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Diabetic by HbA1c, Normal by OGTT: A Frequent Finding in the Mexico City Diabetes Study

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Context: The agreement between glucose-based and hemoglobin A1c (HbA1c)–based American Diabetes Association criteria in the diagnosis of normal glucose tolerance, prediabetes, or diabetes is under scrutiny. A need to explore the issue among different populations exists.

Objective: Examine the results obtained with both methods in the diagnosis of the glycemic status.

Design: The Mexico City Diabetes Study is a population-based, prospective investigation.

Setting: Low-income elder urban community.

Participants: All 854 participants without known diabetes had both oral glucose tolerance test (OGTT) and HbA1c measurements on the same day of the 2008 phase.

Interventions: Standardized protocol: questionnaires, anthropometry, and biomarkers.

Main Outcome: Diagnostic classification of American Diabetes Association criteria.

Results: We found by OGTT normal glucose tolerance (NGT) in 512 (59.9%) participants, prediabetes [impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)] in 261 (30.5%), and diabetes in 81 (9.4%). In total, 232 in the NGT group (45.3%) and 158 in the prediabetes group (60.5%) had HbA1c ≥6.5%. Body mass index, waist circumference, and blood pressure were significantly different among OGTT-defined diabetic status groups but not in the HbA1c-diagnosed group. We identified 404 participants in the NGT group with confirmed NGT throughout all phases of the Mexico City Diabetes Study. Of these, 184 (45.5%) had HbA1c ≥6.5%. In a vital/diabetes status follow-up performed subsequently, we found that, of these, 133 remained nondiabetic, 3 had prediabetes, 7 had diabetes, and 13 had died without diabetes; we were unable to ascertain the glycemic status in 5 and vital status in 23.

Conclusions: Normal OGTT coexisting with elevated HbA1c is a common finding in this cohort. It is possible that this finding is not mediated by hyperglycemia. This might occur in similar populations.

Freeform/Key Words: diabetes mellitus, diagnosis, glucose tolerance test, HbA1c

Abbreviations: ADA, American Diabetes Association; HbA1c, hemoglobin A1c; MCDS, Mexico City Diabetes Study; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PD, prediabetes; T2D, type 2 diabetes.

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The prevalence of type 2 diabetes (T2D) is increasing at alarming rates worldwide. There are regions of the world with a higher impact compared with others. The complex pathogenesis of these metabolic alterations includes genetic, epigenetic, and environmental determinants, all of which are currently under intensive scientific investigation [1]. There is evidence that suggests that around 30% of the excess of T2D, observed in Mexican population, could be mediated by environmental determinants [2]. Moreover, a variant of the *SLC16A11* gene, a recently explored member of a lipid transporter family, was found more frequently in diabetic patients of Mexican origin. This gene variant could explain up to 20% of the excess risk for T2D [3, 4]. This ominous scenario presents a vulnerable population who is exposed to circumstantial conditions promoting the incidence of T2D.

Several initiatives have been launched in Mexico and in other nations that have been designed to mitigate the effects of T2D. A valuable asset in this strategy would be a method that enables timely detection in a cost-effective way. The possibility of using a simpler and efficient method in the diagnosis of T2D is very attractive [5]. The use of hemoglobin A1c (HbA1c) measurement to diagnose prediabetes (PD) or T2D could expedite the process and allow the implementation of preventive actions as well as early therapy.

The diagnosis of T2D by using fasting glucose and/or an oral glucose tolerance test (OGTT) is endorsed by the American Diabetes Association (ADA) and the World Health Organization. Perhaps these tests could be considered gold standards. Recently, HbA1c has been included into the diagnostic armamentarium by the ADA, the European Association for the Study of Diabetes, and the International Diabetes Federation [6–8].

Although these facts suggest that this biomarker could be an attractive element in the strategy to combat T2D, substantial controversy remains. Several investigators have reported considerable diagnostic misclassification when comparing the results of these tests [9]. Adjustment of the diagnostic cutoff for certain populations or an ethnic-specific cutoff value has been suggested [10, 11]. This underscores the need for more information exploring different environmental scenarios and ethnic groups to adequately characterize the performance of this test. This is particularly meaningful in high-risk populations such as the elderly and low-income groups [12].

Proper characterization of the performance of HbA1c in the identification of the glycemic spectrum might illuminate pathophysiologic elements that could enrich the current paradigm. The application of this test might allow the incorporation of pertinent information recently published, describing elements already present in the early phases anteceding the onset of T2D [13, 14]. There is valuable information regarding the performance of these tests in white, African American, and Asian populations but insufficient data in the Mexican population.

