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Correlation among two methods for glycated hemoglobin determination in diabetic Mexican patients for glycemic control

Correlación entre dos métodos de determinación de hemoglobina glicosilada en pacientes diabéticos mexicanos para control glucémico

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Palabras clave:
Hemoglobina glicosilada, control glucémico, electroforesis capilar, cromatografía de intercambio iónico, diabetes mellitus.

ABSTRACT

Glycated hemoglobin (HbA_{1c}) is a molecule derived from the non-enzymatic union of glucose in the β chain of Hemoglobin (Hb) A of red blood cells proposed for the American Diabetes Association (ADA) as the best test to evaluate long term glycemic control. The precision in its determination is a very important issue. The objective of this study was to analyze correlation and to determine glycemic control classification concordance among two methods: Ion-Exchange High-performance Liquid Chromatography (IE-HPLC) and Capillary Electrophoresis (CE) using two commercial instruments. A total of 249 samples from diabetic patients (n) were tested for HbA_{1c} by both methods. Results were analyzed by correlation, Bland-Altman scatter plots and calculating CE's sensitivity (Sn), specificity (Sp), positive and negative predictive values (PPV and NPV) to identify glycemic control (HPLC $HbA_{1c} < 7\%$). The correlation was statistically significant ($r = 0.9906$, $p < 0.0001$), Kappa correlation 0.959 ($p < 0.05$); Bland-Altman plot analysis showed high level of agreement. CE Sn, SP, PPV and NPV were respectively: 98%, 98, 99% and 97%. Considerable differences in glycemic control classification were not observed. CE in Capillarys 2FP seems to be a good alternative method for HbA_{1c} measuring for glycemic control.

RESUMEN

La hemoglobina glicosilada (HbA_{1c}) es una molécula derivada de la unión no enzimática de glucosa en la cadena β de hemoglobina (Hb) A propuesta por la Sociedad Americana de Diabetes (ADA por sus siglas en inglés) como la mejor prueba para evaluar control glucémico a largo plazo. La precisión en su determinación es de gran importancia. El objetivo del presente estudio fue analizar correlación analítica y determinar concordancia en la clasificación de control glucémico de dos métodos: cromatografía líquida de alta resolución de intercambio iónico (HPLC) y electroforesis capilar (EC). Se determinó HbA_{1c} de un total de 249 muestras (n) de pacientes diabéticos por ambos métodos. Se analizó correlación, gráficos de Bland-Altman y la sensibilidad (Sn) especificidad (Sp) y valores predictivos positivos y negativos (VPP y VPN) de EC para identificar pacientes controlados (HPLC $HbA_{1c} < 7\%$). El análisis de correlación fue estadísticamente significativo ($r = 0.9906$, $p < 0.0001$), Kappa de 0.959 ($p < 0.05$), el gráfico Bland-Altman muestra buena concordancia. Sn, Sp, VPP y VPN fueron, respectivamente, 98%, 98%, 99% y 97%. No se apreciaron diferencias considerables en la clasificación de control glucémico. Por lo cual, EC en Capillarys 2FP parece un buen método alternativo para determinación de HbA_{1c} para control glucémico.

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INTRODUCTION

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Diabetes mellitus (DM) is a chronic disease characterized by carbohydrates, protein and lipids metabolism alteration. Four different diabetes categories are currently recognized by ADA: type 1 DM, type 2 DM, gestational diabetes and specific types of diabetes according to its general classification.[1] Type 2 or non-insulindependent DM (T2DM), is characterized by insulin resistance and generally associated to abnormal secretion of this hormone.[2] Insulin resistance, is on the one hand, a result of prolongate exposure of cells to this molecule; resulting in decrease of intracellular signaling activation, and therefore, low physiological function.[3,4]

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Nowadays, treatment of type 2 diabetic population include a non pharmacological approach, that involve changes in lifestyle as diet, physical activity and smoke cessation, along with pharmacologic support, that include oral hypoglycemic agents as biguanides, sulphonylureas, thiazolidinediones, alpha-glucosidase inhibitors, nonsulfonylurea insulin secretagogues, dipeptidyl peptidase-IV inhibitors, sodium glucose-linked transporter-2 inhibitors, Glucagon-like peptide-1 agonists and finally, when therapeutic goal can't be reached and in special cases, insulin.[5,6]

