine analytical examination.

Diabetes mellitus

The diagnosis of DM can be made in the following situations (Table 1): *a)* occasional plasma glycemia ≥200 mg/dL (11.1 mmol/L) (obtained at any time of day and without regard to when food was last ingested) and symptoms of DM (polyuria, polydypsia and inexplicable weight loss); *b)* fasting plasma glycemia (FPA) ≥126 mg/dL (7.0 mmol/L), fasting being a period of at least 8 hours without ingestion of food), or *c)* plasma glycemia ≥200 mg/dL (11.1 mmol/L) at 2 hours after an oral glucose tolerance test (GTT). The test must be carried out according to WHO criteria (published in 1985), with 75 g of anhydrous glucose dissolved in water.

It should be pointed out that in the absence of unequivocal hyperglycemia with acute metabolic decompensation, the criteria must be repeated again.

The change of the cut-off point for FPG to a ≥ 126 mg/dL (previously 140 mg/dL) is based on the fact that *a)* this is equivalent (in population-based studies) to the cut-off point for diagnosing diabetes by a plasma glucose ≥ 200 mg/dL in a GTT; *b)* it represents a better cut-off point for separating the bimodal distribution of fasting plasma glycemia in the population; and *c)* in several studies this number marked the inflection point for establishing the risk of microangiopathy.

While the GTT is not recommended as a routine diagnostic method in daily practice according to ADA recommendations, WHO encourages performing it as some subjects diagnosed with FPG may be different from those in whom the diagnosis has been established by GTT. In addition, the frequency of DM is lower when the ADA criteria are applied, and, in fact, approximately 30% of subjects (in studies on the European population) with a non-diabetic FPG met the criteria for DM once a GTT was performed.[10,11]

Intermediate categories between normal clinical situations and diabetes mellitus

Clinical situations that fall between normal and DM are not classified within the classification of DM itself but as intermediate states within the natural history changes in carbohydrate metabolism. In general, they are recognized as risk situations for the development of DM and cardiovascular disease.[12] The fact that the category «fasting glycemia change» (FGC) has recently been created does not permit complete certainty regarding the developmental characteristics of subjects with FGC.[13]

Within this group, 2 entities are recognized (Table 1):

1. Diminished glucose tolerance (DGT) is defined as the result of a GTT that shows a plasma glycemia at 2 hours of ≥140 and <200 mg/dL. The GTT defines as normal glucose tolerance a plasma glycemia at 2 hours of <140 mg/dL.

2. Per 1997 ADA recommendations, the category of FGC was introduced as a clinical situation in which the FPG is ≥110 and <126 mg/dL. A normal FGC would be <110 mg/dL.

Since the introduction of this new category (FGC), much has been written on the supposed concordance between FGC and DGT, and there are an increasing number of studies demonstrating that these are not equivalent entities as far as their transcendence and prognosis are concerned.[11] It is clear GTT response of subjects with FGC is heterogeneous (normal, DGT, and DM). It seems that an elevated percentage of individuals with FGC have a concomitant DGT, but also that many subjects, in spite of normal glycemia (<110 mg/dL), may also present with DGT and, therefore, an increased risk of DM.[14,15]

In summary, while the diagnostic guidelines continue to use glycemic thresholds associated with an increased risk of developing microvascular disease when defining DM, the greatest mortality-morbidity of this affliction is associated with macrovascular disease and its complications. In general, there is a current consensus that determined by glycemia a GTT is a better indicator of the risk of cardiovascular disease and that, therefore, performing only a fasting metabolic evaluation may not be sufficient.

Diagnosis of gestational diabetes

Diagnosis of gestational diabetes

Gestational diabetes (GD) is defined as all alterations in carbohydrate metabolism that are diagnosed for the first time during pregnancy. The diagnostic criteria have changed over the years and today there are various recommendations for the application of same.