In this study, we provide the results of an investigation designed to compare the performance of both measurements: OGTT and HbA1c. A special focus of this research effort is to explore the longitudinal trajectory prior to the onset of T2D. We used the Mexico City Diabetes Study (MCDS) platform [15, 16]. This is a prospective, population-based research effort designed to characterize the prevalence, incidence, and natural history of T2D in a low-income urban group of participants who live in Mexico City. We assess and compare the cardiometabolic risk profile prior to and at the diagnosis of PD and T2D with both methods.

1. Research Design and Methods

The MCDS began in 1989 with the identification of a homogeneous low-income site. This area encompasses six census tracts. A complete household enumeration and census of the population living in the area (15,532 inhabitants) was performed. All men and nonpregnant women aged 35 to 64 years were defined as eligible. The research protocol, informed consent, procedures, and methods were approved by the Institutional Review Board of the Center for Studies in Diabetes. All participants gave informed consent. Results of the MCDS have been previously published [16].

At baseline (1989 to 1990), a total of 3319 participants were interviewed and 2282 examined (from a total of 3505 eligible individuals). The final cohort (interviewed and examined)

was composed of 941 men and 1341 women. We identified 343 (15%) participants with T2D (prevalent cases). Of these, 179 (52%) were individuals who self-reported T2D. In 164 (48%), the diagnosis was identified as a result of the survey. The MCDS has had three follow-up exams in 1994, 1998, and 2008. During the last phase, in addition to the standardized exam and OGTT, we included HbA1c measurement (Table 1 shows the schematics of the study). T2D was diagnosed using ADA criteria: fasting plasma glucose concentration ≥126 mg/dL and/or a 2-hour plasma glucose concentration ≥200 mg/dL after a standard 75-g glucose load. Participants who self-reported a history of diabetes and were taking oral glucose–lowering agents were considered to have T2D, regardless of their plasma glucose values. PD was diagnosed when an individual had a fasting plasma glucose of 100 to 125 mg/dL and/or a 2-hour postglucose load between 140 and 199 mg/dL. Hypertension diagnosis was established using the Seventh Joint National Commission on Hypertension criteria [17]. These include a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg, Participants who self-reported being hypertensive and were taking antihypertensive medication were considered hypertensive regardless of their blood pressure values.

Height, weight, and waist and hip circumferences were obtained using a standardized clinical device. Systolic and diastolic blood pressure were measured using a random zero sphygmomanometer (Hawksley). We followed the protocol previously published [16]. Biochemical measurements in blood samples were obtained in the fasting state and 2 hours after a standard 75-g oral glucose load. Serum samples were kept on ice for a few minutes until centrifuged in a temperature-controlled device. Samples were divided into aliquots and stored at −70°C until assayed. Fasting concentrations of serum insulin, proinsulin, plasma glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, insulin, and glucose 2 hours after an oral glucose load were determined at baseline and in two follow-up exams (1994 and 1998). In the last follow-up, performed in 2008, we measured fasting glucose, total cholesterol, triglycerides, and glucose 2 hours postload, as well as

Table 1. MCDS Phases and Participants in Each Follow-up

Characteristic	Value
Baseline (1989 to 1990)	
Total population	15,532
Eligible	3505
Examined	2282
Men	941/2282 (41.2)
Women	1341/2282 (58.8)
Second follow-up (1993 to 1994)	
Examined	1773/2282 (77.7)
Men	717/1773 (40.4)
Women	1056/1773 (59.5)
Third follow-up (1997 to 1998)	
Examined	1762/2282 (77.2)
Men	724/1762 (41.0)
Women	1038/1762 (58.9)
Fourth follow-up (2008 to 2009)	
Examined	1174/2282 (51.4)
Men	462/1174 (39.3)
Women	712/1174 (60.6)
854 participants with OGTT and HbA1c on this exam[a]	
Men	343/854 (40.1)
Women	511/854 (59.8)

Values are presented as numbers or number (%).

[a]The study population of the present investigation was selected from the MCDS using the follow criteria: all participated in the 2008 evaluation, all had OGTT and HbA1c on that exam, and all had their nondiabetic glycemic status ascertained throughout all previous phases of the MCDS.

conducted liver function, creatinine, and uric acid tests. For this investigation, we incorporated all participants who had completed previous exams and whose glycemic status was clearly ascertained.

