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Early onset type 2 diabetes in Jamaica and in Mexico. Opportunities derived from an interethnic study

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ABSTRACT

Populations with Amerindian or African heritages are the one with the highest prevalence of diabetes worldwide. A large percentage of these individuals survived famine. However, the survival effect has become detrimental to their descendents living in an environment of caloric surplus. In countries, like Mexico and Jamaica, in which diabetes is highly prevalent, the onset of the disease happens at earlier ages. Our objective is to summarize diabetes data from Mexico and Jamaica and to discuss the opportunities that can result from an interethnic study. On one hand, the prevalence of diabetes in Jamaica is 17.9% in the 15+ age group. Jamaican researchers have built a cohort of families with early onset type 2 diabetes. In this population, this form of the disease is unrelated to MODY genes. On the other hand, the prevalence of diabetes in adult Mexicans is 14.4%. The group in which the greater percentual changes have occurred is the adults who are below the age of 40. More than two thirds of the early onset cases studied have a body mass index that is > 25 kg/m^2 and the clinical characteristics of metabolic syndrome. A minority of them has mutations in the MODY genes. The joint study of Mexican and Jamaican cohorts of early onset type 2 diabetes cases will be useful to identify new genetic and environmental players in the pathogenesis of this entity.

Key words. Early-onset type 2 diabetes. Mexico. Jamaica. Maturity onset diabetes of the young. Obesity.

Diabetes tipo 2 de inicio temprano en Jamaica y em México. Oportunidades derivadas de un estudio interétnias

RESUMEN

Poblaciones con ancestría amerindia o africana son las que tienen la mayor prevalencia de diabetes en el mundo. Un alto porcentaje de sus fundadores estuvieron expuestos a la hambruna. Los fenómenos que les permitieron sobrevivir son patogénicos para sus descendientes que viven en un ambiente con exceso de calorías. En países como México y Jamaica en los que la diabetes tiene una prevalencia alta, la enfermedad inicia a edades menores. Nuestro objetivo es revisar la información sobre diabetes en Mexico y Jamaica, además de discutir las oportunidades que ofrece un estudio interétnico para brindar información nueva de la genética de la diabetes. La prevalencia de diabetes en Jamaica es 17.9% en los mayores de 15 años. Los investigadores de Jamaica tienen una cohorte de familias con diabetes tipo 2 de inicio temprano, en quienes se ha excluido anormalidades en los genes MODY. Por otra parte, la prevalencia de diabetes en adultos Mexicanos es de 14.4%. El grupo de edad en que ha ocurrido un cambio mayor en la prevalencia es el compuesto por menores de 40 años. Más de dos terceras partes de los casos de inicio temprano estudiados en población abierta tienen un índice de masa corporal > 25 kg/m^2 y las características clínicas del síndrome metabólico. Una minoría tienen mutaciones en los genes MODY. El estudio conjunto de las cohortes de México y Jamaica de pacientes con diabetes de inicio temprano será útil para identificar nuevos factores genéticos y ambientales que participan en la patogénesis de la diabetes.

Palabres clave. Diabetes tipo 2 de inicio temprano. México. Jamaica. Diabetes del joven de tipo del adulto. Obesidad.

EARLY ONSET TYPE 2 DIABETES AS A MODEL FOR STUDY OF THE PATHOPHYSIOLOGY OF DIABETES

Diabetes has become a major health problem in less than 50 years. Although its impact is worldwide, remarkable differences exist between ethnic groups. In countries, like Mexico and Jamaica, in which diabetes is highly prevalent in the population, the onset of the diabetes mellitus occurs at an earlier age.[1,2] The longer exposure to hyperglycemia and other diabetes-related abnormalities increases the likelihood that patients will develop chronic complications.[3] This characteristic results in a large number of them being incapacitated before the age of 50. These subjects frequently exhibit a more severe form of the disease and require insulin treatment at an earlier time.[4] In addition, they have specific needs and there are obstacles to achieving adherence to therapy. This subset of patients has become the interest of several research and clinical groups. This variant of the diabetes mellitus is referred as early-onset type 2 diabetes.[5,6] It includes cases that are diagnosed between the ages of 20 and 40 years.

Reasons for the early onset of the disease have been searched for by several research groups.[7,8] The clinical profiles of the cases vary between populations and reports. Cohorts studied in their communities are obese and have the metabolic syndrome. In contrast, patients detected in medical institutions are usually lean and under insulin therapy. Despite the heterogeneous nature of the disease, all cases have an insulin secretory defect, which is responsible for the early onset of the disease.[9]

Few papers have analyzed the pathophysiology of hyperglycemia in patients with early onset type 2 diabetes.[10-12] Nolan, *et al.*, have studied cohorts of obese subjects with early onset type 2 diabetes and age-matched obese control subjects.[10] They showed that both groups were insulin-resistant; glucose disposal was markedly reduced in the type 2 diabetic subjects compared with obese control subjects.[11] In a subsequent study, the same researchers found that young subjects with type 2 diabetes are severely insulin resistant, achieving a glucose disposal rate half of that found in obese control subjects.[10] They extend their observations by studying mitochondrial functionality in muscle biopsies.[12]

