Early-Onset Type 2 Diabetes in Mexico

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Abstract

This review summarizes the clinical, metabolic and genetic characteristics of early-onset type 2 diabetes in Mexico. Early-onset type 2 diabetes is both a clinical challenge and a public health problem. It is calculated that almost 300,000 Mexican diabetics are diagnosed between the ages of 20 and 40. The large Mexican family structure and the high prevalence of the disease provide a unique opportunity to identify the genes and the metabolic abnormalities involved in this form of the disease. In a hospital-based population, our group found that insulin deficiency was the main defect in this form of diabetes. Mutations in the *HNF-1α* or *HNF-4α* genes or autoimmunity to the beta cell were found in a small proportion of cases, leaving unexplained the majority of cases. Also discussed are the epidemiologic and therapeutic implications of early-onset type 2 diabetes, and the possible role of genetic testing for prevention.

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Classification is the very first step in the right approach to any disease. In the last decade the explosive growth of knowledge derived from molecular biology has had two immediate consequences for the classification of diabetes: a huge source of information to enrich the former available classifications, and the unmasking of the real dimension of the task.

The distinction between type 1 and type 2 diabetes mellitus is usually straightforward. However, there may be an overlap in the presentation of the two disorders, creating a diagnostic dilemma. This is especially frequent and relevant in patients whose disease appears between the third and fourth decades of life.

Is there evidence to consider this subset of patients as part of a distinct entity? The answer must be yes. Clinical experience sustains this claim. These patients frequently exhibit a more aggressive form of the disease, require insulin treatment at an earlier age, and suffer from severe chronic complications [1]. There is also epidemiologic, metabolic and genetic data to support this claim.

What could this diabetes subset mean for public health in Mexico? The enormous impact of diabetes mellitus on the country's public health was clearly demonstrated by the 1993 national survey. It was calculated that almost 1.9 million subjects were affected by type 2 diabetes, of whom a large proportion, 300,000, were diagnosed between the ages of 20 and 40 [2]. The socioeconomic and biologic implications of the early onset of type 2 diabetes, as well as the temporal or definitive incapacities in patients under age 50, are enormous.

This review summarizes data on the clinical, metabolic and genetic characteristics of early-onset type 2 diabetes in the Mexican population. We also analyze the possible impact of this subset of diabetes on the country's public health. Finally, the need for a more aggressive approach to prevention, early diagnostic and treatment is suggested.

What does early-onset type 2 diabetes mean?

The evolution of the concept has been a long process. Historically, two main criteria have been used to define the boundaries of this subset of patients: patients must be diagnosed before age 35–40 years and are non-insulin-dependent. Such a broad definition implies heterogeneity. Three main groups have been identified. The first includes maturity-onset diabetes of the young, described by Tattersall in 1974 [3]. This is a monogenic form of diabetes due to deficient insulin secretion [4]. MODY is present in a proportion of patients who develop the disease at an early age (usually before age 25). In the last decade, clinical heterogeneity was well established among MODY patients. Those with mutations in the glucokinase gene (*MODY 2*) present mild hyperglycemia, good glycemic control without the need for insulin, and rare or null appearance of vascular complications [5]. In contrast, patients carrying mutations in the *HNF-4α* or the *HNF-1α* genes (*MODY 1* and *MODY 3*, respectively) exhibit severe fasting hyperglycemia, increased insulin requirement, and a frequent occurrence of microvascular complications. Several studies suggest that the prevalence of mutations in these genes differs considerably among various ethnic groups [6,7].

The second group is more complex. These patients could have inherited a diabetogenic gene or genes from both parents. They may represent a syndrome in which characteristic pedigrees, clinical severity, and lack of evidence of autoimmune diabetes distinguish it from type 1 diabetes, MODY, or late-onset type 2 diabetes [8]. Recently, Doria and co-workers [1] reported the presence of insulin resistance in a large proportion of early-onset patients from families not linked to any known MODY genes.

Finally, some cases may correspond to late-onset autoimmune diabetes. Frequently, insulin dependence is not present at the time of diagnosis.

MODY = maturity-onset diabetes of the young

Metabolic and genetic characterization in the Mexican population

We studied both the metabolic and genetic characteristics in a cohort of early-onset diabetic patients. In an initial study of 68 diabetic patients diagnosed at age 20–40 with a clinical disease of not more than 5 years, we showed that in 72% of cases it was impossible to classify them as type 1 or type 2. Since then, we began to use the term "intermediate diabetes" to refer to these patients [9].