We calculated Homeostasis Model Assessment, Matsuda, and Quickie insulin resistance/sensitivity indices by using the laboratory determinations obtained in the evaluations performed at baseline, 1994, and 1998 [18, 19]. All the biomarkers corresponding to baseline, 1994, and 1998 phases were measured at the research laboratory of the Division of Clinical Epidemiology in the Department of Medicine at the University of Texas Health Science Center, San Antonio. The biomarkers measured in 2008 were performed at the Clinical Laboratory of the American British Cowdray Medical Center, which is a tertiary care facility that holds a quality assurance program certification by the College of American Pathologists. For HbA1c measurement, we used ion exchange/high-performance liquid chromatography for AXSYM Abbott equipment (Abbott Architect/Aeroset). The fully automated method has an interassay coefficient of variation of 1.9% [20]. The assay is not affected by the presence of $<$10% of hemoglobin F or $<$4% of hemoglobin S trait. Samples were delivered to the laboratory when obtained. Assays were run daily (weekdays). Samples were measured on the same day they were obtained.

We performed resting electrocardiograms on each participant on every exam. Tracings corresponding to the baseline, 1994, and 1998 phases were sent for codification and interpretation at an independent reading center using the Minnesota Code [21]. Participants examined in the phases corresponding to 1994 and 1998 had vascular ultrasonography of their carotid system performed in a standardized manner. Measurements of the intimal media thickness and its interpretation were done in a central research unit [22]. We calculated the estimate of the Finnish Diabetic Risk Score using the data obtained at the baseline exam [23].

In 2016, we performed an extensive vital/diabetic status follow-up. We used all possible means to ascertain the status of each participant. Fieldwork was implemented to locate and interview each participant. We sent letters and telegrams and performed phone calls when the numbers were available. The nature of the study population allowed us to locate and interview a substantial number of participants. When this happened, the self-reported information was recorded. Due to lack of resources, we were unable to perform repeated measurement of either glucose or HbA1c.

Descriptive statistics included mean, standard deviation, median, and interquartile range. Variables were compared with parametric and nonparametric tests depending on their characteristics and distribution. We used the receiver operating characteristic curve to explore the performance of both tests in the diagnosis of T2D.

2. Results

In Table 2, we present selected characteristics of 854 participants who met the following criteria: all participated in the last follow-up (2008), had OGTT and HbA1c during that visit, and had their nondiabetic status ascertained during all previous phases of the MCDS. By these means, we excluded preexisting T2D. In the upper portion of the table, we show the results of the diagnostic classification based on OGTT (ADA criteria). We found that 81 (9.4%) participants had new-onset T2D, 261 (30.5%) had PD, and 512 (59.9%) had normal glucose tolerance (NGT). In addition to the expected differences in fasting, 2-hour glucose, and HbA1c, we found statistically significant differences among the three diagnostic groups in the following variables: weight, body mass index, waist circumference, systolic/diastolic blood pressure, and triglycerides. All of these were higher in the T2D group. In contrast, in the same study population, defining the diagnostic groups by HbA1c, we found that 451 (52.8%) participants had T2D, 281 (32.9%) had PD, and 122 (14.2%) had NGT. These results are shown in the middle portion of the table. As expected, fasting, 2-hour glucose, and HbA1c were significantly different between the three diagnostic categories. Interestingly, all the variables previously shown to be significantly different using OGTT lost their significance when the classification was done using HbA1c. Notably, the proportion of participants with T2D

Table 2. Selected Characteristics of the Study Population (n = 854) According to Glycemic Status Defined by OGTT, HbA1c, and Fasting Glucose (ADA Diagnostic Criteria)