Subjects with diabetes showed a defective pattern of mitochondrial protein expression in muscle compared with equally obese young people without diabetes. However, the biggest difference between groups is the abnormally low insulin secretory capacity found in patients with diabetes. The acute insulin response is ten times lower in the group with diabetes. The same conclusion was reached assessing C-peptide response to an intravenous glucose load.[11] The characteristics of beta cell dysfunction in early onset type 2 diabetic subjects are similar to those observed in older diabetic patients. However, this defect occurs two or three decades before the usual course in type 2 diabetes. Reasons for the premature insulin secretory defect are unknown. Obvious candidates are mutations of the causal genes of Maturity Onset Diabetes of the Young (MODY),[13] autoimmunity[14] and exposure to environmental conditions that alter insulin secretion (i.e. undernourishment early in life[15] or arsenite[16]). Six genes have been implicated in MODY.[17] However, it is widely recognized that other genes must also be involved.[18] The contribution of other factors is marginal (i.e. autoimmunity) or have not been sufficiently explored.[19]

Thus, early onset type 2 diabetes is considered a model for genetic and metabolic studies and a prime target for intensive multidisciplinary treatment.[20]

GENETIC FACTORS CONTRIBUTING TO TYPE 2 DIABETES ACROSS ETHNICITIES

Prevalence of type 2 diabetes varies significantly between ethnic groups.[21] Pima and South Sea Island populations have the highest prevalences (close to 50% in adults), followed by Afro-American, Asian and Hispanic groups (14-20% in adults). These prevalence rates are in clear contrast with those found in Caucasians living in the US and Europe, in which the prevalence of diabetes is 5-8%. This variation strongly suggests that ethnic specific factors may determine the susceptibility for type 2 diabetes. Regrettably, the populations with the highest prevalence of diabetes have been poorly represented in the diabetes GWAS (genome wide association studies).[22,23]

As a consequence, the GWAS-derived findings are limited mainly to European populations with the exception of the *KCNQ1* gene, which is a major risk factor in Asians and relatively rare in Europeans. Genome-wide association variants in *TCF7L2*, *CDKAL1*, *SLC30A8*, *IGF2BP2*, *HHEX*, and *CDKN2A/2B* have been replicated in Asian populations.[24] The association with *TCF7L2* has also been confirmed in Mexican Mestizos.[25] However, many of these associations have not been replicated in Pima Indians and in other non-Caucasian populations.[26]

In contrast, other associations not detected in the GWAS reports have been found in linkage studies done in Native American populations.[27-29]

Several researchers have take advantage of the variability between ethnic groups to generate new knowledge about the genetics of complex disorders. For example, by comparing the prevalence of *TNF* polymorphisms in interethnic studies, the existence of a susceptibility locus to ankylosing spondilitis has been confirmed.[30] Other approach is the study of admixed populations. Populations with a recent history of admixture (e.g., less than 20 generations ago), such as populations in Latin America and the Caribbean are ideally suited for admixture mapping.[31,32] Admixture mapping could be useful to localize the genes underlying the prevalence differences.[33]

Populations with Amerindian or African heritages are the among ethnic groups with the highest prevalence of diabetes.[34] Although these groups had remarkable genetic and cultural differences, Amerindian and African-derived populations have suffered similar social events that have made a large percentage of them survivors of famine and other hardships. These individuals had become efficient in the use and storage of nutrients to survive in these adverse environments. It has been proposed that this mechanism of survival has become detrimental to the health to their descendents who are now living in an environment of caloric surplus. The susceptibility to the development of diabetes is heightened when these individuals are chronically exposed to a positive caloric balance.[35] Because diabetes risk is influenced by both, genetic and environmental factors, the comparative assessment of the mechanisms that explains the increased susceptibility for the development of diabetes in populations with different ethnic background offers an opportunity to generate new knowledge in this highly competitive field.

Few papers have described the clinical characteristics, genetics and the consequences of diabetes diagnosed between the ages of 20 and 40.[36,37] No multinational or interethnic studies have been published in this field. Research groups from Jamaica[38] and Mexico[39] had produced evidence showing that early onset type 2 diabetes is a relevant health problem in each country. The joint efforts of these groups may produce genetic and clinical studies in populations with early onset type 2 diabetes with different genetic background. The objective of this report is to summarize the existing information and to discuss the potential opportunities that can result from an interethnic study.

THE JAMAICAN CASE

Jamaica, a country with 2,804,334 inhabitants, is populated mainly by young adults. Their ethnic background is as follows: 76.3% African descent, 15.1% Afro-European, 3.4% East Indian and Afro-East Indian, 3.2% Caucasian, 1.2% Chinese and 0.8% other.[40] The life expectancy is 73.2 years.[41] Over the past several decades, close to a million Jamaicans have emigrated, especially to the United States, the United Kingdom and Canada.

The Arawak and Taino indigenous people were the original residents of Jamaica. However, the conquest by Spaniards and subsequently by the British modified the composition of the Jamaican population. In 1660 the population of Jamaica was about 4 500 whites and some 1 500 blacks. However, as early as the 1670s, those of African descent became the majority of the population. During its first 200 years of British rule, Jamaica became one of the world's leading sugar-exporting nations. By the beginning of the 19th century, African descendents outnumbered whites by a ratio of almost 20 to 1. Jamaica slowly gained increasing independence from the United Kingdom and in 1958, it became a province in the Federation of the West Indies, a federation among the British West Indies. Jamaica attained full independence by leaving the federation in 1962. Strong economic growth, averaging approximately 6% per annum, marked the first ten years of independence. The growth was fueled by strong investments in bauxite/alumina, tourism, manufacturing industry and, to a lesser extent, the agricultural sector. However, the optimism of the first decade was accompanied by a growing sense of inequality, and a sense that the benefits of growth were not being experienced by the urban poor. Despite efforts to create more socially equitable policies in education and health, Jamaica continued to lag economically. In 2009, the gross domestic product per capita was 7,500 US dollars.