In Mexico, T2DM has a very high prevalence according with the last national health & nutrition survey (9.2% in adults older than 20 years, and special affection in 60-69 years old population with 26.3%)[7] and is the main cause of disabling complications during productive life,[8] as blindness, lower limbs amputation, chronic kidney disease, renal insufficiency, vascular and cerebrovascular diseases. At the present, early disease detection and glycemic control, are the two proposed strategies for micro and macrovascular complication diminishing. Both of them, have proved effectiveness in many studies, mainly in delaying microvascular disease.[9]

The most important marker for early detection and glycemic control evaluation is glycated hemoglobin (HbA_{1c}), a non-enzymatic glycation product of hemoglobin A (Hb) β chain molecule.[10,11] After first HbA_{1c} publications at later 70's, and due to the evidence about its utility in clinical field, it was included as most important test for glycemic control goals. Optimal value has varied little since then, being 7.0% (53 mmol/mol IFCC) the most accepted goal for suitable control. This HbA_{1c} value with regard of glycemic control, should be adequated to patients conditions as age, complications, hypoglycemia risk and time of evolution, oscillating around 7.5% (58 mmol/mol) as monitoring marker in diabetes.[5]

Owing to HbA_{1c} testing is indispensable for diabetes management, many assays where designed for its determination, which drove to an inaccuracy increasing. Because of this, in 1996 *National Glycohemoglobin Standardization Program* (NGSP) was founded as a regulator and standardization organism for HbA_{1c} assays and for their harmonization. In 2002, IFCC reference method for HbA_{1c} determination was released, based in High Performance Liquid Chromatography/Mass Spectrometry (HPLC/MS) or HPLC/Capillar Electrophoresis (HPLC/CE) approaches which were basis for routine assays performance standardization around world and their traceability.[12]

In these days, great variety of commercial approved by United States Food and Drugs Administration (FDA) instruments, exists in market as well as diverse of methodologies for HbA_{1c} determination.[13] Recently, CE for HbA_{1c} measuring has been introduced in world market, demonstrating reliability when compared with HPLC methods.[12,14] Both of them have an additional advantage for determining Hb most common varieties with non or scarce interference, even though, some IE-HPLC have demonstrate interference with some of them.[13]

The objective of the present research was to analyze correlation among CE using Capillarys 2 Flex Piercing Sebia (Capillarys 2FP) and IE-HPLC in Bio-Rad D-10 Hemoglobin Testing System (D-10 System) instruments for HbA_{1c} measuring in Mexican diabetics patients, for concordance determination in glycemic control among CE and IE-HPLC as reference method, making use of ADA current classification[1,5] looking for important differences.

To the knowledge of the authors, EC against IE-HPLC performance in these instruments has not been evaluated in diabetic Mexican population for glycemic control until this day.

MATERIALS AND METHODS

A total of 249 peripheral blood samples (n) drawn by venipuncture in EDTA K2 tubes for routine HbA_{1c} analysis were done, obtained from Mexican diabetes outpatients who attainted to control laboratory tests to Laboratorios Ruiz, Puebla, Mexico during January and February 2016. Such patients were subsequent and previously diagnosed with T2DM, reason for why were selected in order to study concordance among these two methods in glycemic control. Specimens analyzed in

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this work were used according to internal protocols for research and under supervision of institutional authorities for ethical and compliance of Helsinki Declaration of 1975.

Study population was composed by 97 male (39%) and 152 female subjects (61%) with a median age of 58 years old and mean of 54 (± 15). Not all patients had fasting serum glucose in the same day that control studies were analyzed.

HbA_{1c} determination was done for all blood samples in primary tube in the same day of extraction, by IE-HPLC method in D-10 System and then, almost simultaneously, by CE in Capillarys 2FP.

D-10 System precision was determined by using first opinion control material Lyphochek Diabetes Control® in two levels with Lot Number 33910; a 3.1% and 3.0% of coefficient of variation (CV) for level 1 and 2 (respectively), were obtained. Accuracy was evaluated by participation in Bio-Rad External Quality Assurance (EQAS) program®, registering satisfactory Z-Score of -1.8 and -0.73 for January and February, respectively. On the other hand, Capillarys 2FP instrument was subjected to an analytical protocol for imprecision, performing 2.55% and 1.79% CV in levels 1 and 2 (respectively) with target value of 3%. Then, another exercise was carried out for accuracy, obtaining a relative bias of 2.5 in level 1 and 1.74 in level 2 with target value of $\leq$ 3.5%.