The Spanish diabetes and pregnancy group in 2000 adopted criteria similar to those promoted by the ADA.[16,17] These criteria establish the performance of a screening test (O´Sullivan test with 50 g of glucose independent of the presence or absence of a prior period of fasting), which consists of the evaluation of glycemia upon administration of 50 g of oral glucose. The test is considered positive when plasma glucose is ≥140 mg/dL. This test must be performed universally in the second trimester (24-28 weeks) of every pregnancy and in the first trimester if risk factors exists such as a history of fetal macrosomy, polyhydramnios, familial history of DM, previous GD, DGT, obesity, or in women ≥35 years of age. A diagnosis of GD would be confirmed by a GTT with 100 g of oral glucose (blood draw for glycemia at 0, 1, 2, and 3 hours). The test is considered positive if 2 values are ≥ a 0=105, 1 h=190, 2 h=165 and 3 h=145 mg/dL.

There is a less-used diagnostic guideline (WHO) that does not include screening and is based on performing a GTT with 75 g of oral glucose during the 24th and 28th weeks of gestation, with blood draw for glycemia at 0 and 2 hours and values based on the GTT values given above for the diagnosis of DM or DGT in the general population (glycemia ≥ 126 or glycemia at 2 hours ≥ 140 mg/dL).[9]

Taking into account that GD constitutes a risk for the later development of DM, it is also advisable, that patients with a previous history of GD undergo a glucose tolerance evaluation after pregnancy has been completed with a GTT with 75 g of glucose.[18]

Recommendations for diabetes mellitus screening

Recommendations for diabetes mellitus screening

In their 1997 publication, the ADA recommended performing diabetes screening on asymptomatic subjects without a prior diagnosis of change in glucose homeostasis in 2 circumstances:[8]

1. On all subjects age>45 years. If the results are normal, the test should be repeated every 3 years.

2. Screening should be performed on younger patients or more frequently (annually) on subjects who are:

- Are obese (IMC ≥ 27 kg/m^2 or a weight ≥120% of ideal weight).
– Have immediate family members with DM.
– Have a clinical history of GD or macrosomy.

– Have a clinical history of arterial hypertension.
– Have HDL-C values ≤ 35 mg/dL and/or triglycerides ≥ 250 mg/dL.
– Have previous glucose homeostasis changes in the form of DGT or FGC.

Evaluation of fasting plasma glucose is recommended for screening. According to these recommendations, performing a GTT can be considered a specific study protocol or in the screening of subjects at special risk of developing diabetes.

Classification of diabetes mellitus and its etiopathogenesis

If any characteristic can define the new intentions for DM classification, it is the intention to consolidate etiological views concerning DM.

The old and confusing terms of insulin-dependent or non-insulin-dependent DM have disappeared and the terms DM type 1 and 2 remain. The other types of DM included in the classification refer to: *a)* other specific types of diabetes associated with genetic β-cell defects, genetic defects in insulin action, disease associated with processes that affect the exocrine pancreas, endocrinopathies, pharmacological or chemical substances, infections, infrequent forms of autoimmune diabetes, and other syndromes that are at times associated with the disease, and *b)* GD. It should be noted that the diagnosis one or another type of DM is not easy. The categorization of DM can depend, among other factors, on the circumstances that produce the diagnosis, whether the diagnosis is early, the initial intensity of hypoglycemia and the presence of concomitant illnesses or treatments. Similarly, it must always be kept in mind that DM is not an inert process but constitutes a continually evolving entity. Therefore, it can increase in severity, can improve or become worse, and the amount of metabolic control is intimately tied to the natural history of the illness or the treatment considered ideal at any given time.[8,9]

Diabetes mellitus type 1

DM1 corresponds to the entity formerly called insulin-dependent or juvenile diabetes. The actual classification of DM1 is subdivided into type DM1 A or autoimmune DM1, and DM1 B, or idiopathic DM1.

Diabetes mellitus type 1A

Diabetes mellitus type 1A

Approximately 1 of every 10 patients with diabetes has DM type 1A. In our country, approximately 10 new cases per 100 000 inhabitants are diagnosed each year. Although many of these cases are children between 10 and 12 years of age, half of the cases

diagnosed are patients of more than 15 years of age.