Atypical forms of diabetes were reported in Jamaicans during the 50's.[42] These cases were characterized by severe hyperglycemia and resistance to ketosis. Subsequent studies showed that these cases were caused by severe undernourishment. The prevalence of type 2 diabetes grew during the 80's and 90's. In 1995, diabetes in Jamaica was documented to have a prevalence of 17.9% in the 15+ age group and was noted to be the second leading cause of death with an annual total estimated cost in 2000 of 409.5 million US dollars.[43] The per capita direct cost was 750 US dollars. Regrettably, the majority of the expenditure

was dedicated to covering the indirect consequences (273.4 million US dollars).[44] Possible reasons for the rapid increment in diabetes have been searched in cross sectional and longitudinal studies. Ragoobirsingh, *et al.*, reported a survey in 2004.[45] A two-stage-stratified random sampling design was applied. Individuals aged 15 years and over were interviewed. A total of 2105 individuals responded to the all island survey. The prevalence of obesity was 13.5%. An additional 20.6% had a body mass index between 25 and 29.9 kg/m^2. The highest prevalence was found in women, aged 45-54 years. Almost half of the obese cases had a central distribution of body fatness, a profile linked to an increased risk for having type 2 diabetes and cardiovascular outcomes. Durazo, *et al.*,[46] studied adults (n = 35) from a working class community in Spanish Town, Jamaica. They were followed for during six years. They found that increased caloric intake and decreased physical activity were the major determinants of weight gain. Similar data were reported by Ferguson and coworkers in the Jamaica Lifestyle Survey done in 2000-2001.[47] They completed a population-based survey that included 2012 adults aged 15 years or older. The prevalence of overweight and obesity were 46% and 19.7% respectively. In addition, they found that 36.3% of the participants had a low physical activity level.

Other components of the metabolic syndrome are also common in Jamaicans. For example, arterial hypertension was found in 30.8% of the participants of the survey published by Ragoobirsingh, *et al.*, above described.[45] On the other hand, 30.6% had prehypertension, 14.6% had hypercholesterolemia and 17.8% was smokers in the Jamaica Lifestyle Survey. In summary, chronic non transmissible diseases have become a major health problem for Jamaica. Social and environmental changes are the drivers of the remarkable changes that have occurred in a few decades.

The adaptation of individuals to an affluent environment varies significantly. Not everybody exposed chronically to a positive caloric balance may become affected by chronic non-communicable diseases. The incidence of the outcomes is modulated by partially known genetic factors. Several approaches had been used to study this phenomenon. One example is the study of extreme phenotypes. These rare conditions increase in prevalence if the individuals have susceptibility alleles for suffering the disease. This is the case for early onset type 2 diabetes.[43]

Based on the above described, fifteen Jamaican families with a history of early onset type 2 diabetes were screened for sequence variants in each of the known MODY genes by PCR-SSCP analysis (Table 1). The analysis included the exons, intron-exon boundaries and proximal promoter regions (about 1000 bp) of each MODY gene. For the HNF-4a gene, a distal promoter was also studied. Fragments with altered mobility in the SSCP analysis were directly sequenced to identify the responsible variants.

The genomic scan concluded that the genes variants of glucokinase and the transcriptional factor

Table 1. Clinical characteristics of twelve Jamaican Pedigrees (n = 192).

Parameter	Affected	Unaffected	P-Value
Sex M/F	68/13	45/46	
Age at diagnosis (years)	29.7	–	
Age of cohort ≤ 40years (%)	68	79	
% cohort with diabetes +IGT	50	–	
Fasting glycemia (mmol/L)	12.5 ± 1.6	5.5 ± 0.2	< 0.05
HbA1C (%)	13.7 ± 1.5	5.6 ± 0.2	< 0.05
Fasting serum insulin (mU/L)	15.7 ± 2.5	18 2 ± 1.5	< 0.05
Fasting C-peptide (ng/mL)	3.1 ± 0.3	1.7 ± 0.5	< 0.05
HOMA-IR	8.7 ± 2.5	4.4 ± 0.4	< 0.05
HOMA-B (%)	35.0 ± 10.8	181.0 ± 33.3	< 0.05
Positive islet cell antibody (ICA)	0%	0%	
Body Mass Index (kg/m^2)	27.2 ± 1.5	22 2 ± 1.6	< 0.05
Total cholesterol (mmol/L)	4.7 ± 0.3	4.6 ± 0.6	NS
HDL-C (mmol/L)	1.1 ± 0.1	1.2 ± 0.1	NS
LDL-C (mmol/L)	2.9 ± 0.3	2.9 ± 0.3	NS
Triglycerides (mmol/L)	2.0 ± 0.2	1.3 ± 0.1	< 0.05
Systolic pressure (mmHg)	118.4 ± 5.9	110.2 ± 7.8	< 0.05
Diastolic pressure (mmHg)	85.3 ± 2.1	75.4 ± 0.01	< 0.05

Table 2. Two point LOD scores between 11 markers and MODY genes in five Jamaican families.

