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Capillarys 3 Octa®: Analytical Performance Assessment for HbA1c Quantification

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Abstract

Objective: Determination of HbA1c level is a precious indicator for therapeutic follow-up of patients with type 1 or type 2 diabetes. Our study aimed to evaluate the analytical characteristics of Capillarys 3 Octa® HbA1c measurement by capillary electrophoresis.

Materials and Methods: Our study involved 265 venous whole blood specimens repeatability, intermediate fidelity, accuracy, linearity, and correlation with the Arkray HA-8180 analyzer which uses HPLC as a dosing method. We studied interferences such as hematocrit, triglycerides, total bilirubin, labile fraction, and hemoglobin abnormalities.

Results: The linearity correlation was between 4.4% and 20.3%. There was a strong correlation with HPLC ($r > 0.99$, $P < 0.0001$). No interference from hematocrit (20-93%) (P: 0.888), triglycerides (until 25 mmol/L) (P: 0.388), total bilirubin (< 587 µmol/L) (P: 0.993), and labile fraction was observed. No problem related to inter-sample contamination was observed. The sensitivity was zero for homozygous sickle cell disease and S/C composite hemoglobinosis. However, sensitivity was high for heterozygous forms (69% for A/S and 60% for A/C). The analyzer was able to separate and quantify HbA2 fraction, allowing ß-thalassemia accidental detection.

Conclusion: Capillarys 3 Octa® based on capillary electrophoresis proved to be precise and a linear instrument for HbA1c measurement. Several clinical interferences and Hb variants had no effect on the results. The results of this evaluation suggest that this analyzer is suitable for routine use in clinical chemistry laboratories.

Keywords: HbA1c, Capillarys 3 Octa®, Capillary electrophoresis, Analytical performance, Hemoglobinopathies

QR Code:

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Introduction

The determination of HbA1c level is a precious indicator for the diagnosis and the follow-up of patients with type 1 or type 2 diabetes. Professional recommendations make it an essential parameter concerning therapeutic appropriation and make it possible to guide therapeutic decisions (1). With the increased prevalence of diabetes all over the world (2), accentuated by a recent report from the International Diabetes Federation in 2022 which indicates a diabetes prevalence equal to 10,5% (3), the interest is more and more urgent and crucial to ensure a suitable strategy to control diabetes and reliable glycemic control. HbA1c is the product of the non-enzymatic reaction of Hb glycation, characterized by the formation of an aldimine bond, following the fixation of glucose on the N-terminal valine of the beta chain (4-5).

The concentration of HbA1c reflects the average concentration of glucose during the last two to three months, unlike glycemia, which represents the current concentration of glucose. On the other hand, HbA1c measurement does not require any particular preparation concerning the patient such as fasting and it is the preferred biomarker to evaluate glycemic balance and an element for measuring the risk of developing diabetic complications (microvascular and increased risk of cardiovascular disease) (6,7).

Several methods for the determination of HbA1c have been commercialized. Capillary electrophoresis is a new technique for HbA1c determination. The aim of this study is to evaluate the analytical characteristics of Capillarys 3 Octa® HbA1c measurement by capillary electrophoresis.

Materials and Methods

Specifications of Capillarys 3 Octa® analyzer

Capillarys 3 Octa® (Sebia©, France) and C2FP (Capillarys 2 flex piercing) are two fully automated protein capillary electrophoresis (hemoglobin electrophoresis, HbA1c), equipped with eight capillaries capable of several concurrent electrophoretic separations without handling and with a high cadence of 43 tests/h for HbA1c for Octa® analyzer. Capillarys 3 Octa® allows to perform automatically all the electrophoresis sequences from the sample tube to obtaining the electrophoretic profile: identification of samples by a bar code system, dilution of the samples from the sampling tubes in single-use cups, washing of the capillaries, injection of the samples into the capillaries, migration, detection, treatment of the results and computer transmission of the results obtained, the automaton is connected to the PHORESIS software allowing the display of the results of the analyzes in progress and the treatment of the results. The analyzer uses capillary electrophoresis which consists in the separation of the different fractions of hemoglobin as a function of their electrophoretic mobility in a micro channel under high electrical field. Fraction identification is automatically performed, and electrophoretic profiles are visually analyzed for anomalies. The software allows the calculation of HbA1c according to the formula recommended by IFCC HbA1c = HbA1c / (HbA1c + HbA0) and the results are expressed with both units (IFCC and NGSP).

