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Risk factors associated to diabetes in Mexican population and phenotype of the individuals who will convert to diabetes

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Abstract

Objective. To describe risk factors associated to the incidence of type 2 diabetes (T2D) in Mexican population and to define phenotypic (clinical, anthropometric, metabolic) characteristics present in the individual who will convert to diabetes, regardless of time of onset. **Materials and methods.** The Mexico City Diabetes Study began in 1990, with 2 282 participants, and had three subsequent phases: 1994, 1998, and 2008. A systematic evaluation with an oral glucose tolerance test was performed in each phase. For diagnosis of T2D, American Diabetes Association criteria were used. **Results.** The population at risk was 1 939 individuals. Subjects who were in the converter stage (initially non diabetic that eventually converted to T2D) had, at baseline, higher BMI (30 vs 27), systolic blood pressure (119 vs 116 mmHg), fasting glucose (90 vs 82mg/dl), triglycerides (239 vs 196mg/dl), and cholesterol (192 vs 190mg/dl), compared with subjects who remained non converters ($p<0.05$). **Conclusion.** The phenotype described represents a potentially identifiable phase and a target for preventive intervention.

Key words: Diabetes mellitus; risk factors; incidence; phenotype; Mexico

González-Villalpando C, Dávila-Cervantes CA, Zamora-Macorra M, Trejo-Valdivia B, González-Villalpando ME. Factores de riesgo asociados con diabetes en la población mexicana y fenotipo de los individuos que desarrollarán diabetes. Salud Publica Mex 2014;56:317-322.

Resumen

Objetivo. Describir los factores de riesgo asociados con la incidencia de diabetes tipo 2 (T2D) en la población mexicana, así como el fenotipo de los sujetos que desarrollarán diabetes, independientemente del tiempo que lleve el desarrollo de esta nueva condición. **Material y métodos.** El Estudio de la Diabetes de la Ciudad de México inició en 1990 y tuvo un total de 2 282 participantes a los que se dio seguimiento en tres ocasiones: 1994, 1998 y 2008. Se realizó una curva de tolerancia a la glucosa para diagnosticar T2D, para lo cual se siguieron los criterios de la Asociación Americana de Diabetes. **Resultados.** La población en riesgo fue de 1 939 sujetos. Los individuos en proceso de desarrollo (aquellos inicialmente no diabéticos que desarrollaron T2D) mostraron niveles más altos de IMC (30 vs 27), presión arterial sistólica (119 vs 116 mmHg), glucosa en ayuno (90 vs 82 mg/dl), triglicéridos (239 vs 196 mg/dl) y colesterol (192 vs 190 mg/dl), comparados con los sujetos que no desarrollaron T2D ($p<0.05$). **Conclusiones.** El estado de los individuos que se convertirán en diabéticos es discernible y representa una fase del padecimiento con potencial para la prevención.

Palabras clave: diabetes mellitus; factores de riesgo; incidencia; fenotipo; México

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The epidemic of type 2 diabetes (T2D) continues its relentless incremental growth, afflicting more than 550 million people all over the globe.[1,2] Some regions are considered the epicenter of this unprecedented phenomenon, particularly China and India.[3,4] It is recognized that a complex interaction of genetic and environmental factors are key elements of the driving forces behind this enormous challenge.[5,6] Substantial evidence is available to suggest that at least 30% of the excess in the prevalence of T2D is the result of influences by environmental determinants; this estimate has been previously documented in Mexican origin population.[7] Moreover, a new light has been shed on this complex phenomenon, as a result of the recent identification of a gene, previously unrecognized as an associated genetic signal in Mexican origin population.[8] This gene, SLC16A11, with functions still insufficiently studied, could explain about 28% of the excess of T2D seen in Mexican origin population.