Characteristic	T2D	PD	NGT	*P* Value
OGTT diagnostic criteria				
N (%)	81 (9.4)	261 (30.5)	512 (59.9)	
Men, n (%)	33 (40.7)	101 (38.6)	209 (40.8)	0.843
Age, y[a]	61.7 (7.6)	62.2 (7.7)	62.4 (7.7)	0.736
Weight, kg	72.5 (19.0)	70.5 (17.0)	68.5 (15.0)	**0.000**
BMI, kg/m^2	31.6 (6.8)	30.3 (4.9)	28.1 (5.3)	**0.000**
Waist, cm	105 (13)	101 (13)	97 (14)	**0.000**
Systolic BP, mm Hg	129 (23)	128 (21)	123 (21)	**0.000**
Diastolic BP, mm Hg	81 (9)	79 (11)	78 (11)	**0.000**
Fasting glucose, mg/dL	118 (44)	101 (14)	87 (10)	**0.000**
2-hour/glucose, mg/dL	233 (83)	153 (30)	105 (31)	**0.000**
HbA1c, %	7.3 (2.2)	6.8 (1.1)	6.4 (1.1)	**0.000**
Total cholesterol, mg/dL	196 (46)	194 (43)	193 (46)	0.544
Triglycerides, mg/dL	167 (94)	164 (79)	143 (83)	**0.000**
Smokers, n (%) yes	15 (18)	41 (15)	103 (20)	0.329
HbA1c diagnostic criteria				
N (%)	451 (52.8)	281 (32.9)	122 (14.2)	
Men, n (%)	172 (38.1)	121 (43.0)	50 (40.9)	0.409
Age, y[a]	62.5 (7.7)	62.5 (7.7)	61.0 (7.3)	0.134
Weight, kg	70 (16.4)	69 (16.8)	68 (13.0)	0.569
BMI, kg/m^2	29.2 (5.7)	29.0 (5.6)	28.2 (5.2)	0.088
Waist, cm	99 (15)	99 (13)	96 (15)	0.103
Systolic BP, mm Hg	128 (22)	124 (18)	124 (21)	0.165
Diastolic BP, mm Hg	79 (11)	78 (10)	79 (11)	0.457
Fasting glucose, mg/dL	94 (17)	89 (11)	87 (11)	**0.000**
2-hour/glucose, mg/dL	131 (57)	114 (50)	111 (32)	**0.000**
HbA1c, %	7.1 (0.8)	6.2 (0.4)	5.2 (0.4)	**0.000**
Total cholesterol, mg/dL	197 (48)	191 (46)	193 (34)	0.321
Triglycerides, mg/dL	154 (83)	148 (87)	149 (82)	0.172
Smokers, n (%) yes	104 (23)	41 (14)	14 (11)	**0.001**
Fasting glucose diagnostic criteria				
N (%)	35 (4)	172 (20.1)	647 (75.7)	
Men, n (%)	17 (48.5)	70 (40.6)	256 (39.5)	0.563
Age, y[a]	60.1 (8)	61.5 (7)	62.6 (7.8)	0.056
Weight, kg	73.9 (13.1)	73.3 (13.5)	69.1 (12)	**0.000**
BMI, kg/m^2	30.8 (4.4)	30.7 (4.4)	29 (4.7)	**0.000**
Waist, cm	103 (10.2)	102.2 (10.9)	98.9 (12.4)	**0.001**
Systolic BP, mm Hg	135.8 (18.4)	131.4 (15)	127.4 (16.6)	**0.000**
Diastolic BP, mm Hg	82.1 (9.2)	80 (8.5)	78.4 (8.6)	**0.007**
Fasting glucose, mg/dL	178.8 (62)	107.1 (6)	87.3 (6.9)	**0.000**
2-hour/glucose, mg/dL	309.4 (126.2)	159.1 (44.5)	116.9 (33.7)	**0.000**
HbA1c, %	10.1 (3.2)	6.9 (0.8)	6.4 (0.9)	**0.000**
Total cholesterol, mg/dL	206.6 (45.2)	196.9 (37.8)	196.2 (36.1)	0.266
Triglycerides, mg/dL	259.8 (238.6)	184.7 (95.9)	161.9 (79)	**0.000**
Smokers, n (%) yes	10 (28.5)	32 (18.6)	117 (18)	0.299

The study population of the present investigation was selected from the MCDS using the following criteria: all participated in the 2008 evaluation, all had OGTT and HbA1c on that exam, and all had their nondiabetic glycemic status ascertained throughout all previous phases of the MCDS. Values of $P < 0.05$ are indicated in bold.
Abbreviations: BMI, body mass index; BP, blood pressure.
[a]Data are mean ± standard deviation or median ± interquartile range, depending on the distribution for all the rest of the variables. These data were obtained from the results of the 2008 exam.

(defined by HbA1c) who self-reported being smokers was significantly higher than that observed in the other two groups; this finding was not seen in the T2D group defined by OGTT. This result confirms a previously demonstrated finding [24].