We find ourselves confronting an immuno-inflammatory disease that causes selective destruction of the β-cells of the pancreas mediated by activated lymphocytic T cells.[19] In this disease and after a preclinical period of varying length in which the patient is asymptomatic, the mass of cells producing insulin attains a critical value and the patient presents with the classic symptomatology generated by insulinopenia and hyperglycemia: polyurea, polydypsia, polyphagia, loss of weight, and an uncontrollable tendency to ketosis if treatment with exogenous insulin is not instituted. Although at the moment of diagnosis the presence of obesity is infrequent, it does not at all preclude the possibility of DM1 A. Nevertheless, in addition to the classic form with more or less abrupt presentation and more frequently than not a young age at the time of diagnosis, today we know that an autoimmune DM1 can also be diagnosed in people of more than 35 to 40 years of age, and that the clinical presentation may be much more subtle and not require insulin at the time of diagnosis, but will require this type of treatment in accordance with disease development and the decrease in the individual´s capacity to secrete insulin. Today, this type of DM is known as LADA DM (Latent Autoimmune Diabetes of the Adult).[20]

As in the majority of autoimmune diseases, the process results from the interaction of environmental and genetic factors, and, as in most autoimmune diseases we know little about the environmental triggers (*Coxsackie* type virus, protein fragments in cow´s milk, among others) and we only know some of the genetic factors that make a specific individual susceptible to the disease. There is a risk factor of approximately 30% for the disease when it is associated with the presence of certain haplotypes in the region encoded for HLA genes on chromosome 6, and particularly with DR and DQ random HLA.

Independently of a specific genetic susceptibility that predisposes an individual to the development of DM1 A, in daily clinical practice 70% to 80% of cases diagnosed with this disease for the first time do not have familial antecedents.[21,22] In 80% to 85% of patients with DM1 A a serological marker of some kind can be detected in the form of autoantibodies against pancreatic carcinoma, insulin(anti-insulin antibodies), decarboxilase of glutamic acid (anti-GAD antibodies), and tyrosine phosphatase (anti-IA-2). The absence of these antibodies in approximately 10% to 15% of patients does not preclude the diagnosis of DM1 A. In patients with DM1 A the presence of an autoimmune reaction against other tissues can be detected, with the presence of anti-thyroid antibodies being found in 25% of patients.[23,24]

Diabetes mellitus type 1B or idiopathic diabetes mellitus type 1

DM1 B is a recently described entity and little is known about its etiology, development, or prognosis. In contrast to DM1 A, it occurs in patients with initial insulinopenia, a tendency to ketosis or ketoacidosis, and absence of autoimmune data and predisposing HLA haplotypes.[8] Of note, the insulinopenia can fluctuate throughout the illness, but in some populations (Japanese) it can be fulminate in character.[25] Initially, and with a strong familial component, it has been described most frequently in the Afro-American, Asian, or USA Hispanic populations.[26] There are few data on its existence and characteristics in our population.

Diabetes mellitus type 2

This form of DM is what was previously called non-insulin-dependent or adult (older then 40 years of age) diabetes mellitus. The non-insulin-dependent character of the disease only refers to the treatment required during the natural history of the disease, which caused confusion in the past. Now we also know that DM2 is increasingly diagnosed in young people, adolescents, and children. DM2 comprises 80% to 90% of all cases of DM, affecting 6% to 10% of the Spanish population and constituting, as we commented in the introduction, a social health and economic problem of the first magnitude; in in the coming years it will take on epidemic proportions, particularly in western countries.