	Recombination fraction						
Order	0.0	0.01	0.05	0.1	0.2	0.3	0.4
D12S395							
Sum	-10.85	-7.02	-3.94	-2.46	-1.14	-0.60	-0.29
Ca	-3.67	-2.87	-1.84	-1.25	-0.63	-0.30	-0.11
R	-0.09	-0.09	-0.10	-0.11	-0.11	-0.08	-0.05
As	0.30	0.29	0 26	0.21	0.13	0.06	0.02
Su	-7.37	-4.34	-2.24	-1.31	-0.53	-0.28	-0.16
H	-0.02	0.02	0.01	0.01	0.00	-0.00	-0.00
D13S221	-5.67	-3.58	-1.62	-0.65	0.11	0.27	0.17
Ca	-2.98	-1.89	-1.06	-0.61	-0.17	0.00	0.04
R	0.60	0.59	0.55	0.51	0.40	0.29	0.16
As	0.18	0.17	0.15	0.12	0.07	0.03	0.01
Su	-2.84	-1.88	-0.85	-0.39	-0.06	0.00	-0.01
H	-0.62	-0.57	-0.41	-0.28	-0.13	-0.05	-0.01
D13S217	-5.59	-3.74	-1.93	-1.03	-0 24	0.05	0.10
Ca	-5.26	-3.48	-1.89	-1.15	-0.48	-0.18	-0.04
R	-0.07	-0.02	0.12	0.20	0.26	0.23	0.14
As	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Su	0.21	0.21	0.19	0.16	0.10	0.05	0.01
H	-0.48	-0.45	-0.34	-0.24	-0.12	-0.05	-0.01
D17S1293	-8.50	-6.50	-3.84	-2.27	-0.86	-0.31	-0.12
Ca	-4.52	-4.33	-3.01	-2.01	-1.00	-0.48	-0.19
R	-1.97	-1.34	-0.76	-0.51	-0.29	-0.17	-0.08
As	-0.02	-0.02	-0.01	-0.01	-0.01	-0.00	-0.00
Su	-2.02	-0.82	-0.07	0.25	0.42	0.34	0.16
H	0.02	0.02	0.02	0.01	0.01	0.00	0.00
D17S1788	-1.38	-1.13	-0.42	0.04	0.37	0.36	0.19
Ca	0.17	0.17	0.14	0.12	0.07	0.03	0.01
R	0.12	0.12	0.14	0.15	0.14	0.12	0.07
As	0.07	0.07	0.06	0.05	0.03	0.01	0.00
Su	-1.96	-1.70	-0.94	-0.43	0.04	0.15	0.10
H	0.22	0.22	0.19	0.15	0.09	0.04	0.01
ATC6A06	-5.79	-4.36	-2.85	-1.83	-0.78	-0.31	-0.09
Ca	-1.86	-1.16	-0.56	-0.32	-0.12	-0.04	-0.01
R	0.00	-0.01	-0.04	-0.07	-0.11	-0.12	-0.07
As	0.26	0.25	0 22	0.18	0.11	0.05	0.01
Su	-4.41	-3.66	-2.65	-1.77	-0.75	-0.25	-0.03
H	0.22	0.21	0.18	0.15	0.09	0.04	0.01
D2S1391	-3.72	-3.15	-1.48	-0.57	0.12	0.21	0.07
Ca	-1.10	-0.92	-0.45	-0.14	0.13	0.19	0.14
R	0.08	0.07	0.04	0.02	-0.02	-0.03	-0.02
As	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Su	-2.67	-2.27	-1.06	-0.43	0.02	0.05	-0.05
H	-0.02	-0.02	-0.02	-0.02	-0.01	-0.00	-0.00
D20S478	-11.17	-8.55	-5.77	-3.92	-2.00	-0.99	-0.38
Ca	-1.99	-1.94	-1.46	-1.02	-0.59	-0.36	-0.18
R	-1.44	-1.26	-0.88	-0.65	-0.38	-0.21	-0.09

As	-2.08	-1.32	-0.71	-0.44	-0.19	-0.07	-0.02
Su	-5 29	-3.67	-2.44	-1.60	-0.73	-0.30	-0.08
H	-0.38	-0.35	-0.28	-0.21	-0.11	-0.04	-0.01
D20S481	-7.27	-6.17	-4.17	-2.72	-1.28	-0.57	-0.19
Ca	-4.57	-3.68	-2.67	-1.89	-1.01	-0.52	-0.21
R	0.45	0.44	0.41	0.36	0.27	0.17	0.08
As	-0.13	-0.13	-0.10	-0.08	-0.04	-0.02	-0.00
Su	-2.40	-2.24	-1.39	-0.83	-0.36	-0.15	-0.04
H	-0.62	-0.57	-0.41	-0.28	-0.13	-0.05	-0.01
D7S2846	-3.51	-2.50	-1.23	-0.61	-0.14	0.01	0.03
Ca	-2.19	-1.96	-1.21	-0.74	-0.28	-0.08	-0.01
R	0.30	0 29	0 24	0.19	0.11	0.05	0.01
As	-0.14	-0.14	-0.11	-0.09	-0.05	-0.02	-0.00
Su	-1.70	-0.91	-0.34	-0.13	-0.01	0.01	0.01
H	0.22	0 22	0.19	0.15	0.09	0.04	0.01
D7S1818	-6.44	-4.51	-2.63	-1.68	-0.77	-0.34	-0.12
Ca	0.65	0.63	0.53	0.41	0.22	0.09	0.02
R	-1 97	-1.34	-0.76	-0.51	-0.29	-0.17	-0.08
As	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Su	-5.35	-4.01	-2.59	-1.74	-0.80	-0.32	-0.07
H	0.23	0 22	0.19	0.16	0.10	0.05	0.01