It is reasonable to consider that the growth of the T2D epidemic might be the result of the interaction between genetic predisposition and a high risk environment.[9] The epidemic of T2D is a major cause of mortality and morbidity, its care and complications represent already an enormous and growing health problem of the highest priority.[10] The prevalence of obesity and impaired glucose tolerance[11,12] was reported already high more than 20 years ago in Mexico. Predictably these determinants have increased and fueled the growth of the T2D epidemic. Since there are several determinants inherent to each particular environment/population interaction, it is potentially useful to identify those risk factors playing the most significant role in any given time and circumstances. Hereby we present an analysis of the risk factors associated with the long term incidence of T2D in Mexican population and describe phenotypic characteristics amenable for preventive intervention.

Materials and methods

The Mexico City Diabetes Study (MCDS) is a population-based, prospective research designed to characterize the prevalence, incidence and natural history of T2D and cardiovascular risk factors, in low-income urban inhabitants of Mexico City. Methods have been previously described.[13] The baseline phase started in 1990 with 2 282 men and non-pregnant women (35 to 64 years of age). There has been three subsequent phases with similar study protocols (1994, 1998 and 2008). This research was approved by the Institutional Review Board of the Instituto Nacional de Salud Pública and the Centro de Estudios en Diabetes. Informed consent was obtained from the participating subjects, in accordance with the ethical principles for medical research involving human subjects.

Those individuals who reported that they had a previous diagnosis of T2D by a physician and were receiving pharmacological treatment for diabetes were considered to have T2D regardless of their blood glucose values. For subjects not known to be diabetic, we used the American Diabetes Association (ADA) diagnostic criteria (fasting glucose ≥126 mg/dl, or two-hour plasma glucose ≥200mg/dl after a standard, 75g oral glucose load).[14] We accepted T2D diagnosis if it was stated in the death certificate. We defined impaired fasting glucose as >100 and <126mg/dl and impaired glucose tolerance as >140 and <200mg/dl in the two hour postglucose load, as the ADA recommends.

Individuals who met the diagnostic criteria for T2D at baseline (prevalent diabetic cases) were excluded from this analysis. The population at risk was 1 939 subjects.

All participants who subsequently developed T2D, regardless of time of onset, where compared with those who remained non diabetic throughout the study, with complete information. We used baseline characteristics in both groups for comparison. Individuals who had incomplete follow-up were excluded.

We identified all subjects with incomplete follow-up (586) and compared baseline characteristics, with the corresponding variables of converters and non converters.

Data were processed using the statistical package STATA 11.0.* Descriptive statistics of all variables were obtained. Multiple logistic regression analysis was used to explore variables potentially associated with the conversion to T2D. We investigated the following variables: Positive family history for T2D, body weight, age at baseline, body mass index, other anthropometric variables used to estimate the distribution of body adiposity, fasting, and 2hrs post load insulin and glucose. We also included total cholesterol, HDL, LDL, tobacco consumption, triglycerides, maximum weight in life and physical activity. Variables with heavy asymmetric distribution were converted to logarithmic scale in the logistic regression model.

Results

With the established diagnostic criteria, we found 732 cases of T2D (32%). Of these, 343 (15%) were found at baseline (137 men and 206 women). This group was labeled as prevalent cases and was excluded from this analysis. During the following phases of the study, 389 (17%) par-

* StataCorp. Stata Statistical Software: Release 11. Texas: StataCorp LP, College Station; 2009.

ticipants converted from non diabetic status to T2D and were labeled as converters (164 men and 225 women). The individuals that were non diabetic at baseline and that had complete follow-up information in order to ascertain their non diabetic status throughout the entire follow-up were 964, and were labeled as non converters.

In table I, we present the results of the comparison of selected baseline variables between converters and non converters. It can be noted that individuals in the converter stage had more often a positive family history for T2D, 4 vs 1% for both parents, 4 vs 1% for both brother and/or sister. Also, converters had significantly higher maximum weight in life compared to non converters, 76 kg vs 70 kg, $p<.05$. Similarly, BMI, weight, waist and hip circumferences, waist/hip ratio, subscapular and tricipital skin folds, subscapular/tricipital ratio, and systolic and diastolic blood pressure were all significantly higher in converters compared to non converters.

In table II we present the results of the comparison of selected baseline metabolic variables of converters vs. non converters. It can be noted that converters had significantly higher fasting glucose and two hours post glucose load (though still in normal range) and insulin, total cholesterol and triglycerides compared to the mean values observed in non converters. As expected, HDL cholesterol was lower in converters.