The relative importance of defects in insulin secretion or in the peripheral action of the hormone in the occurrence of DM2 has been and will continue to be cause for discussion. Keeping in mind the intimate relationship between the secretion of insulin and the sensitivity of hormone action in the complicated control of glucose homeostasis, it is practically impossible to separate the contribution of each to the etiopathogenesis of DM2. In addition, we must take into account the fact that both phenomenon tend to coexist and participate to a different degree in the physiopathology of the illness, not only according to the population studied, but also according to its evolution (Figure 1).[27] On the other hand, the phenotypic expression of genetic defects that coincides with changes in insulin secretion and its peripheral action is modulated by various environmental factors, many of them the direct consequence of the changes themselves. Faced with this complex situation, and with the application of good criteria, the new ADA classification of DM avoids pointless and protracted discussion, and proposes that in DM2 both defects coexist, but 1 or the other will prevail according to the specific case in
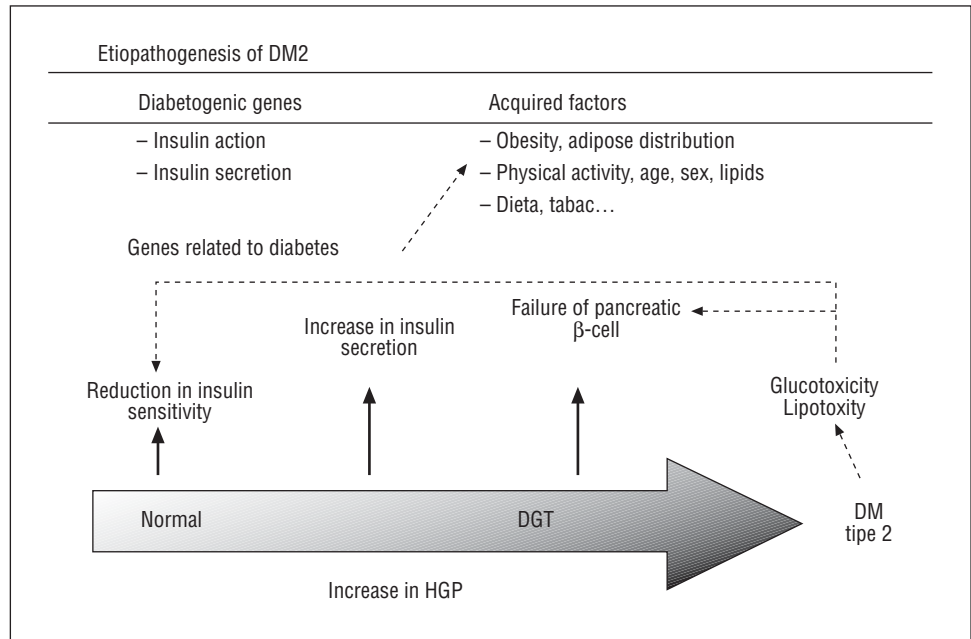
Fig. 1. Etiopathogenesis of diabetes mellitus type 2. HGP indicates hepatic glucose production; DGT, decreased glucose tolerance.glucosa.

question. In situations where resistance to insulin predominates, the mass of β-cells undergoes a transformation capable of increasing the insulin supply and compensating for the excessive and anomalous demand. Whatever the initial defect is in the pathogenesis of DM2, it is obvious that the failure of the pancreatic β-cell is a condition *sine qua non* in the final development of the disease and its clinical presentation.[28-30]

The clinical presentation of DM2 may be very diverse. DM2 can be diagnosed on routine analysis or specific diabetes screening. It can present with typical hyperglycemic symptomatology. But, unfortunately, in a great number of cases the diagnosis has not been made for years because of the absence of accompanying symptomatology and the slow course of the disease, and when it is first diagnosed the lesions or other chronic complications of the disease are already present.

In summary, we can affirm that there are a series of premises that characterize the pathogenesis of DM2 on which most authors agree:

– We are confronting an entity with physiopathological and heterogeneous clinical translation.

– The disease is determined by genetic and environmental (Western diet, sedentary lifestyle, etc) components.

– Its inheritance is clearly polygenetic, which means various genetic anomalies must be present for it to occur.

– In its natural history we must not confuse diabetogenic genetic determinants: essential, specific to diabetes but not sufficient on their own to cause the disease (genes that determine the defects in insulin sensitivity and genes that determine defects in the secretion of insulin) and genetic determinants related to diabetes: non-essential, nonspecific for diabetes but related to it and not sufficient on their own to produce the disease (obesity, distribution of adipose tissue, longevity, etc).

– Sensitivity defects and insulin secretion defects tend to coexist, and both are important phenomena in the physiopathology of the disease. They are directly genetically determined and modulated by acquired factors.

– A large percentage of patients with DM2 are obese (80%) and obesity, particularly abdominal obesity, generates a resistance to insulin *per se* and is genetically controlledl. Nevertheless, DM2 also can be diagnosed in non-obese subjects, especially in elderly people.