Specification of the comparative method (ADAMS™ A1c HA-8180V (Arkray, Kyoto, Japan))

ADAMS™ A1c HA-8180V (Arkray, Kyoto, Japan) uses HPLC for HbA1c determination with the principle of ion exchange chromatography to separate the Hb fractions into six fractions. The blood is hemolyzed by a lysis solution and then injected through a column consisting of a non-porous cation exchange resin. Three buffers are utilized to separate different fractions of hemoglobin. The machine can operate in two modes: a Variant mode (assay of HbA1c, HbF, and detection of the main variants of Hb (HbS,

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HbC, HbD and HbE) need 3.5 minutes/test and a fast mode (assay of HbA1c and HbF only) which needs 48 s/test.

Blood samples and controls

The study was carried on 265 whole venous blood samples collected in lithium heparin or K_3-EDTA tubes, addressed to the laboratory of Biochemistry and Toxicology from the university hospital of Monastir, Tunisia, for HbA1c quantification chosen from the working series. Two bi-leveled «Sebia©» HbA1c control samples (lot: 02038): a normal control (NC) of 5.0% (31 mmol/mol) and a pathologic control (PC) of 8.0% (64 mmol/mol) were used in this study.
For the study of the accuracy, the results of an external control sample were necessary.

Precision study

Four samples with initial HbA1c values between 4.4% (25 mmol/mol) and 8.0% (64 mmol/mol) for the precision study were used (4.4, 5.0, 6.5 and 8.1%).

Study of the repeatability

Four previously selected samples and two controls (NC and PC) were assayed five times per day, under the same conditions and on the same automaton.

Study of intermediate fidelity

These same samples were dosed two times/day while the controls were dosed 8 times/day for five days. The means, standard deviations (SD), and coefficients of variation (CVs) of the measurements for each sample were calculated.

Study of accuracy

The external control sample was assayed under the same conditions as the previously mentioned samples. The result obtained was compared to the average of the peers and total bias was calculated according to the following formula (8):

$$\text{Total bias} = \left[\frac{|\text{value found} - \text{initial value}|}{\text{initial value}}\right] * 100$$

Linearity study

Linearity was evaluated by simple quantification of HbA1c concentrations obtained by mixing variable proportions of two samples: one with a high HbA1c (20.0% or 195 mmol/mol) and the other with a low HbA1c (5% or 31 mmol/mol). Linear regression analysis was established between observed and calculated values to examine linearity.

Interference study

We studied 5 types of interference on Capillarys 3 Octa®: percentage of hematocrit (from 20% to 91%), triglycerides (from 1.61mmol/L to 25.5mmol/L), total bilirubin (from 4.6 µmol/L to 587.0 µmol/L), the labile fraction (LA1C) and, Hb variants.

Hematocrit Interference study

1st step: For each of the three blood samples (S1, S2, and S3), we proceeded as follows:

- HbA1c determination in each of the samples. Hematocrit determination.
- Centrifugation of the tubes.
- Subtraction of 0.5 mL of plasma.
- HbA1c dosage.
- Hematocrit determination.

These steps were repeated twice with subtraction of 1mL of plasma in total.

2nd step: The volumes of plasma subtracted were added to the red blood cell pellet.

Steps 1, 2, 3, 5 and 6 were repeated with the replacement of step 4 by the addition of 0.5 mL of physiological water.

