

Management of maturity-onset diabetes of the young (MODY)

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Resumen

La diabetes de tipo MODY (maturity-onset diabetes of the young) afecta entre 1 y 5% de los pacientes con diabetes en los Estados Unidos y otras naciones industrializadas. Las tres características más importantes de esta entidad son: desarrollo de diabetes antes de la edad de 25 a 30 años en ausencia de autoanticuerpos pancreáticos, transmisión genética autosómica dominante y evidencia de secreción residual de insulina. Existen seis subtipos de MODY de los cuales, el tipo 2 (mutación de la glucoquinasa-GKS) y el tipo 3 (mutación del factor nuclear hepático 1 alfa (HNF-1- α)) son los más prevalentes (70% de todos los casos de diabetes de tipo MODY). Las sulfonilureas son la medicación de primera línea tanto en los niños como en los adultos, cuando la terapia dietética no es suficiente para normalizar la glicemia. Aunque los pacientes con subtipos 1, 3, y 4 usualmente responden bien a la terapia oral con sulfonilureas, un porcentaje significativo de pacientes con los subtipos 1 y 3 necesitan terapia con insulina debido a un deterioro progresivo de las células beta del páncreas. El mantenimiento de un estilo de vida activo y un peso normal, son recomendaciones esenciales en todos los pacientes con diabetes de tipo MODY.

Palabras clave

Diabetes, Insulina, MODY, Sulfonilureas

SUMMARY

Management of Maturity-Onset Diabetes of the Young

Maturity-Onset Diabetes of the Young (MODY) affects 1-5% of people with diabetes in the USA and other industrialized countries. The three main features of MODY include: Development of diabetes before the age of 25 to 30 in absence of pancreatic antibodies, autosomal dominant inheritance, and evidence of residual insulin secretion. There are six subtypes of MODY of which, MODY2 (GCK mutation) and MODY3 (HNF1- α mutation) are the most prevalent, accounting for more than 70% of cases. Sulfonylureas (SUs) remain the medication of first choice in children and adults when dietary

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therapy is insufficient to maintain normoglycemia. Although patients with MODY1, 3, and 4 usually respond very well to oral SUs, due to progressive β -cell failure, a significant proportion of MODY1 and MODY3 patients may eventually require insulin therapy. Leading an active lifestyle and maintaining a normal weight are essential recommendations for all MODY patients.

Key words

Diabetes, Insulin, MODY, Sulfonylureas

Maturity-Onset Diabetes of the Young (MODY) affects 1-5% of people with diabetes in the USA and other industrialized countries.¹⁻³ This type of diabetes very often goes unrecognized. The three main features of MODY include: Development of diabetes before the age of 25 to 30 years in absence of pancreatic antibodies, autosomal dominant inheritance (present in at least two family generations), and evidence of residual insulin secretion, that allows for treatment of this condition most of the time with diet or hypoglycemic agents and does not always require insulin therapy. The table depicts the six types of MODY and their characteristics. We will focus on the management of MODY2 (GCK mutation) and 3 (HNF1- α mutation), which are the most common subtypes, accounting for more than 70% of cases.⁴⁻⁷

Good evidence regarding effects and prognosis of various treatments is still limited for this increasingly recognized cause of diabetes. Although obesity and insulin resistance are not typical features of MODY in comparison with type 2 diabetes mellitus (T2DM); leading an active lifestyle and maintaining a normal weight are essential recommendations for all MODY patients. Weight loss will improve insulin resistance as well as glucose tolerance in obese patients with MODY.⁸ Sulfonylureas (SUs) remain the medication of first choice in children and adults when dietary therapy is insufficient to maintain normoglycemia.⁹⁻¹¹ The use of metiglinides has been implemented in some patients to control post-prandial hyperglycemia.¹² Although MODY1, 3, and 4 usually respond very well to oral SUs, due to progressive β -cell failure, a significant proportion of MODY1 and MODY3 patients may eventually require insulin therapy.¹³

Mutations in the Hepatic nuclear factor 1 alpha gene (HNF1- α) result in MODY3, the most common subtype,

which accounts for 8 to 63% of MODY cases.^{4,5,6} Patients with MODY 3 have a progressive deterioration in glycemic control and are at risk for microvascular and macrovascular complications.¹⁴ Pancreatic exocrine dysfunction has been reported in 12% of adult patients.¹⁵ These patients will need pancreatic supplements. Affected individuals usually present with severe hyperglycemia after puberty, which can be treated initially with diet. However, post prandial hyperglycemia will be present in the course of the time due to insufficient insulin production.¹⁶ At this point, most patients will need pharmacological treatment.

Compared to other types of diabetes, MODY3 patients are extremely sensitive to the hypoglycemic effect of SUs.¹⁷ To avoid hypoglycemia, the initial dose in children should be low (approximately $\frac{1}{4}$ of the usual starting dose in adults).^{9,18} Successful management of hyperglycemia with administration of SUs for decades has been reported.⁹ HbA1c levels should be repeated at 3 month intervals. If this regimen fails to control blood glucose levels as indicated by a rise in HbA1c, the use of a long acting insulin alone or in combination with SUs should be considered. Insulin is the treatment of choice in pregnant women with MODY3 especially if there is excess in fetal growth.¹⁹

Patients with heterozygous Glucokinase (GCK) gene mutations (MODY2) have sustained lifelong mild asymptomatic hyperglycemia, very often present from birth. HbA1c is typically on the upper normal limit. Microvascular and macrovascular complications are rarely developed even in untreated patients.^{20,21} It is very rare for patients with mutations in the GCK gene to have symptomatic hyperglycemia or to need treatment other than diet. There is very little evidence of clinical benefit with pharmacological therapy.²²

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Table n.º 1. Maturity-onset diabetes of the young (MODY)

Tip	Mutation	How common	Usual age of onset	Type of inheritance or mutation	Causes IUGR*	Transient or permanent	Treatment	
MODY 1	<i>HNFA4</i>	Hepatocyte nuclear factor 4 α	Rare	Adolescence or early adulthood	Autosomal dominant	No	Permanent	For most, oral sulfonylureas; some patients may need insulin
MODY 2	<i>GCK</i>	Glucokinase	MODY 2 is the second-most common form of MODY	Mild hyperglycemia may be present at birth; otherwise, early childhood	Autosomal dominant	Lower than normal birth-weight can occur	Permanent	Diet modification and physical activity; medications are usually not required; some patients do not require any treatment during childhood
MODY 3	<i>TCF1</i>	Hepatic nuclear factor 1 α or HNF1 α or HNF1A	Rare	Adolescence or early adulthood	Autosomal dominant	No	Permanent	Initially, treat with diet modification; it can be treated with oral sulfonylureas; some patients may need insulin
			MODY 3 is the most common form of MODY. MODY 2 and MODY 3 account for about two-thirds of all cases of MODY					
MODY 4	<i>IPF1</i> ; also known as <i>PDX1</i>	Insulin promoter factor 1	Rare	Early adulthood but it can present later	Autosomal dominant	No	Permanent	Oral sulfonylureas; some patients may need insulin
MODY 5	<i>TCF2</i>	Hepatic nuclear factor 1 β or HNF1B	Rare	Adolescence or early adulthood	Autosomal dominant	No	Permanent	Insulin; patients may also need treatment for related conditions such as kidney failure or cysts
MODY 6	<i>NeuroD1</i> , or <i>BETA2</i>	Neurogenic differentiation factor 1	Rare	In the fourth decade of life	Autosomal dominant	No	Permanent	Insulin

*IUGR: intrauterine growth retardation

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