The hiperinsulinemic condition of the converters is evidenced by the results of the fasting and two hours post

Table I

Comparison of sociodemographic, physiological and physical features among non converters and converters to T2D. Mexico City Diabetes Study (1990-2008). Distrito Federal, Mexico, 2014

Variables	*Non converters n=964*			*Converters n=389*		
	n (%; 95%CI)	*Men n=397*	*Women n=567*	*n (%; 95%CI)*	*Men n=164*	*Women n=225*
Parents						
Mother	120 (13;10.0-15.0)	58	62	74 (20; 16.0-24.0)	24	50
Father	77 (8; 6.0-10.0)	28	49	32 (8; 6.0-12.0)	17	15
Both	9 (1; 0.4-1.7)	6	3	16 (4; 2.0-7.0)	6	10
None	732 (76; 73.0-79.0)	297	435	250 (67; 62.0-72.0)‡	110	140
Brothers						
Brother	62 (7; 5.0-8.0)	33	54	22 (6; 4.0-9.0)	12	10
Sister	57(6; 5.0-8.0)	33	56	37 (10; 7.0-13.0)	10	27
Both	13 (1; 0.7-2.0)	10	14	15 (4; 2.0-6.0)	4	11
None	818 (86; 82.0 -87.0)	550	774	305 (80; 7.0-8.0)‡	133	172
Hypertension	100 (10; 8.0-12.0)	44	56	66 (17; 13.0-21.0)	37	29
	Mean (95%CI)	*Men n=397*	*Women n=567*	*Mean (95%CI)*	*Men n=164*	*Women n=225*
Wt (kg)	67 (66-68)	71	64*	74 (72-75)*	78	71*
MWL (kg)	70 (69-71)	75	66*	76 (75-78)*	82	72*
20ys weight (kg)	54 (53-54)	58	50*	54 (52-55)	57	51*
BMI (kg/m^2)	27 (27-28)	26	28*	30 (30-31)*	29	31*
WC (cm)	95 (94-95)	93	96*	101 (100-102)*	98	104*
HC (cm)	98 (98-99)	96	100*	102 (102-104)*	99	106*
W/h ratio	0.96 (0.96-0.97)	0.97	0.96	0.98 (0.98-0.99)*	0.99	0.98
Subscapular SF (cm)	26 (26-27)	23	29	32 (31-33)*	28	34*
Tricipital SF (cm)	21 (20-22)	14	26*	25 (23-26)*	17	30*
Sub/tri	1.5 (1.4-1.5)	1.9	1.2*	1.5 (1.4-1.6)	2	1.2*
Systolic-BP (mmHg)	116 (115-117)	118	114*	119 (118-121)*	122	118*
Diastolic-BP (mmHg)	72 (71-73)	74	70*	76 (74-77)*	78	74*

U * $p<.05$

‡ Pearson´s $x^2<.05$

T2D: type 2 diabetes
Wt: weight
MWL: maximum weight in life
20ys: 20 years of age
BMI: body mass index
WC: waist circumference
HC: hip circumference
W/h: waist/hip ratio
SF: skin fold
BP: blood pressure

Table II
Metabolic differences between non converters and converters to T2D. Mexico City Diabetes Study (1990-2008). Distrito Federal, Mexico, 2014

Variables	Non converters n=964			Converters n=389		
	Mean (95%CI)	Men n=397	Women n=567	Mean (95%CI)	Men n=164	Women n=225
Fasting glucose (mg/dl)	82 (81.7-83)	83	82	90 (89-91)*	90	90
Two hours post-glucose load (mg/dl)	98 (96-100)	90	103*	123 (119-126)*	118	126*
Fasting insulin (IU/ml)	14 (13-15)	13	15*	20 (19-21)*	20	20
Two hours insulin post glucose load (IU/ml)	82 (77-87)	68	92*	128 (119-137)*	112	141*
Total cholesterol (mg/dl)	190 (187-193)	190	189	192 (188-197)*	197	189*
Triglycerides (mg/dl)	196 (186-204)	234	169*	239 (222-256)*	288	204*
HDL (mg/dl)	34 (33-34)	31	35*	31 (30-32)*	28.6	32*
LDL (mg/dl)	122 (120-124)	123	122	123 (120-126)	126	120

U* $p<.05$

T2D: Type 2 diabetes
HDL: High density lipoproteins
LDL: Low density lipoproteins

glucose load, glucose and insulin levels. The difference in BMI among the groups should be taken into account for an appropriate interpretation of these results.