We compared the results obtained when we used only fasting glucose as a diagnostic criterion. Results are shown in the lower portion of Table 2. As expected, the number of

participants with T2D diminished from 81 (9.4%) using OGTT to 35 (4%). The same effect was observed with the proportion of individuals with PD that diminished from 261 (30.5%) using OGTT to 172 (20.1%) using only fasting glucose as a diagnostic criterion. The variables that were found to be significantly different between the three diagnostic groups using OGTT were the same when only fasting glucose was used as a diagnostic criterion.

In Table 3, we present selected cardiometabolic variables corresponding to the same study population shown in Table 2. These are shown according to their glycemic status classification using only OGTT, HbA1c, and fasting glucose as diagnostic tests. These variables represent the longitudinal trajectory throughout the evaluations performed, to each participant, during previous visits at the MCDS (*i.e.,* prior to the exam performed on 2008). It can be noted that, using OGTT as a diagnostic criterion, the mean heart rate in all previous exams (electrocardiogram interpretation, Minnesota Code) was significantly higher in participants who eventually converted to T2D or PD. The prevalence of nonfatal possible or probable myocardial infarction was not significantly different between the groups, although suggestively higher in the T2D group. As expected, when the glycemic status classification was done using OGTT or fasting glucose, we found that the results of the exploration of the insulin sensitivity/resistance indices revealed a consistent pattern. Participants who eventually developed T2D had significantly different values compared with the individuals who remained NGT. In contrast, when the diagnostic tool was HbA1c, the results lost the coherent pattern seen with OGTT or fasting glucose for diagnostic classification. The results of the adapted instrument used to estimate the risk for T2D (Finnish Diabetic Risk Score), using the data obtained at the baseline exam, are shown next. As expected, we found that when OGTT was used as a diagnostic criterion, participants who eventually converted to T2D had higher scores compared with the ones who developed PD, and these, in turn, had higher values than the ones obtained in the participants who remained NGT. This consistent pattern lost its trend when the diagnostic classification was done using HbA1C or fasting glucose, although in the latter, values are significantly different among the three categories. When the diagnostic criterion was OGTT, the proportion of participants with hypertension was higher in the T2D and PD groups compared with NGT group; this finding was not reproduced using fasting glucose or HbA1c.

For the intimal media thickness of the internal carotid measurement, the comparisons of the values obtained using OGTT, fasting glucose, and HbA1c revealed no significant differences.

Because a group of participants had normal OGTT coexisting with elevated HbA1c, we performed a comparison of these individuals with the ones who had normal OGTT and normal HbA1c. To do this, we first identified 404 participants who met the following criteria: normal OGTT throughout the entire study and, during their evaluation at the 2008 phase, had both OGTT and HbA1c. Of these, 220 (54.4%) had normal OGTT and HbA1c $<6.5\%$, and 184 (45.5%) had normal OGTT and HbA1c $\geq 6.5\%$. The comparison of selected variables including educational attainment and socioeconomic status revealed no significant differences between the two groups.

Interestingly, when we removed the group of participants who had normal OGTT coexisting with elevated HbA1c ($n = 184$) and performed the comparisons shown in Tables 2 and 3, we found that some variables that had lost their significance, when classified by HbA1c, regained their significance (body mass index, waist circumference, systolic blood pressure, triglycerides, heart rate, and certain insulin sensitivity indices).

The findings obtained in the vital/diabetic status follow-up performed in 2016 of the participants who had normal OGTT coexisting with elevated HbA1c revealed that, of 184 individuals with these characteristics, 133 (72.2%) remained alive and self-reported being nondiabetic, 3 (1.6%) had prediabetes, 7 (3.8%) developed diabetes, and 13 (7%) had died without diabetes; we were not able to ascertain the diabetic status in 5 (2.7%) or the vital status in 23 (12.5%).

Using as cutoff point of 6.5% for HbA1c as a diagnostic criterion for T2D, we estimated the performance of the receiver operating characteristic curve. We used the population selected from the entire MCDS who participated in the 2008 exam with a clearly ascertained

Table 3. Selected Characteristics of the Study Population (n = 854) According to Glycemic Status Defined by OGTT, HbA1c, and Fasting Glucose (ADA Diagnostic Criteria)