Triglycerides Interference study

1st step: For each of the three blood samples (S1, S2, and S3), we proceeded as follows:

1. HbA1c determination in each of the samples.
2. Triglycerides determination.
3. Tube centrifugation.
4. Subtraction of 50 µL of plasma.
5. Addition of 50µL of Perikabiven®.
6. HbA1c dosage.
7. Triglycerides dosage.

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These steps were repeated four times with subtraction of 200µL of plasma and addition of 200µL of Perikabiven® in total.

Total bilirubin Interference study

For the study of the interference of total bilirubin, we proceeded by repeating the exact same steps when studying the interference of triglycerides, but with replacement of the Perikabiven® solution by a bilirubin solution to perform the overload.

Labile fraction Interference study

To evaluate the potential effect of LA1C, the samples were incubated with different concentration glucose solutions for 3 hours at 37°C to promote formation of the labile fraction in vitro. HbA1c was assayed before and after different time intervals of experiments.

Variants influence study

Whole blood samples of 107 with a quantitative or qualitative abnormality of Hb in the heterozygous and homogenous state: A/S (n= 26), S/S(n= 2), A/C(n= 15), S/C (n= 1), ß+ (n= 53), ß0 (n= 1), A/F (n= 9); (A: hemoglobin A; S: hemoglobin S; C: hemoglobin C; F: hemoglobin F; ß+: minor thalassemia; ß0: major thalassemia) were used for the study.

These samples were analyzed on Capillarys 3 Octa® to check for possible interference on the measurement of HbA1c. Variants or abnormalities of Hb were confirmed on C2FP, by the mode "Hemoglobin".

Sample to sample carry over study

To examine the potential sample contamination of low concentration by a sample of high concentration, we selected two samples without hemogobin abnormalities: Sample A with low HbA1c (5,0% or 31mmol/mol) and sample B with high HbA1c (20,0% or 195mmol/mol). Samples A and B were analyzed by the same capillary by placing them on different racks. As for cross-sample contamination study with an Hb variant 4 samples were selected according to the following criteria: without any abnormality of hemoglobin (N), with HbS variant (S), with HbC variant (C) and with high HbF value (F). The samples N, S, C and F were analyzed by the same capillary by placing them on different racks according to the following sequences: S-N, S-C, S-F, F-C.

We also calculated the Central Limit Theorem (CLT).This theorem states that the means of large numbers of samples follow a normal distribution and it was used in our study to express the maximum tolerable error bias according to the following formula (9):

$CLT = 2.77 * \sqrt{CVa^2 + CVb^2}$

With CVa: CV repeatability

CVb: CV within individual variability

Statistical analysis

For the repeatability study, the mean, SD, and CV of the measurements for each sample were calculated. For the normality study, we used the Kolmogorov–Smirnov test. Quantitative variables were expressed in mean (± SD). For the correlation study, Pearson's chi-squared test was used. Sensitivity is the probability that the Hb variant is identified by Capillarys 3 Octa® in samples containing this variant identified by Capillarys 2® and for thalassemia syndromes, the sensitivity is the probability that a quantitative variation of one or more peaks is present on the electropherogram in samples with β-thalassemia (10). Specificity is the probability that the Hb variant is not identified by Capillarys 3 Octa® in samples not containing this variant identified by Capillarys 2® (10).The software used for this work were: SPSS 22.0.0.0, Medicalc 19.0.7, Analysis it 5.40.0 and Excel 2019.

Ethical considerations

The validation of methods in clinical biology is required by Tunisian regulations and by international standards. It is a daily activity in a medical biology laboratory.

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Results

Precision study

All the precision parameters (repeatability, intermediate fidelity) were assessed in this study. CVs for repeatability and intermediate fidelity calculated for all assessed pools vary between 1.0% and 3.2%. All these CVs were inferior to the CVs fixed by FSBC (French Society of Clinical Biology) (Table 1).