The results here obtained from both instruments were analyzed with Pearson correlation (R) and Bland-Altman graphic, done by statistics software MedCalc 12.5.0.0 (Ostend, Belgium). Additionally, Cohen's Kappa index was calculated by using SPSS 8.0 (Chicago, EUA) and a contingency table was done with Catmaker 1.1 (Oxford, England) for Sensibility (Sn) Specificity, Positive (PPV) and Negative (NPV) Predictive Values for CE in glycemic control identification for diabetic patients (defined as HbA_{1c} < 7.0% o 53 mmol/mol), according to American Diabetes Association (ADA)[5] for comparation to reference method (HPLC de IC D-10 System).

RESULTS

An R coefficient of 0.9906 ($p < 0.0001$) was obtained; it demonstrates a good correlation among two measuring series *(figure 1)*. Bland-Altman graphic demonstrate that most of determinations were between agreement limits (-0.6733 a 0.4219), with narrow two standards deviation (SD) of ~ 1.1% (~ 12.0 mmol/mol) HbA_{1c}, with mean differences (MD) among two methods of -0.13 (IC -0.1606 a -0.0908) and with aleatory scatter *(figure 2)*.

Differences in glycemic control classification for IE-HPLC method in D-10 System and Capillarys 2FP is shown in *table I*. There can be observed a small difference of 1 from 249 patients, misclassified as uncontrolled by the last device.

When evaluating concordance for clinical stages in glycemic control, Sn y Sp of 98% (IC 95%; 96-100%), PPV of 99% and NPV of 97% (IC 95%; 97-100% for CE method by Capillarys 2FP instrument were obtained when comparing with reference method *(table II)*. Furthermore, Cohen's Kappa index of 0.959 ($p < 0.05$) was shown. Hemoglobin variants were not detected among studied patients by none of these methods.

DISCUSSION

The confidence in method for HbA_{1c} determination is currently a basis in surveillance of diabetic patients and

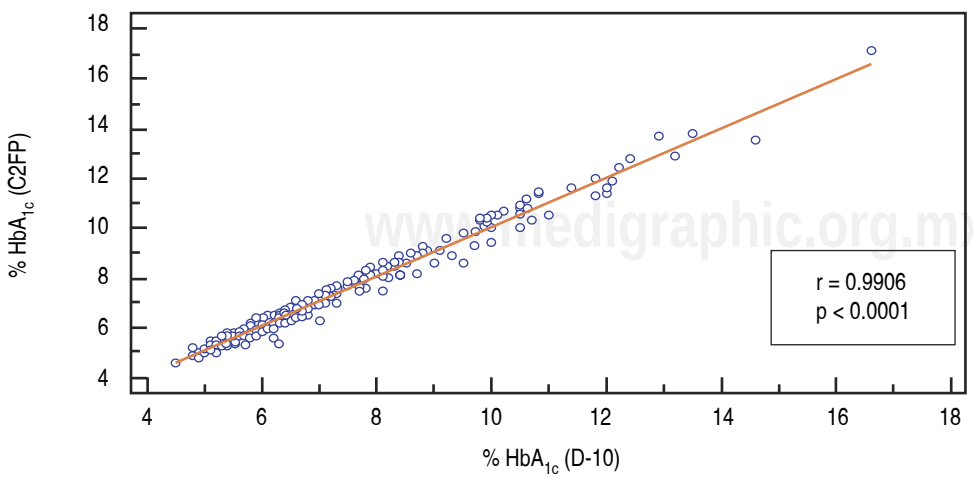

Figure 1.

Scatter diagram correlation among methods (CE and IE-HPLC) with Capillarys 2FP (C2FP) and D-10 System (D-10), respectively.