Characteristic	T2D	PD	NGT	*P* Value
OGTT diagnostic criteria				
N(%)	81 (9.4)	261 (30.5)	512 (59.9)	
ECG heart rate, baseline[a]	68 (12.2)	65 (10.8)	63 (13.0)	**0.001**
ECG heart rate, W2[a]	66 (11.2)	64 (12.8)	63 (11.0)	**0.000**
ECG heart rate, W3[a]	64 (8)	63 (12)	60 (11)	**0.000**
Possible or probable MI, baseline,[a] n (%)	5/6.1	13/4.9	21/4.1	0.658
Possible or probable MI, W2,[a] n (%)	6/7.4	12/4.5	24/4.6	0.551
Possible or probable MI, W3,[a] n (%)	3/3.7	4/1.5	10/1.9	0.471
HOMA index baseline[a]	0.4 (0.5)	0.3 (0.5)	0.2 (4.3)	**0.000**
HOMA index W2[a]	2.1 (2.7)	1.9 (1.9)	1.4 (1.5)	**0.000**
HOMA index W3[a]	4.0 (3.0)	2.9 (2.1)	2.4 (1.7)	**0.000**
Matsuda index baseline[a]	8.6 (9.1)	9.8 (12.7)	14.4 (21.2)	**0.000**
Matsuda index W2[a]	3.8 (4.9)	4.6 (4.6)	6.5 (9.1)	**0.000**
Matsuda index W3[a]	2.4 (2.1)	3.2 (2.8)	4.8 (4.6)	**0.000**
Quickie index baseline[a]	0.4 (0.1)	0.5 (0.1)	0.5 (0.2)	**0.000**
Quickie index W2[a]	0.4 (0.1)	0.3 (0.1)	0.4 (0.1)	**0.000**
Quickie index W3[a]	0.3 (0.1)	0.3 (0.1)	0.4 (0.1)	**0.000**
FINDRISK score baseline[a]	8 (4)	7 (6)	6 (5)	**0.000**
Hypertension, n (%)	56 (69.1)	147 (56.3)	261 (50.9)	**0.007**
Internal carotid artery IMT, W2,[a] mm	0.7 (0.1)	0.7 (0.1)	0.7 (0.2)	0.966
Internal carotid artery IMT, W3,[a] mm	0.7 (0.2)	0.7 (0.20)	0.7 (0.2)	0.441
HbA1c diagnostic criteria				
N(%)	451 (52.8)	281 (32.9)	122 (14.2)	
ECG heart rate, baseline[a]	64 (12)	64 (14)	63 (10)	0.894
ECG heart rate, W2[a]	63 (11)	63 (11)	63 (11)	0.775
ECG heart rate, W3[a]	61 (11)	61 (13)	59 (11)	**0.044**
Possible or probable MI, baseline,[a] n (%)	22 (4.8)	11 (3.9)	6 (4.9)	0.815
Possible or probable MI, W2,[a] n (%)	28 (6.2)	8 (2.8)	6 (4.9)	0.123
Possible or probable MI, W3,[a] n (%)	11 (2.4)	5 (1.7)	1 (0.8)	0.499
HOMA index baseline[a]	0.3 (0.4)	0.2 (0.5)	0.2 (0.5)	0.960
HOMA index W2[a]	1.7 (1.8)	1.6 (2.7)	1.3 (1.4)	**0.039**
HOMA index W3[a]	2.7 (2.2)	2.5 (2.0)	2.2 (1.6)	**0.002**
Matsuda index baseline[a]	11.6 (16.1)	11.7 (20.1)	13.1 (16.4)	0.633
Matsuda index W2[a]	5.2 (6.6)	5.7 (7.5)	6.6 (8.5)	**0.012**
Matsuda index W3[a]	3.8 (4.1)	4.4 (4.6)	4.6 (3.7)	**0.047**
Quickie index baseline[a]	0.5 (0.1)	0.5 (0.2)	0.5 (0.1)	0.989
Quickie index W2[a]	0.3 (0.1)	0.4 (0.1)	0.4 (0.1)	**0.032**
Quickie index W3[a]	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	**0.002**
FINDRISK score baseline[a]	7 (5)	7 (5)	6 (4)	0.317
Hypertension, n (%)	250 (55.4)	147 (52.3)	67 (54.9)	0.705
Internal carotid artery IMT, W2,[a] mm	0.7 (0.2)	0.7 (0.2)	0.6 (0.1)	0.143
Internal carotid artery IMT, W3,[a] mm	0.6 (0.2)	0.7 (0.2)	0.6 (0.2)	0.241
Fasting glucose diagnostic criteria				
N(%)	35 (4)	172 (20.1)	647 (75.7)	
ECG heart rate, baseline[a]	65.3 (10.5)	65.6 (8.8)	64.3 (9.1)	0.225
ECG heart rate, W2[a]	64.5 (8.8)	65.2 (9.5)	63.6 (9.1)	0.119
ECG heart rate, W3[a]	63 (6.4)	63.5 (9.2)	61.2 (8.4)	**0.004**
Possible or probable MI, baseline,[a] n (%)	3 (8.5)	11 (6.3)	25 (3.8)	0.188
Possible or probable MI, W2,[a] n (%)	3 (8.5)	11 (6.3)	28 (4.3)	0.319
Possible or probable MI, W3,[a] n (%)	1 (2.8)	6 (3.4)	10 (1.5)	0.250
HOMA index baseline[a]	0.7 (0.9)	0.8 (2.2)	0.9 (4)	0.911
HOMA index W2[a]	3 (2.6)	2.5 (1.6)	1.9 (1.5)	**0.000**
HOMA index W3[a]	4.1 (2)	3.9 (2.6)	2.9 (1.9)	**0.000**
Matsuda index baseline[a]	10.7 (8.3)	15 (16.2)	24.3 (39.6)	**0.001**
Matsuda index W2[a]	9.1 (17.7)	5.7 (5.4)	9.5 (14.2)	**0.003**
Matsuda index W3[a]	3.1 (2.1)	3.7 (3.2)	5.8 (4.7)	**0.000**
Quickie index baseline[a]	0.4 (0.07)	0.4 (0.1)	0.5 (1)	0.357
Quickie index W2[a]	0.3 (0.05)	0.3 (0.03)	0.3 (0.2)	**1**