Linearity correlation study

Our study shows recovery rates from 97% to 105%, revealing the absence of systematic bias regardless of HbA1c concentrations. The linear regression analysis of measured values and pre-assigned concentrations showed a highly significant correlation (r= 0.998; *P*< 0.0001). The equation of regression was: HbA1c (%)= 1.02* pre-assigned concentration (%) - 0.03, using the NGSP system (Figure 1).

We examined the correlation between Capilarys 3 Octa® and ADAMS™ A1c HA-8180V using samples with and without hemoglobin abnormalities. For normal samples without hemoglobin abnormalities, values distribution was nearly identical for the 2 techniques. For 77 patients, Capilarys 3 Octa®'s mean was 8.4%± 2.7 whereas ADAMS™ A1c HA-8180V's mean was equal to 8.7%± 2.7. Using the Passing-Bablok diagram, mean difference was equal to -0.25 with a CI of 95% (-0.29 to -0.209) (t= 0.689

Table 1. Precision study results

Variable	HbA1c (%)	SD Repeatability (%)	CV Repeatability (%)	FSCB CV (%)	SD Intermediate fidelity (%)	CV Intermediate fidelity (%)	FSCB CV (%) / CLT (%)	Total bias
S1	4.4	0.10	2.2	3.8	0.10	3.1	4.0/6,08	1.1
S2	5.0	0.16	2.2		0.16	3.2		0.8
S3	6.5	0.08	1.3		0.16	2.7		0.9
S4	8.1	0.16	2.0		0.16	2.8		0.1
NC	5.0	0.08	1.6		0.08	2.2		2.2
PC	8	0.08	1.0		0.08	1.4		1.3

NC: normal control; PC: pathological control; S: specimen; CV: coefficient of variation;
CLT: central limit theorem; FSCB: French Society of Clinical Biology; SD: standard deviation