Other specific types of diabetes mellitus

Other types of diabetes mellitus include a series of entities of polymorphic physiopathology. The form of presentation of these types of DM varies enormously depending on the underlying cause. In the majority, family history, accompanying pathologic antecedents, and the history of medications taken can help us identify the illness. Overall, as compared to DM1 and DM2, they comprise less than 10% of DM cases. Individually, some forms are extremely rare. Therefore, we mention only some of them, in particular MODY type DM.

MODY Diabetes

TABLA 2. Classification of diabetes mellitus (ADA, 1997)

1. Diabetes mellitus type 1	E. Pharmacologically or chemically induced
A. Autoimmune	1. Vacor
B. Idiopathic	2. Pentamidine
2. Diabetes mellitus type 2	3. Nicotinic acid
1. Insulin resistance predominates over the relative defects	4. Glucocorticoids
in hormone secretion	5. Thyroid hormones
2. Defects in insulin secretion predominate over the presence	6. Diazoxide
of insulin resistance	7. β-adrenergic agonists
3. Other specific types of diabetes mellitus	8. Tiazides
A. Genetic defects in β-cell function	9. Dilantin
1. Chromosome 12, HNF-1α (MODY 3)	10. α interferon
2. Chromosome 7, glycosidase (MODY 2)	11. Others
3. Chromosome 20, HNF-4α (MODY 1)	F. Infections
4. Mitochondrial DNA	1. Congenital rubeola
5. Others	2. Cytomegalovirus
B. Genetic defects in insulin action	3. Others
1. Type A insulin resistance	G. Infrequent forms of autoimmune diabetes
2. Leprechaunism	1. Stiff-man syndrome)
3. Rabson-Mendenhall syndrome	2. Antibodies against insulin receptors
4. Lipotrophic diabetes	3. Others
5. Others	H. Other syndromes occasionally associated with diabetes
C. Disease of the exocrine pancreas	1. Down syndrome
1. Pancreatitis	2. Klinefelter syndrome
2. Pancreatectomy/trauma	3. Turner syndrome
3. Neoplasia	4. Wolfram syndrome
4. Cystic fibrosis	5. Friedreich ataxia
5. Hemochromatosis	6. Huntington's chorea
6. Fibrocalcific pancreatopathy	7. Lawrence-Moon-Biedel syndrome
7. Others	8. Myotonic dystrophy
D. Endocrinopathies	9. Porphyria
1. Acromegaly	10. Prader-Willi syndrome
2. Cushing syndrome	11. Others
3. Glucagonoma	4. Gestational diabetes mellitus
4. Pheochromocytoma	
5. Hyperthyroidism	
6. Somatostatinoma	
7. Aldosteronoma	
8. Other	

MODY indicates mature onset diabetes of the young.

MODY diabetes (mature onset diabetes of the young) is a monogenetic form of diabetes characterized by autosomal dominant transmission that presents early and is associated with β-cell defects that limit insulin secretion. MODY diabetes affects approximately 5% of the total number of patients with DM.

In contrast to the original descriptions of MODY diabetes as a homogenous entity with a generally good prognosis, today we know: *a)* the entity is heterogeneous from a genetic, metabolic, and clinical point of view, and *b)* the prevalence of chronic complications associated with MODY diabetes in some cases is similar to that observed in patients with DM1 and DM1.

As of the date, 5 types of MODY diabetes have been described (only 3 were included in the 1997 ADA classification) (Table 2), associated with mutations in different chromosome locations: in the gene encoded for the glycosidase enzyme (MODY 2), nuclear hepatic factor 1α (MODY 3), nuclear hepatic factor 4α (MODY 1), nuclear hepatic factor 1β (MODY 5), and insulin promotion factor 1 (MODY 4).[31] The most frequently occuring forms are MODY 2 and 3.[32] Patients with MODY 2 present in the early stages with discrete hyperglycemia that remains stable throughout life and rarely requires pharmacologic treatment. The course of the disease is closely associated with specific diabetes complications. In the case of MODY 3, there is a progressive deterioration in glucose tolerance from puberty on that is often symptomatic and in two-thirds of cases requires oral anti-diabetic medication or insulin for metabolic control of the disease. In patients with this type of disease chronic complications associated with diabetes often occur.[31]

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