Ca, R, As, Su, H: Pedigree/Family. LOD score = 3 indicates significant evidence for linkage. LOD of < -2 indicates significant evidence against linkage. -Θ = 0.5: Unlinked. The first row of each group of LOD scores indicate combined family values. Markers: D12S395, D13S221, D13S217, D17S1293, DS2846, ATC6A06, D2S1391, D20S478, DS0S481, D17S1788, D2S1391, D7S1818.

genes *HNF-1α*, *HNF-1β*, *HNF-4α*, *IPF-1* and *NeuroD1* associated with this diabetes in Caucasians are not present in this Jamaican population (Table 2). These observations suggest that early onset type 2 diabetes is a different entity from MODY. A large amount of research is required to identify loci and genes associated to early onset type 2 diabetes in Jamaicans.

In addition, Irving, *et al.*, conducted a prospective study evaluating the odds for and incidence of gestational diabetes in pre-gravid women with and without a family history of early onset type 2 diabetes.[48] A total of 698 pregnant Jamaican women with a family history of early onset autosomal dominant type 2 diabetes were identified from March 2000-September 2003. Early onset autosomal dominant type 2 diabetes was defined as having a family history of diabetes in multi-generations, at least two first degree relatives diagnosed with type 2 diabetes before 35 years of age, and diabetes only on the maternal or paternal side of the family. In addition, 1,000 pregnant women without a family history of diabetes were identified at the same clinic during the same time period. Twelve percent of the women with a family history of early onset autosomal dominant type 2 diabetes were diagnosed with gestational diabetes during the second trimester of pregnancy. In contrast, only 1.5% of the women without a family history of diabetes were diagnosed with gestational diabetes (OR 9.0%, 95% confidence interval: 5.00- 16.38, P < 0.0001). Mutation screening via SSCP , sequencing , and linkage analysis was negative for the six known MODY genes (*HNF-4 alpha, GCK, HNF-1 alpha, IPF-1, HNF-1 beta*, and *Neuro-D1*). The Jamaicans with a family history of early onset autosomal dominant type 2 diabetes who developed GDM were normotensive and younger than normal pregnant women and had normal pregnancy BMI at 24–27 weeks of gestation suggesting that underlying factors, such as genetic and intrauterine, may have taken more prominent roles in the pathophysiology of gestational diabetes in this population.

In summary, Jamaican researchers has built a cohort of families with early onset type 2 diabetes. Their studies provide evidence that makes it improbable that this form of the disease is related to MODY genes. The large number of cases made it possible to assess the risk for having gestational diabetes in early onset type 2 diabetes kindreds.

Additional studies are required to identify the environmental and genetic factors that are associated with this form of diabetes.

THE MEXICAN CASE

Mexico, a country with 110 million inhabitants is populated mainly by young individuals. Almost half of the population is 25 years of age or younger. Their ethnic background varies between regions of the country. European ancestry ranges between 34.8-70.8%, the proportion of Native American ancestry between 27.6-56.2% and the proportion of African ancestry between 0.9-6.2%.[49] The life expectancy is 75.4 years. Over the past several decades, close to ten million Mexicans have immigrated, especially to the United States.

Multiple indigenous groups were the original residents of Mexico. Contrary to what happened in Jamaica, the conquest by Spaniards did not exterminate the native groups. An extensive mixture between the ethnic groups took place during the colonization of the country. Mexico gained independence in 1821. The post-independence period was characterized by economic instability, territorial secession and civil war, including foreign interventions, two empires and domestic dictatorships. The latter led to the Mexican Revolution in 1910, which culminated with the generation of the country's current political system. Between 1940 and 1980, Mexico experienced a substantial economic growth. Although the economy continued to flourish, social inequality persists. The end of the XX century was characterized by periods of economic crises followed by rebounds of the productivity. The 2009 gross domestic product per capita was 10,211 US dollars.[50]

Diabetes and cardiovascular events have been the major causes of death in Mexico since the year 2000.[51] There was a significant increase in the prevalence of diabetes over the past two decades. Mexico has performed three nationwide, population-based surveys (1994, 2000 and 2006). In the 1993 survey, the prevalence of type 2 diabetes was 6.7 % (previously diagnosed 4.6% and newly diagnosed 2.1%).[52] In the 2000 study,[53] the overall prevalence was 7.5% (5.8% previously diagnosed and 1.7% newly diagnosed). In the 2006 survey,[54] the prevalence reached 14.4% (7.3% previously diagnosed and 7.1% newly diagnosed). The prevalence increased in both genders. For women, the prevalence was 6.8, 7.8 and 13.2% in the 1993, 2000 and 2006 surveys respectively. The corresponding percentages were 6.6, 7.2 and 15.8% in men. In both the 2000 and 2006 surveys, the prevalence was higher in urban (8.2 *vs.* 15.5% respectively) populations compared to rural ones (5.6 and 10.4% respectively). Another probabilistic survey which was confined to a lower socioeconomic population which was living in Mexico City, reported a diabetes prevalence of 13.1% in 1996 and 13.8% in 2002.[55]