As a first step in the molecular characterization of Mexican families displaying early-onset type 2 diabetes, we searched for mutations in the glucokinase gene through SSCP analysis and/or direct sequencing in 26 individuals from 22 different families, where at least four could be classified as MODY. No mutations were detected in the exons or the gene in any of the screened individuals [10]. More recently, we studied 40 Mexican patients diagnosed between age 20 and 40 [11]. The aim of the study was to investigate possible defects in the insulin sensitivity and/or acute insulin response in a group of Mexican patients displaying early-onset type 2 diabetes and to evaluate the contribution of mutations in three of the genes linked to MODY.

Table 1 presents the general characteristics of the study population. Type 1 and 2 diabetic controls are very representative of the vast majority of patients affected by these disorders. In the patients with early-onset type 2 diabetes the mean age at diagnosis was 28 years. The majority was lean at the time of evaluation and required insulin treatment; 73% had a first-degree relative who also had type 2 diabetes, and only 20% of them had a history of diabetes in both parental lines. Significant differences were found between the early-onset group and the type 2 diabetes cases in body mass index, percentage of cases that required insulin treatment, and fasting triglyceride concentrations. The early-onset group required insulin several years later than the type 1 diabetics.

The fasting C peptide concentrations in the early-onset type 2 group were different from the type 1 and 2 patients, being intermediate between the other two groups. In the early-onset type 2 group, all cases had either low (72%) or inappropriately normal (28%) concentrations (reference range 0.12–1.2 nmol/L).

The insulin secretory defect observed was confirmed during the insulin-modified intravenous glucose tolerance test. The mean acute insulin response was 67.5 ± 44.2 mU/ml. An acute insulin response lower than 100 mU/ml (a cut-off point used for severe insulin deficiency) was found in 34 of the 40 cases. Insulin sensitivity was measured using the sensitivity index obtained during the insulin-modified IV glucose tolerance test. The mean SI of the early-onset type 2 group was 3.73 ± 2 (normal 4–6). Thirteen patients (32.5%) had a SI below 4 and were classified as insulin resistant.

The plasma lipid profile of the early-onset type 2 group was different from the type 2 patients. They had significantly lower plasma triglycerides and higher high density lipoprotein-cholesterol levels. No differences were found when compared with the type 1 patients.

SI = sensitivity index

Table 1. Clinical characteristics in type 1, type 2 and early-onset type 2 diabetics

		Early-onset		*P* value
	Type 1 (n=20)	Type 2 (n=40)	Type 2 (n=20)	
Age (yr)	20.6 ±3.6	35.6 ±7.6	55 ±9	< 0.001
Gender (M/F)	9/11	11/29	11/9	NS
Age at diagnosis (yr)	16.7 ±2.4	28.1 ±6	48 ±5	< 0.001
BMI (kg/m^2)	21.1 ±1.3 [c]	22.9 ±3.1 [b]	26 ±4.1	< 0.05
Insulin treatment (%)	100 [c]	87 [b]	10	< 0.001
Time that insulin therapy was required (yr)	0.3 ±0.7[bc]	3.11 ±3.8[ac]	13.5 ±2.2[ab]	< 0.001
Glucose (mmol/L)	10.3 ±2[c]	12.1 ±2.6[c]	8.1 ±3.4	< 0.05
HbA1c (%)	10.9 ±1.9[c]	11.2 ±2.8[c]	9.5 ±2	< 0.05
Cholesterol (mg/dl)	5.18 ±1.1	5.3 ±0.8	5.5 ±1.5	NS
Triglycerides (mg/dl)	1.49 ±0.75	1.1 ±0.4[c]	2.08 ±1.4	<0.05
HDL-cholesterol (mg/dl)	1.23 ±0.34	1.31 ±0.28	1.15 ±0.3	NS
C-peptide (nmol/l)	0.01 ±0.01[c]	0.26 ±0.33[c]	1.2 ±2	< 0.05

a = versus type 1 group, b = vs. early-onset type 2 group, c = vs. type 2 group

Cases with a SI below 4 had significantly higher concentrations of plasma triglycerides and low density lipoprotein-cholesterol; the predominance among the LDL particles of the smaller and denser LDL subclasses was also more common in these subjects. The insulin-resistant cases also had lower levels of HDL and HDL3-cholesterol and lipoprotein(a). A striking difference was observed in the prevalence of arterial hypertension between the insulin-sensitive (0%) and insulin-resistant (30%) subjects.