In the non converter group (964) we identified 37 subjects (4%) with impaired fasting glucose and 75 (8%) with impaired glucose tolerance. In the converters (389) we identified six (1.5%) individuals with impaired fasting glucose and 110 (28%) with impaired glucose tolerance.

In table III we present the results of the multiple logistic regression analysis, including selected variables potentially associated to an increased probability of conversion to T2D. Significant differences can be noted at: age at baseline, OR 0.96 (95%CI 0.94-0.98); BMI at baseline, OR 1.1 (95%CI 1.05-1.15); maximum weight in life, OR 3.9 (95%CI 1.3-11.0); fasting glucose, OR 1.02 (95%CI 1.0-1.03); glucose two hours post load, OR 1.02 (95%CI 1.01-1.02); years of smoking, OR 1.02 (95%CI 1.01-1.03), and HDL, OR 0.98 (95%CI .96-.99). The total physical activity, estimated in metabolic equivalents (METs) by the questionnaire we used, had neutral OR 1.00 (95%CI 1-1.01). Goodness of fit tests were carried out showing good concordance of the model.

In table IV we present the comparison of selected baseline characteristics corresponding to converters and non converters compared to individuals who had incomplete follow-up (attrition) and consequently we were unable to unequivocally ascertain their diabetic status. It can be noted that the differences observed suggest that the group with incomplete follow-up has an intermediate profile between converters and non converters.

Even though there are some differences, the glucose values of the attrition group (both fasting an two hours) resemble those of the non converter group.

Table III
Logistic regression model for the risk of conversion to T2D. The Mexico City Diabetes Study (1990-2008). Distrito Federal, Mexico, 2014

Variable	OR	95%CI	p
Diabetes background			
None	Ref	–	–
Mother	0.72	(0.32-1.56)	.396
Father	0.71	(0.42-1.18)	.163
Both	2.5	(0.65-13.33)	.188
Baseline age (years)	0.96	(0.94-0.98)	.000
Baseline BMI (kg/m²)	1.1	(1.05-1.15)	.000
Log-MWL (kg)	3.9	(1.3-11.0)	.014
Fasting glucose (mg/dl)	1.02	(1.00-1.03)	.007
Two hours post-load glucose (mg/dl)	1.02	(1.01-1.02)	.001
Log-triglycerides (mg/dl)	1.05	(0.99-1.11)	.096
Tobacco use (years)	1.02	(1.01-1.03)	.002
Physical activity (METs)	1.00	(1.00-1.01)	.004
HDL cholesterol (mg/dl)	0.98	(0.96-0.99)	.040

*Adjusted by sex, education and total calories
T2D: type 2 diabetes
Log-MWL: log transformation of maximum weight of life
HDL: High density lipoproteins

Discussion

The stage that precedes the conversion to T2D is a phase of the natural history of T2D that is being explored intensively. Evidence shows that significant dysfunctional alterations exist before the occurrence of the disglycemic

Table IV

Comparison between individuals with incomplete follow up (attrition group) vs non converters group and vs converters. The Mexico City Diabetes Study (1990-2008). Distrito Federal, Mexico, 2014