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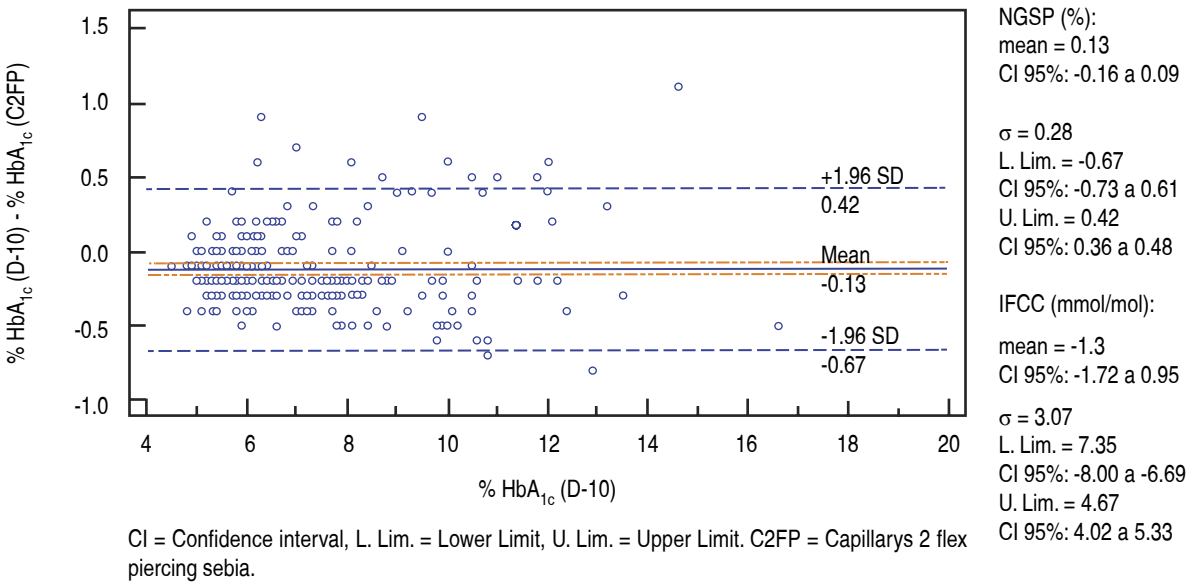

CI = Confidence interval, L. Lim. = Lower Limit, U. Lim. = Upper Limit. C2FP = Capillarys 2 flex piercing sebia.

Figure 2. Bland-Altman Scatter diagram for CE and IE-HPLC comparison in capillarys 2FP (C2FP) and D-10 System (D-10), respectively.

Table I. Differences in glycemic control classification in diabetic patients according to ADA criteria.

	HbA_{1c}				Difference	
% (mmol/mol)	HPLC (n)	%	CE (n)	%	Patients	%
< 7.0 (< 53)	143	57.4	142	57.0	1	0.4
≥ 7.0 (≥ 53)	106	43.0	107	43.0	-1	-0.4
Total (n)	249	100.0	249	100.0		

χ^2 = 0.0; p = 1.0000.

decision making for therapeutics. Almost all medical associations, mainly ADA and American Association of Clinical Endocrinologists, and their different algorithms, define HbA_{1c} < 7% (< 53 mmol/mol) as suitable glycemic control; even though, this goal should be adapted for each patient according to its clinical conditions. Starting from accomplishment of such therapeutic goal, is from decisions are taken and a prognostic is established.

Diversity of developed methods for HbA_{1c} measuring since DCCT study publishing, had as main consequence a poor correlation among them and reference method, which forced to establish a standardization in HbA_{1c} determination. In this context, studies as the here present, aid in decision making in HbA_{1c} new methods choosing.

The excellent correlation described in this work, among two methods agree with those reported in literature.[15]

Some discrepancies were observed, exhibiting positive values that surpass the superior limit of agreement, which can be appreciated in Bland-Altman graphic *(figure 2)*. This suggests that in evaluated instruments, CE appear to underestimate occasionally HbA_{1c} values when comparing with IE-HPLC for unknown reasons. Moreover, mean difference among D-10 System and Capillarys 2FP (-0.13%), show a hardly positive bias, which can be corroborated in clinical classification *(table I)*. Other works comparing CE with IE- HPLC in Tosoh G7 system, rather suggest a negative bias.[16] Nonetheless, this can be a finding related with instrument and no to method.

Table II. Nosographic evaluation among methods.

		HbA_{1c} HPLC (D-10)	
	n = 249	< 7.0 (53 mmol/mol)	≥ 7.0 (53 mmol/mol)
HbA_{1c} CE (Capillarys)	< 7.0 (53 mmol/mol)	140	2
	≥ 7.0 (53 mmol/mol)	3	104

*NGSP (IFCC): % (mmol/mol).

Table III. Potential interferences for the evaluated instruments.