Three cases (7.5%) in the early-onset type 2 group had positive titers for glutamic acid decarboxylase antibodies. Insulin treatment was required in all three cases for a mean 3.1 ± 4 years after diagnosis. Their C-peptide level was below 0.12 pmol/ml. In this group we identified two individuals carrying missense mutations in exon 4 of the hepatocyte nuclear factor-1α (*HNF-1α*) gene (Asp126-His/Tyr and Arg154-Gln, respectively), and one carrying a nonsense mutation in exon 7 of the *HNF-1α* gene (Gln486-stop codon).

We have described a group of Mexican diabetic patients who presented as diabetics at age 20–40, but who subsequently displayed atypical metabolic features of type 2 diabetes. The genetic pattern, the early insulin requirement, the lack of insulin dependence for a few years, and the type or onset, are clinical patterns that are difficult to assign to a single type of diabetes. Several degrees of insulin deficiency or insulin resistance have been described in other ethnic groups, including African-American, Chinese, and Native Americans [12–14].

The absence of insulin resistance in 65% of the cases and the demonstration of insulin deficiency in almost every case suggest that insulin deficiency was the main abnormality responsible for the premature presentation of diabetes in the patients studied. It would appear that there are multiple causes for the insulin deficiency. The presence of markers of autoimmune destruction of the β cell was

LDL = low density lipoprotein
HDL = high density lipoprotein

observed in 7.5% of the cases, and mutations in the *HNF-1α* and *HNF-4α* genes were identified in our group of patients. Two of the subjects with detected mutations most likely represent MODY individuals, suggesting that this monogenic type of diabetes is present in at least 3% of the early-onset cases in our population. However, in the vast majority of cases, the reason for the severe insulin deficiency was not identified.

Insulin resistance was identified in 35% of cases and had a significant impact on lipid profile and blood pressure. It is important to note that even in the absence of endogenous hyperinsulinemia, insulin resistance is associated with an adverse lipid profile. No differences were found between insulin-sensitive and insulin-resistant cases regarding glycemic control, body mass index or insulin dosage. The presence of hypertension and major abnormalities in the lipid profile are the only clinical data suggestive of insulin resistance.

The studies described here were not designed to answer epidemiologic questions; nonetheless, our results seem to suggest that the most prevalent subgroup of early-onset type 2 diabetes in Mexico comprises patients without evidence of autoimmune disease or mutations in the genes related to MODY.

It may be possible that other known MODY genes as well as other as yet unidentified genes contribute to the expression of early-onset diabetes in our population. On the other hand, due to the high prevalence of type 2 diabetes in the Mexican population, marriage between diabetic subjects is not uncommon and most of the early-onset type 2 diabetics may develop the disease at an early age as a consequence of having both maternal and paternal inheritance. In recent years, other related ethnic groups with a high prevalence of diabetes, such as Pima Indians and Mexican-Americans, have also shown earlier appearance of type 2 diabetes. As we discuss below, the genetics of diabetes may be expressed more easily as a consequence of environmental factors.

Natural history

In this subset of patients, the paramount goal for the next few years will be to describe as precisely as possible the natural history of the disorder. In this process it may be important to identify subsets of early-onset type 2 diabetes.

Type 2 diabetes is usually a progressive disease. Individuals at risk initially develop impaired glucose tolerance or impaired fasting glucose before developing diabetes. Initially, diabetes is responsive to treatment with diet or individual oral agents, but over the course of years the disease becomes more difficult to treat, requiring the administration of multiple oral agents and finally insulin in a large proportion of patients.

The age at the onset of diabetes and the time until insulin dependence are crucial. The earlier age of onset aggravates and prolongs the influence of metabolic disturbances on the vascular and neurologic systems.

A poorly evaluated aspect of early-onset type 2 diabetes is its psychological effect. Depressed diabetic patients have been demonstrated to have poor metabolic control [15]. To the best of our knowledge, the prevalence and the effects of depression in patients with early-onset type 2 diabetes have not been evaluated systematically. It may be speculated that these patients have greater difficulties in coping with this chronic disease, because of the circumstances of life and the negative psychological effect of early diagnosis.