Table 3. Continued

Characteristic	T2D	PD	NGT	*P* Value
Quickie index W3[a]	0.3 (0.02)	0.3 (0.02)	0.3 (0.02)	**1**
FINDRISK score baseline[a]	7.2 (3)	7.6 (3.9)	6.7 (3.8)	**0.019**
Hypertension, n (%)	22 (62.8)	104 (60.4)	338 (52.2)	0.091
Internal carotid artery IMT, W2,[a] mm	0.6 (0.1)	0.67 (0.1)	0.7 (0.2)	**0.001**
Internal carotid artery IMT, W3,[a] mm	0.7 (0.4)	0.7 (0.3)	0.7 (0.3)	1

The study population of the present investigation was selected from the MCDS using the following criteria: all participated in the 2008 evaluation, all had OGTT and HbA1c on that exam, and all had their nondiabetic glycemic status ascertained throughout all previous phases of the MCDS. Values of $P < 0.05$ are indicated in bold.
Abbreviations: ECG, electrocardiogram; FINDRISK, Finnish Diabetic Risk Score; HOMA, Homeostasis Model Assessment; IMT, intimal media thickness; MI, myocardial infarction.
[a]These values are taken from the previous exams corresponding to the phases anteceding the last evaluation of 2008. Baseline, W2 = first follow-up (1994), and W3 = second follow-up (1998).

nondiabetic status in all previous exams (n = 854). We obtained an area under the curve of 0.6343 with a 95% confidence interval of 0.564 to 0.685. The corresponding sensitivity was 0.753, and the specificity was 0.495, with a positive likelihood ratio of 1.493 and a negative likelihood ratio of 0.498. The general performance was poor, although it is worth noticing that the sample includes only 81 cases of newly diagnosed T2D using OGTT-based ADA criteria. To explore the performance of this test in a more general manner, we considered the entire data obtained from all participants who attended the 2008 phase (n = 1155). We calculated an area under the curve of 0.6967, with a 95% confidence interval of 0.666 to 0.737. The corresponding sensitivity was 0.897 and the specificity was 0.495, with a positive likelihood ratio of 1.776 and a negative likelihood ratio of 0.208.

3. Discussion

In the Standards of Medical Care in Diabetes [6], published by the ADA in 2017, HbA1c is considered a useful tool to diagnose T2D. Among the recognized limitations, the ADA states that HbA1c has low sensitivity. Our research findings confirm this limitation. The poor specificity observed in our data is another serious obstacle. We identified up to 45.5% of individuals who had elevated HbA1c coexisting with normal OGTT. This misclassification would have very important clinical implications because participants would be frequently diagnosed in an erratic form, dramatically changing the epidemiologic profile in our population. As stated, the group of individuals with normal OGTT and normal HbA1c is not different from the group of participants with normal OGTT and high HbA1c except for this fact. Of interest is that, when we remove the "discordant group" and perform the comparisons shown in Tables 2 and 3, we restore significant differences congruent with the expected pattern. These limitations would not be handled appropriately by using a different diagnostic cutoff point, as has been suggested.