Interference	D-10 System	C2FP
Frequent Hb variants (HbS, HbC, HbD, HbE)	No[22]	No[19,22,30,31]
HbF	No (≤ 10%)[22]	No ≤ 15%[22,30,32]
β-thalassemia	No[23]	No[32]
Hb concentration	—	No (2.1-19.5 g/dL)[30,32]
Bilirubin	No (≤ 60 mg/dL)[33,34]	No (≤ 60 mg/dL)[17,30,32,35]
Triglycerides	No (≤ 6,000 mg/dL)[33,34]	No (≤ 2,890 mg/dL)[17,30,32,35]
Cholesterol	—	No (≤ 397.9 mg/dL)[17]
Glucose	No (≤ 2,000 mg/dL)[33]	No (≤ 5,000 mg/dL)[17]
Vitamin C	No (≤ 300 mg/mL)[33]	No (≤ 300 mg/mL)[17,35]
Total protein	No (≤ 21 g/dL)[33]	No (≤14.9 g/dL)[35]
Rheumatoid factor	No (≤750 IU/mL)[33]	No (≤ 1,076 IU/0mL)[35]
Acetylsalicylic acid	No (≤ 1,000 mg/dL)[33]	No (≤ 1,000 mg/dL)[35]

Otherwise, difference among two methods in glycemic control classification was in 1 of 249 patients, which is certainly, a minimal difference. Such disagreement looks like an acceptable thing when comparing the advantages that CE offers. When look at Sn, Sp, PPV y NPV for glycemic control by using CE, it can be observed that this new method has an excellent agreement when comparing with reference method. Is remarkable, due to the high NPV obtained, a scarce probability of a misdiagnose glycemic dyscontrol by this methodology in Capillarys 2FP (3%). To the knowledge of the authors, this comparison has not been made in the past.

Based on results, CE method by Capillarys 2FP looks like it accomplishes with similar analytic and clinical characteristics in glycemic control when comparing with IE-HPLC in D-10 System in Mexican diabetic patients. The differences here found, looks like minimal at analytic level and agrees with results from other works related to other instruments correlation with the same methods, in which Capillarys 2FP is used, and concludes that this latter, CE by this device is a suitable one for de HbA_{1c} quantification.[15-17]

It has been documented before, that CE by using Capillarys 2FP is, besides being suitable for HbA_{1c}, so it is for other analytes such as serum protein electrophoresis and Hb variants. Further, HbA_{1c} determination by this instrument is not interfered by most of common Hb variants[15,18] or total Hb concentration.[19] Whereas instruments based in IE-HPLC for HbA_{1c} determination have demonstrated being interfered by some of these, overestimating or underestimating real concentration.[13,16,18]

At least, 14 Hb variants have been described in Mexico,[20] the most frequent is HbS as a result of African-

Mexican miscegenation. The frequency of this latter is widely variant in order of the geographical zone; mainly in some communities in east (4.11%)[21] and west coasts of Mexico, where it is estimated that there are places where prevalence is as high as in some African regions.[21] Given this, it is imperious having a methodology for HbA_{1c} determination not being interfered by Hb variants. In our institution, some of these variants have been detected in routine HbA_{1c} measuring (data not shown).

As far as is known, evaluated instruments in this work, are not interfered by most common Hb variants (HbS, HbC, HbD, HbE). The only difference is in HbF case; where Capillarys 2FP is able to measure HbA_{1c} confidently as high values as 15%; unlike its homologue, that show impairment after 10% of HbF.[22] HbA_{1c} determination in these devices, has not been interfered neither by β-thalassemia.[19,23] Other researches have proved these instruments against less frequent Hb variants, concluding that D-10 System do not show interference by many of them.[24] Albeit, contrary evidence about interference exists for some of such rare variants in this instrument,[25-28] reason for why still being an active field of study. *Table III* show characteristics for both of these analyzers against some common interferences in HbA_{1c} determining.

On the other hand, CE by Capillarys 2FP allows a trustworthy determination of samples stored in refrigeration (4 ºC) up to 7 days after collected.[29] Whereas that experimentally, samples stability has been observed is not threatened up to 4 days at room temperature (25 ºC), which is a reasonable time lapse for samples shipment.[17]

Moreover, for best determining of convenience for the use of one or the other; it is appropriate to additionally make a cost-benefit evaluation, as no research of this type is available in literature, as far as authors know, and such goals are out from those set for the present work.

According to the results here obtained, it looks suitable using one method or the other with the evaluated instruments. No considerable differences among them were observed in glycemic control. For that reason, CE by Capillarys 2FP seems to be a very good alternative for HbA_{1c} determination for Mexican diabetes patients by virtue of its comparable Sn and Sp when compared with reference method, and due to its scarce probability of glycemic decontrol underestimation; in addition, to its technical advantages previously discussed.

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