The impact on public health in Mexico

In people diagnosed with diabetes when they are still economically productive, the development of serious complications presents a double jeopardy for developing societies – namely, loss of productivity and increased demand for medical attention.

Type 2 diabetes is caused by the interaction of genetic and environmental factors. Its final prevalence in a given population results from quantitatively different proportions of the causal factors: a high genetic predisposition or an unfavorable environment needs only a mild environmental or genetic complement to produce diabetes, as shown by the wide variations in prevalence in the same ethnic group over time or under different conditions.

The high vulnerability to changes in eating habits and physical activity in several ethnic groups has been attributed to the long-time selection of a "thrifty" genotype [16], which confers an advantage during periods of precarious living conditions but becomes disadvantageous given a socioeconomic milieu of abundance and a sedentary lifestyle. Mexico is undergoing socio-economic changes in its transition from the status of an underdeveloped country to that of a developing one. In this setting of epidemiologic transition, the prevalence of diabetes is rapidly and continuously increasing.

The distribution of diabetes in Mexico increases with age, reaching almost 25% in people aged 65–69 years old. However, 57.5% of cases belong to the productive sector, aged 20–59 [17]. Moreover, when data on the age distribution of diabetes are extrapolated to each age group of the total population, 1,406,286 of 1,880,582 calculated cases of diabetes (74.77%) belong to the economically active population, and 16.56% (311,481 diabetics) are 20–39 years old [Table 2].

Early-onset type 2 diabetes has a longer potential exposure to risk factors related to the development of diabetic complications. Diabetes duration and hyperglycemia are strong predictors of retinopathy and nephropathy, and perhaps other microangiopathic

Table 2. Characteristics of the diabetic population in Mexico

Age (yr)	Total population	Prevalence of diabetes	No. of diabetics
20–24	5,559,859	0.87	48,370
25–29	4,430,756	1.34	59,372
30–34	3,923,773	1.91	74,944
35–39	3,203,870	4.02	128,795
40–44	2,747,131	7.69	211,254
45–49	2,237,306	12.79	286,151
50–54	2,041,189	14.02	298,421
55–59	1,553,947	19.24	298,979
60–64	1,229,342	18.70	229,886
65–69	1,000,451	24.43	244,410
20–69	27,927,624	6.73	1,880,582

complications, when the type of diabetes and the genetic predisposition of the patients are taken into account [18].

In Mexico, the highest prevalence of diabetes is strongly associated with the lowest levels of education. Recent and sudden changes in traditional lifestyles, as seen in newly arrived migrants to urban centers and large cities such as Mexico City, Guadalajara and Monterey, can precipitate the clinical expression of the high genetic susceptibility to develop diabetes, which is an established characteristic of the Mexican population. Since complete acculturation is a long process, the migrants acquire many of the negative traits of westernized urban life, such as inadequate diet and lack of physical exercise, before they reach the educational and economic status necessary to care about preventive health maintenance and to gain access to medical care. The earlier age of onset of diabetes in Mexicans and the more limited access to optimal medical and preventive care will aggravate and prolong the influence of metabolic disturbances on the vascular and neurologic systems.

Treatment of early-onset type 2 diabetes

Treatment of hyperglycemia is the primary, but certainly not the only, goal for patients with diabetes. Obesity, hypertension, adverse lipid profile and other related disorders must also be treated. It is clear today that the epidemic proportions of this disease make a prevention strategy mandatory. The role of environmental factors in the pathogenesis of diabetes leads us to expect a clear benefit of favorable changes in lifestyle. Unfortunately, a plethora of forces is moving in the wrong direction. Education of the entire population, primary and secondary prevention in the groups at high risk, and precise treatment strategies will be necessary.

In spite of its heterogeneity, we believe there is sufficient evidence to sustain the claim that early-onset type 2 diabetes represents a distinct entity. The question arises: Is a special therapeutic approach necessary for this subset of patients? Again, we affirm that it is. However, in the absence of evidence-based conclusions, we recognize that recommended therapeutic strategies must be supported by common sense and the fragmentary evidence available. We present below a very general approach, which requires further research.