There are multiple reasons for the observed changes in the prevalence of diabetes. These include a shift in the age distribution of the population and a growing prevalence of obesity, principally related to changes in lifestyle. The prevalence of obesity in Mexico has increased in parallel with the prevalence of diabetes. In year 2006, 30.8% of the adults aged 20 to 69 years were obese nationwide. In addition, 39.8% had overweight (defined as a body mass index between 20 to 25 kg/m^2). In both, diabetes and obesity there has been a 25% increase in prevalence over a 6 year-period (2000-2006). These changes have occurred mainly in the urban and semi-rural communities of Central and Northern Mexico.[56]

Type 2 diabetes has a remarkable social and economic impact in Mexico. The large and growing number of cases, the complexity of therapy and the coexistence of several co-morbidities are major determinants of the burden imposed by this disorder to the Mexican health system. Treatment of diabetes and its co-morbidities represents 7% of the total health budget of Mexico in 2006. The annual diabetes-related cost in 2000 was 15,118.3 million US dollars.[44] The per capita direct cost was 528 US dollars. Regrettably, the majority of the expenditure is dedicated to covering the indirect consequences (13,144 million US dollars).

The assessment of the impact of early onset type 2 diabetes was included in all three nationwide Mexican surveys.[57,58] The initial report was a substudy of the 1994 survey. In 1994, the prevalence of diabetes was 1.8% for the age group 20-40 years. Early onset type 2 diabetes was present in 14.8% of the population with diabetes. There were 318 400 cases nationwide. Later in 2000, the prevalence was 2.3% for the age group 20-40 years. Early onset type 2 diabetes was present in 13.2% of the population with diabetes. In the 2006 study, the prevalence of diabetes was 5.8 % in the age group 20-40 years (Table 3). Thus, in a twelve years period the prevalence of diabetes in the 20-40 years group have had a 3.22 fold increment. Early onset type 2 diabetes is more common among subjects with a body mass index > 25 kg/m^2, hypoalphalipoproteinemia or hypertriglyceridemia. The number of cases of early onset type 2 diabetes moved from 318,400 to 1,662,870. As a result, the growth of diabetes in Mexico will mean that a greater number of cases and a greater proportion of the affected subjects will be exposed to the disease for a longer period of time. This may result in an in-

crease in the incidence of the chronic complications diabetes.

The contribution of early onset type 2 diabetes is now similar in Mexico to that reported in countries with the highest prevalence of diabetes worldwide. This form of the disease is present in 25% of the population with diabetes in India,[59] 36% in the Middle East and 26% in Native Americans living in the US.[60] Because obesity and unhealthy life styles are very prevalent in Mexican young adults, it is expected that the number of young adults will continue to increase in the years to come.

More than two thirds of the early onset type 2 diabetes cases evaluated in the 2006 survey[54] had a body mass index above 25 kg/m^2. The remaining cases (22%) had a clinical profile that is usually seen in insulin deficient states (i.e. Maturity onset diabetes of the young or late-onset autoimmune diabetes). The patients with early onset type 2 diabetes was the group with the highest prevalence of the use of insulin or oral glucose-lowering agent in all the patients with diabetes. Their mean HDL cholesterol concentration was lower compared to that found in the older group. However, they had a lower prevalence of hypercholesterolemia and arterial hypertension. Strategies to prevent the chronic complications of diabetes such as the use of low dose acetyl salicylic acid, regular ophthalmologic or foot examination were being followed in only a few cases. In addition, 70% of these patients paid little attention to their disease.

The metabolic and genetic characteristics of a cohort of Mexican patients with early onset diabetes who were being treated in a hospital were reported by Aguilar Salinas, et al.[61] Their clinical profiles were compared to that of patients with type 1 and type 2 diabetes. In this group, the mean age at diagnosis of diabetes was 28 yr. The majority was lean at the time of evaluation and required insulin therapy. Seventy-three percent 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 group with type 2 diabetes in the BMI, the percentage of cases who required insulin therapy and the fasting triglycerides levels.

The early onset group required insulin several years later than the group with type 1 diabetes. The

Table 3. Prevalence of diabetes in Mexican adults younger than age 40 and its comparison against the corresponding older controls. Results from the Encuesta Nacional de Salud y Nutrición 2006.