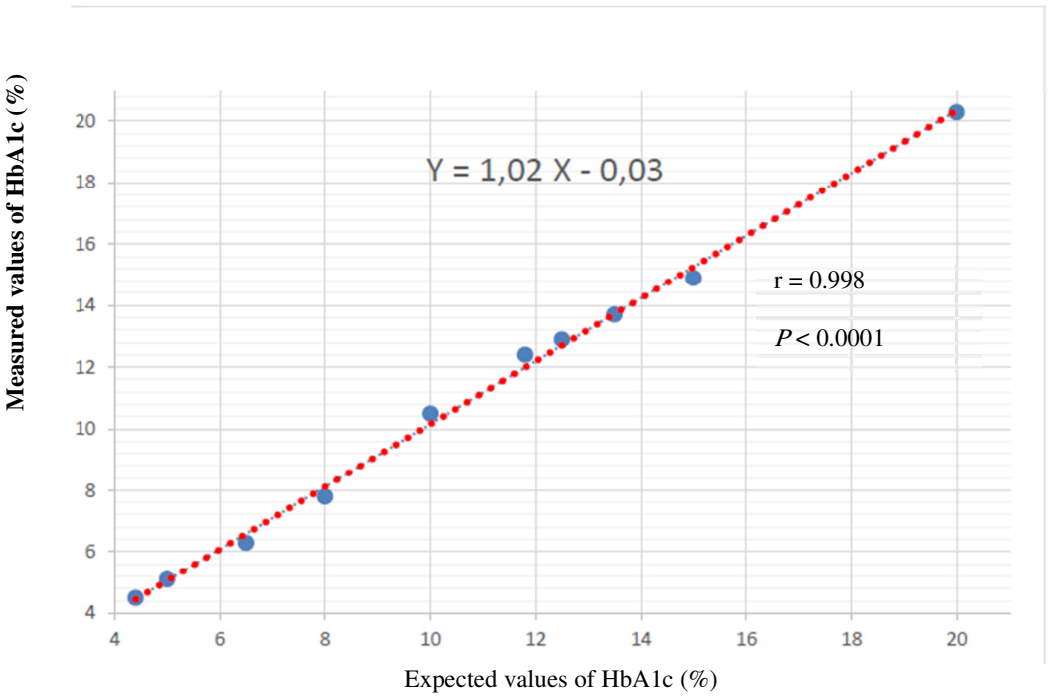


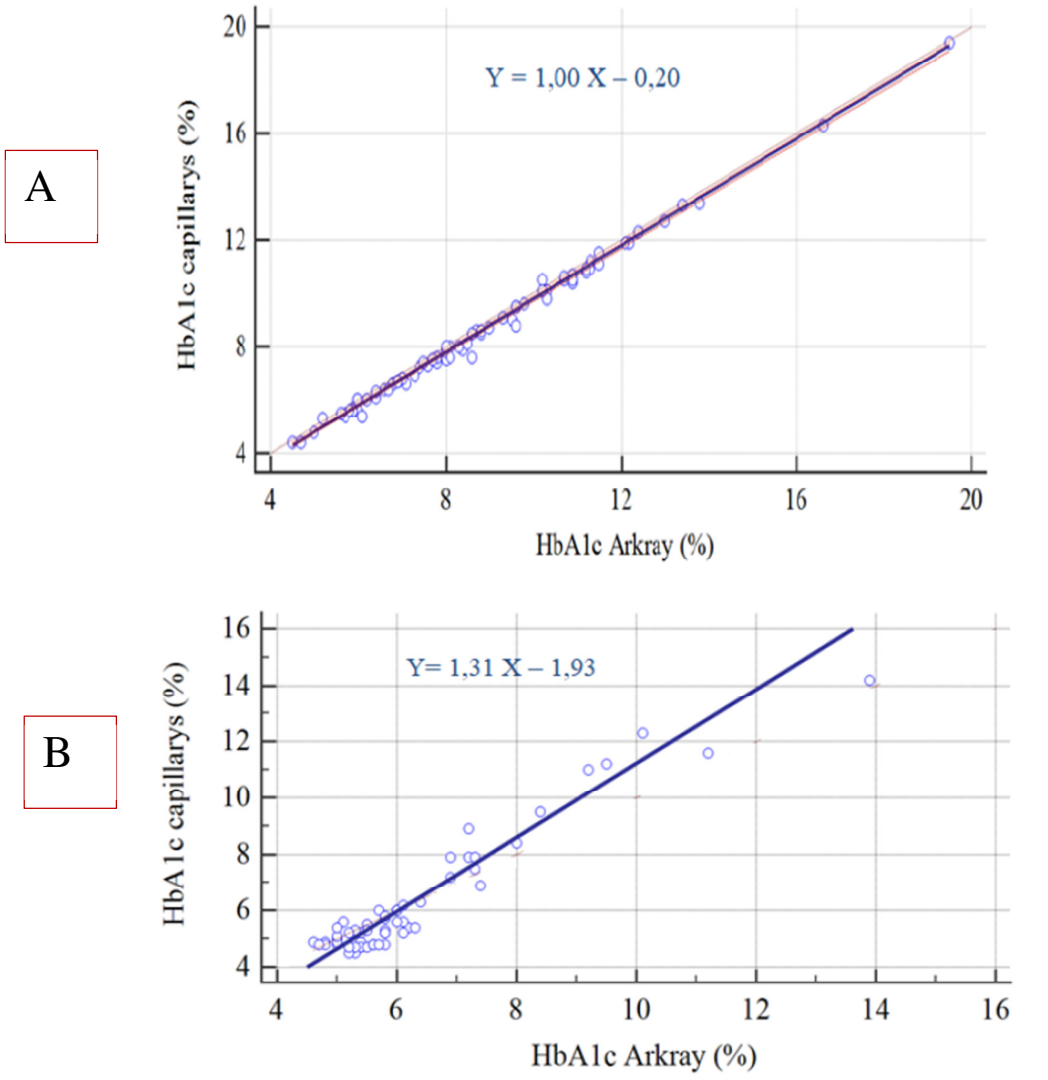
Figure 1. Linearity study on Capillarys 3 Octa®

and *P*< 0.0001) which shows a non-significant correlation. For samples with hemoglobin abnormalities and concerning 57 patients, Capilarys 3 Octa®'s mean was 6.21%± 2.1 whereas ADAMS™ A1c HA-8180V's mean was equal to 6.2%± 1.7. Passing-Bablok diagram revealed a mean difference equal to -0.03 with a CI of 95% (-0.22 to 0.16) (t= 0.027 and *P*= 0.7428) which shows a significant correlation (Figure2).