Variables[§]	*Attritions n=586 Mean (SD)*	*Non converters n=964 Mean (SD)*	*Converters n=389 Mean (SD)*
Sex[‡]	0.59 (0.02)	0.59 (0.02)	0.58 (0.03)
Age (years)	46.3 (8.1)	46.4 (8.1)	46.2 (7.5)
Marital status[‡]	0.81 (0.01)	0.81 (0.01)	0.81 (0.2)
Years of education	5.2 (3.8)	5.8 (3.8)*	5.6 (3.8)
Years of smoking	17.4 (11.7)	16.6 (11.5)	18.4 (12.9)
Fasting glucose (mg/dl)	83.7 (12)	82.5 (11.2)*	89.7 (12.4)*
Two hours post-glucose load (mg/dl)	104 (32.4)	98.3 (27.7)*	123 (33.8)*
BMI (kg/m^2)	27.7 (4.2)	27.3 (3.9)*	30 (4.7)*
Weight at age 20 (kg)	52.5 (8.4)	53.8 (9.2)*	53.8 (9.2)*
Triglycerides (mg/dl)[#]	200.6 (134)	195.5 (136)	239.5 (172)*
Total cholesterol (mg/dl)[#]	186.6 (41)	190 (43)	192.2 (44)*
Systolic blood pressure[#] (mmHg)	117.4 (17.2)	115.9 (17.2)*	119.6 (16.2)*
Diastolic blood pressure[#] (mmHg)	73.1 (11)	72 (10)*	75.7 (10)*
Waist circumference (cm)	96.3 (13.2)	94.6 (10.9)*	101 (13.2)*
Waist/hip ratio	0.97 (0.07)	0.96 (0.07)	0.98 (0.06)*
Physical activity (Met)[#]	278 (47)	276 (44)	281 (44)

* Statistically significant for a difference means test
‡ Proportions
§ At baseline stage
# Log transformed

T2D: type 2 diabetes
SD: standard deviation

disruption, recognized as the onset of T2D. The phenotypic characteristics hereby described, that mark the differences between converters and non converters, even at the non diabetic stage (like glucose) are amenable to identification at the primary care setting. Consequently, this information can be used in preventive intervention. We pursue through this investigation to draw the attention of all involved actors, to focus in this stage of the natural history of T2D. The differences between the mean values of certain metabolic variables, although subtle (apparently normal) are of significance. This should raise the level of alertness of the system.

Results shown in table I imply that converters have indicators that could be heralding the eventual conversion to T2D, or perhaps have a "subclinical" form of the disease in the process of declaring itself with more evident manifestations. The anthropometric variables, shown to be different between the converters and the non converters, are important since they represent the magnitude and type of distribution of body adiposity, a recognized risk factor associated with the conversion to T2D. The self-reported maximal weight in life is of interest, in that converters report a maximal weight in life significantly higher than the reported by individuals remaining without conversion to T2D. This information should trigger action at much earlier phases of the disease, as it has been recommended recently.[15] The vulnerability of the Mexican origin population to the deleterious consequences of obesity has been informed.[16] Data from table II reveal consistent and expected findings. Fasting glucose and insulin found within "normal" range in both groups are higher in the converter group, suggesting the stage of insulin resistance, well recognized as an indicator of future T2D.

The results of the multiple logistic regression model show that recognized factors have an important contribution to the risk of conversion to T2D and are confirmed by our study.[17,18] Smoking has a significant impact in the model studied. This information should be considered in the description of the phenotype of the subject at risk, especially since in our cohort a substantial proportion of participants (predominantly males) were smokers.[19]

The comparison of the variables of the group with incomplete follow-up (attrition group) with the converters and the non converters gives us margin to consider that bias, although occurring, is under reasonable level.

It is of practical importance to underscore the fact that more than 70% of converters emerge from normal

glucose tolerance. The current paradigm tends to consider that high risk starts at impaired fasting glucose or impaired glucose tolerance, so perhaps this could imply a missed opportunity for timely preventive intervention.

The interplay between length of follow-up and selection bias as a natural result of the long follow-up should be recognized as the strength/limitation ratio. This is the only study in Mexico with these characteristics.

The conversion to T2D in Mexican population is high and could get even higher,[20] reaching levels seen in the Mexican American and Pima Indian population.[21,22] Since the cost associated to T2D care is already high and will increase,[23,24] and the results of the current model of care are recognized as not effective,[25] this ominous scenario demands a systematic translational effort in order to investigate strategies designed to apply evidence-based information in preventive endeavors. The call for innovative action is now.[26]

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Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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