	Aged 40 years and younger	Older than 40 years of age	p value between age groups
Total prevalence (%)	5.8 (0.01)	25.7 (0.01)	< 0.001
Self-reported	1.6 (0.003)	14.8 (0.01)	< 0.001
Finding	4.2 (0.01)	10.9 (0.01)	< 0.001
Sex			
Men	6.4 (0.1)	27.8 (0.2)	< 0.001
Women	5.3 (0.01)	23.8 (0.2)	< 0.01
BMI			
Normal	4.1 (0.1)	19.1 (0.03)	< 0.001
Overweight	5.0 (0.01)	27.8 (0.02)	< 0.001
Obesity	9.4 (0.02)	27.0 (0.02)	< 0.001
HDL-C (mmol/L)			
< 1.05 in men and < 1.31 in women	6.1 (0.01)	27.3 (0.02)	< 0.001
≥ 1.05 in men and ≥ 0.31 in women	3.6 (0.01)	19.2 (0.02)	< 0.001
Triglycerides mmol/L			
≥ 1.68	9.8 (0.02)	29.8 (0.02)	< 0.001
< 1.68	3.4 (0.01)	20.2 (0.02)	< 0.001
Hypertension			
Yes	7.8 (0.02)	30.9 (0.02)	< 0.001
No	5.2 (0.01)	21.0 (0.02)	< 0.001

Data are presented as medians (Standard error). Modified from: Jimenez CA, Rojas MR, Gómez-Pérez FJ, Aguilar-Salinas CA. Early onset type 2 diabetes in a Mexican, population-based, nation-wide survey: Results of the Encuesta Nacional de Salud y Nutrición 2006. *Sal Púb Méx* 52 (Suppl. 1) [In press].

fasting C peptide concentrations of the early onset type 2 group were different from the patients with type 1 and 2 diabetes. Their C peptide levels were 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 (AIRg) was 67.5 ± 44.2 mU/mL. An AIRg lower than 100 mU/mL, a cut-off point used for severe insulin deficiency was found in 34 of the 40 cases. In the early-onset type 2 group, three cases (7.5%) had positive titers for GAD antibodies. They had C-peptide levels below 0.12 pmol/mL. Insulin treatment was required in all three cases a mean 3.1 ± 4 yr after the diagnosis of diabetes. Insulin sensitivity was measured using the sensitivity index (SI) obtained during the insulin-modified intravenous glucose tolerance test. The mean SI of the early-onset type 2 group was 3.73 ± 2 (normal range, 4-6). Thirteen patients (32.5%) had a SI below 4; these cases were classified as insulin resistant.

In this cohort of cases, the plasma lipid profile of the early-onset type 2 group was different from the older adults with type 2 patients. They had significantly lower plasma triglycerides and higher HDL cholesterol levels. No differences were found in plasma lipid profiles between the early-onset type 2 groups and the type 1 patients. Among the early onset type 2 individuals, cases with a SI below 4 had significantly higher concentration of plasma triglycerides and LDL cholesterol. Smaller and denser LDL subclasses were 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.

The evaluation of the hospital-based cohort of early onset cases was complemented with the search for mutations in the MODY genes. Only three mutations were found. Two individuals had a missense mutations in exon 4 of the *HNF1alpha* gene and one subject had a nonsense mutation in exon 7 of the *HNF-1beta* gene. Additional studies are required to assess the contribution of the MODY genes to early onset type 2 diabetes in population-based surveys.

The data derived from this hospital-based cohort suggest that insulin deficiency is the main abnormality responsible for the premature presentation of diabetes. There seems to be multiple causes of the insulin deficiency. The presence of markers of autoimmune destruction of the beta cell was observed in 7.5% of the cases. Also, mutations in the *HNF-1 alpha* and *HNF-4 beta* genes were identified among our group of patients. Two of the subjects with detected mutations are likely to represent MODY individuals, suggesting that this monogenic type of diabetes is present in a minority of the early-onset cases treated in a hospital. However, in the vast majority of the cases, the reason for the severe insulin deficiency was not identified.

However, it must be emphasized that the clinical characteristics of the cases with early onset type 2 who are being treated in a hospital is different from those found in the community. The 2006 survey[54] showed that more than two thirds of the cases are obese or have overweight. This feature is in contrast with the leanness found in the majority of the participants of the hospital-based cohort (Figure 1).

The study of the genes involved in the pathogenesis of type 2 diabetes in Mexicans is in its early stages. Polymorphisms of several genes (*Calpain-10,IRS-2, HNF 4 alpha* and *TCF7L2*) have been reported associated to the disease in Mexicans.[25,62,64] Villarreal-Molina, *et al.*,[65] found that the R230C variant of the ATP binding cassette A1 (*ABCA1*) gene is associated with type 2 diabetes, especially in the early onset group. This variant is exclusively found in Amerindian populations. The amino acid substitution decreases the activity of the transporter leading to an intracellular accumulation of cholesterol. In vitro studies done in animal models have shown that abnormally high cholesterol concentrations within some cell compartments induces apoptosis and causes decreased insulin secretion. This variant may result from a survival selection process that

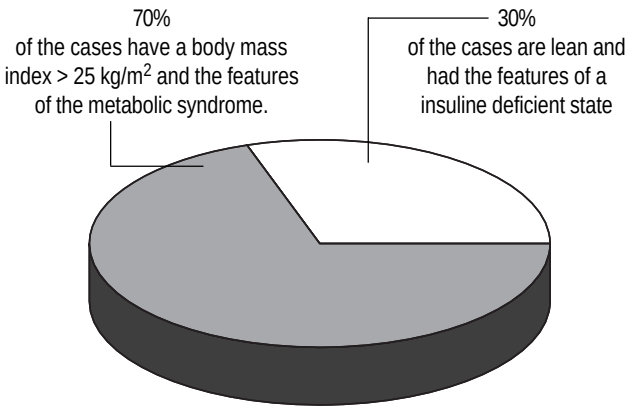

Figure 1. Early onset type 2 diabetes is an heterogenous condition in Mexican adults.