We recognize that these findings have been previously reported (25, 26), but to our knowledge, this is the first time this issue has been explored in a low-income, elderly, urban, and predominantly obese Mexican population. Perhaps the previously-mentioned characteristics might explain the magnitude of its frequency. It is also possible that we are experiencing a cohort effect. The MCDS has a long follow-up that has focused on a low-income, urban population who, as a result of the long follow-up, is now an elderly group. The MCDS has identified throughout all its phases a substantial number of participants with T2D, and these were excluded from the present analysis. In addition, throughout the MCDS, a proportion of individuals died, and consequently, they are not part of this report. As a result of this process, we might have a final population that is enriched with participants with normal OGTT and high HbA1c.

The lack of concordance between both diagnostic tools has been demonstrated in other populations. The various studies report different levels of sensitivity and specificity, but most tend to alert to the significant possible misclassifications [27]. We also recognize that the lack of repeated measurements of HbA1c, ambulatory glucose estimates, and complete blood count is a significant limitation. However, we performed a clinical evaluation for each participant on the days of their exams and excluded significant signs or symptoms relative to anemia, hemolysis, or bleeding. Given the low prevalence of possible hemoglobin alterations, it would be difficult to consider that these could explain a substantial proportion of the numerous participants with high glycation coexisting with NGT. We explored the performance of the method used in our clinical laboratory to measure HbA1c and concluded that there is no evidence of significant analytic instability throughout the time that it took to gather and measure the samples. Even if we increment the coefficient of variation up to 6%, we would still end up with a significant number of participants with elevated HbA1c and normal OGTT.

It is recognized that renal insufficiency can play a role in the level of HbA1c. The availability of a normal or near-normal serum creatinine in all participants allows us to estimate that chronic renal insufficiency is not a main contributor to these findings. Because we have previously demonstrated that this population has a high prevalence of microalbuminuria [28], renal function status is of particular interest to us. We confirm the role of obesity and age as contributors to higher HbA1c [29]. The results of our efforts to explore the longitudinal trajectory of each participant's history to exclude preexisting undiagnosed T2D suggest that the elevation of HbA1c is possibly not mediated by unrecognized hyperglycemia.

Because the identification of the level of cardiovascular risk is ultimately a determinant factor with the utmost clinical relevance, we explored this aspect using the database that contains the trajectories of all MCDS participants. When we used OGTT, the phenotype identified was congruent with the expected pattern: higher cardiovascular risk in the T2D group, intermediate in the PD group, and lower in the NGT group. This pattern was totally eclipsed when the diagnostic tool was HbA1c. The clinical implications of this aspect of the discordance are very significant. These findings are in agreement with a recently published investigation performed compiling 73 studies involving 294,998 individuals [30].

It is worth mentioning that the results of the HbA1c-based diagnostic classification identified a higher proportion of smokers in the T2D group, a finding that has been recognized and requires further investigation.

The pattern observed with the results of the insulin sensitivity/resistance indices suggests that the OGTT-diagnosed group does have a congruent profile with a higher likelihood of a future incidence of T2D. The lack of this congruency, observed in the HbA1c-diagnosed group, suggests a different phenotype. It is important to recognize that our results could be influenced by a cohort effect, and this might magnify the frequency. The results of the vital/diabetic status follow-up support the idea that high HbA1c is not mediated by elevated plasma glucose.

It is known that certain individuals are prone to higher glycosylation rates through somewhat incompletely understood mechanisms [31]. This phenomenon has been identified in the African American group. Our finding suggests that this characteristic occurs in the Mexican population as well and possibly at an even higher frequency than what has been estimated, based on the findings obtained in the African American population [32]. We recognize that our findings might not be representative of the entire Mexican population.

We must also consider the possible case in which both situations might occur: true T2D coexisting with a high tendency for excessive glycosylation. The implications of this circumstance are evident. We should keep in mind this scenario, particularly in a high-risk individual.

It is unfortunate that HbA1c is not the optimal tool to diagnose T2D or PD. In our population, the proportion of participants with elevated glycosylation pattern is high enough that we should warn clinicians and the health care system about the risks of a costly misclassification.

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