As a public health problem, efforts must be directed toward two main objectives: education of the population, and early diagnosis to avoid the silent phase of the disease. More information about this variant of the disease must be given to the general practitioner. The role of the primary physician must be centered on early detection rather than on long-term treatment. The target population for screening can be identified by the high diabetes prevalence in the family. Obesity, hypertension, lipid abnormalities and ethnicity must also be taken into account when conducting screening tests. The need for intensive treatment makes early-onset type 2 diabetics candidates for treatment by an endocrinologist. Specialized centers should be assigned for coordination of treatment and research.

The approach to individual cases should be based on two certitudes. First, early-onset type 2 diabetes is an aggressive disease in the majority of cases. Second, due to the patient's young age, the psychological, social and economic problems resulting from this disorder will be greater than in cases with adult-onset type 2 diabetes. Adherence to therapeutic principles seems to be less stringent in younger subjects. A team including a dietitian, a psychologist, and perhaps a physical therapist or the equivalent for supervised exercise training may be helpful to improve the results and adherence to the treatment [19].

These patients warrant more intensive treatment. Early-onset type 2 diabetes is accompanied by a high probability of micro and macrovascular complications. The presence of a plurimetabolic syndrome justifies the multiple-purpose drug approach – one drug for each symptom or abnormality. There are no clear rules regarding the consequences of insulin dependence. The rapid loss of β cell function is a frequent feature, which forces us to adopt a flexible clinical attitude to face the unpredictable clinical course. The measurement of plasma insulin or C peptide at presentation and before treatment is of uncertain value. Hyperglycemia causes transient insulin deficiency (glucose toxicity), and a low initial plasma insulin concentration does not necessarily mean β cell failure. Measurement of islet cell antibodies and glutamyl acid decarboxylase may be useful in special cases. Oral drugs can be used as long as they are effective to maintain excellent glycemic control. Insulin treatment must be started as soon as failure to oral drugs is suspected. Evaluation of the impact of education, prevention and different pharmacologic treatments in cohorts of this group of diabetics is still necessary.

Perspectives

Molecular perspectives of early-onset type 2 diabetes are exciting. New abnormal genes will be described and their pathophysiologic role will be defined. There is an intrinsic value in this process, and the construction of a model of disease will provide a heuristic tool for questions that may arise.

The identification of subsets of type 2 diabetes is encouraging to test the potential impact of oral drugs in each of these possible patient groups [20]. Additional research is needed to determine whether these proposals are valid and whether some treatments will be relatively subset-specific for type 2 diabetes. Nowadays it is argued that new therapeutics will change the face of the disease. Unfortunately, this does not seem likely. One of the most disappointing conclusions drawn from the UK Prospective

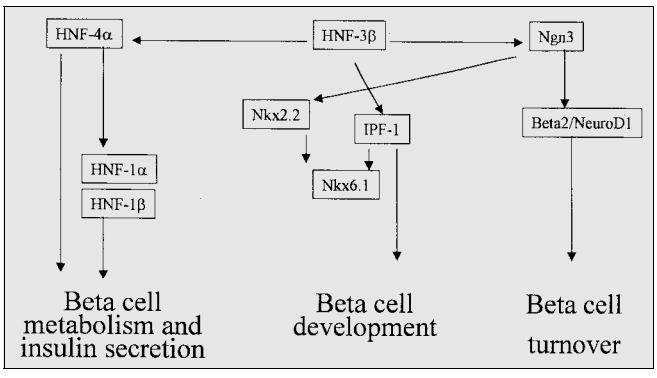

Figure 1. Candidate genes for explaining the insulin deficiency observed in early-onset type 2 diabetes.

Diabetes Study is the progression of β cell failure in spite of treatment [21].

The large structure of Mexican families and the high prevalence of the disease provide us with a unique opportunity to identify the clinical and genetic characteristics of this group of patients. Six genes linked to MODY have been identified (Glucokinase, *HNF-1α*, *HNF-4α*, IPF1/PDX1, *HNF-1β*, and neurod1/beta2) [22]. Other candidate genes include *IRS-1*, *IRS-2*, *CD-3* transporter and *Calpain-10*. Genes regulating β cell survival should be added to the list [Figure 1]. Meanwhile, until the identification of new genes and the information that will be derived from them, a clinical approach to early-onset type 2 diabetes is necessary. While names and classifications are important for clinical reasons, precise and flexible concepts are even more valuable. A syndromatic approach will allow us to cope – at least from a theoretical position – with the heterogeneity of diabetes.

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