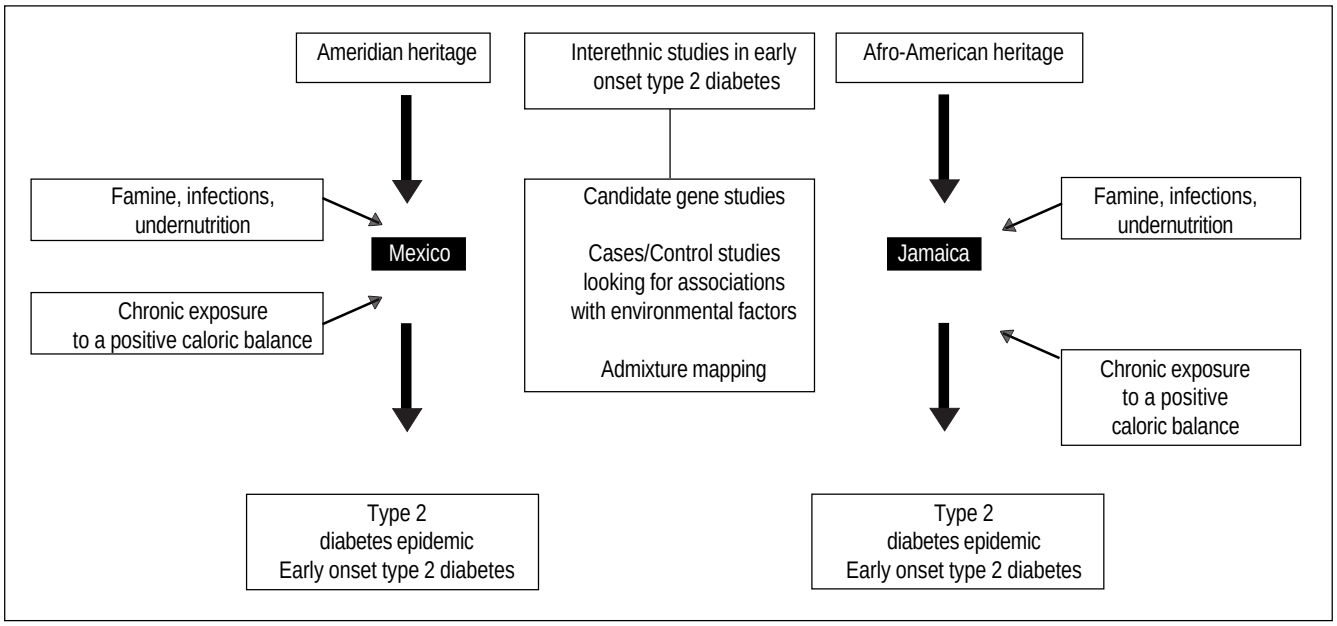

Figure 2. Interethnic studies: An approach to generate new knowledge in the study of early onset type 2 diabetes.

allowed the preservation of cholesterol in times of food deprivation.

In summary, Mexico is facing a rapidly growing diabetes epidemic. The group in which the greater percent changes in prevalence have occurred is composed mostly of adults younger than age 40. Additional studies are required to identify the pathophysiology behind the early onset type 2 diabetes phenotype and its social, psychological and economical consequences.

PERSPECTIVES AND CONCLUSIONS

Jamaica and Mexico are among the countries with the highest prevalence of diabetes worldwide. Their populations have different historic and ethnic backgrounds. However, they have had in common, exposure to famine for several generations followed by social changes that have led to an affluent environment. The chronic exposure of these populations to a positive caloric balance has revealed the remarkable susceptibility for the development of diabetes in these two populations.

As it has been reported in other countries with a high prevalence of diabetes, the prevalence of early onset cases in Mexico and Jamaica is greater than that seen worldwide. Research groups in both countries have identified early onset type 2 diabetes as a model to study the interactions between genetic and environmental factors (Figure 2). The comparison of populations from different ethnic background offers unique opportunities to generate new knowledge. The large structure of the Mexican and Jamaican families gives us the chance to identify new loci or genes linked to the disease. In addition, the population attributable risk of the currently known diabetes susceptibility alleles could be compared in samples of adults representative of each country.

In addition, admixture mapping could helpful to identify new genes associated to early onset type 2 diabetes in our populations. Admixture mapping offers advantages over alternative mapping methods.[66,67] Admixture mapping does not require recruitment of families with multiple affected members, in contrast with traditional linkage studies. In addition it has higher power to detect variants of modest effect than linkage studies. Also, it requires fewer genetic markers (1,500-3,000) than haplotype or direct association studies (300,000–1 million). It is not as affected by allelic heterogeneity as other approaches and it can be implemented for affected-only designs. Finally, the differences in lifestyle, environment and source of nutrients that exist between these populations could be useful for evaluating the effect of environment on the age of onset of the diabetes. We believe that interethnic studies of populations that have been exposed to a similarly adverse environment will be useful in identifying new players in the pathogenesis of early onset type 2 diabetes.

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