Interferences study

For hematocrit (*P*= 0.888), total bilirubin (*P*= 0.388), and triglycerides (*P*= 0.993), CVs calculated were inferior to the limits fixed by FSBC and we noted no change in the electrophoretic profile (Tables 2,3 and 4).

For the detection of Hb variant and thalassemia syndromes, sensitivities range from 0 to 92%, but specificities are at 100% (Table 5).



A: In the absence of an anomaly

B: In the presence of an anomaly

Figure 2. Passing-Bablok regression line between HbA1c (%) measured on Capillarys 3 Octa® and Arkray® in the absence and existence of hemoglobin abnormality

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Table 2. Hematocrit interference study results

Variable	HbA1c (%)	Hct (%)	Bias (%)	Average (%)	SD (%)	CV (%)	CV FSBC (%)	CLT (%)
	5.1	35	-					
S1	5.2	26	2.00	5.13	0.11	2.15		
	5.2	88	2.00					
	6.4	50	-					
S2	6.3	20	1.56	6.43	0.15	2.33	4.0	6.08
	6.5	80	1.56					
	9.9	36	-					
S3	10.0	26	1.01	10.00	0.15	1.50		
	10.2	91	3.03					

Hct: hematocrit; S: specimen; CV: coefficient of variation; CLT: central limit theorem;
FSBC: French Society of Clinical Biology

Table 3. Triglycerides interference study results

Variable	HbA1c (%)	TG (mmol/L)	Bias (%)	Mean (%)	SD (%)	CV (%)	CV FSBC (%)	CLT (%)
	5.0	5.84	-					
S1	5.1	10.30	2.00	5.07	0.05	0.98		
	5.1	15.1	2.00					
	5.1	20.1	2.00					
	6.2	3.04	-					
S2	6.4	10.8	3.22	6.3	0.11	1.74	4.00	6.08
	6.4	13.2	3.22					
	6.2	25.5	0.00					
	7.9	1.61	-					
S3	7.9	8.12	0.00	7.8	0.10	1.21		
	7.7	9.72	2.53					
	7.8	15.32	1.26					

TG: triglycerides; S: specimen; CV: coefficient of variation; CLT: central limit theorem;
FSBC: French Society of Clinical Biology

Table 4. Total bilirubin interference study results

Variable	HbA1c (%)	Bilirubin (µmol/L)	Bias (%)	Mean (%)	SD (%)	CV (%)	CV FSBC (%)	CLT (%)
	5.1	11	-					
S1	4.1	186	5.88	4.9	0.14	2.85		
	4.8	361	5.88					
	4.9	587	1.96					
	6.4	10	-					
S2	6.1	144	4.68	6.2	0.14	2.25	4.00	6.08
	6.1	254	4.68					
	6.2	278	3.12					
	8.0	4	-					
S3	4.7	355	1.25	7.9	0.05	0.63		
	8.0	446	0.00					
	8.0	509	0.00					

TG: triglycerides; CV specimen: coefficient of variation; CLT: central limit theorem;
FSBC: French Society of Clinical Biology

Table 5. Capillarys 3 Octa® analytical performance in Hb variant detection and thalassemia syndromes

Variable	A/S (n= 26)	S/S (n= 2)	A/C (n= 15)	S/C (n= 1)	ß+ (n= 53)	ß0 (n= 1)	A/F (n= 9)
Sensitivity	92	0	73	0	92	0	44
Specificity	100	100	100	100	100	100	100

A: hemoglobin A; S: hemoglobin S; C: hemoglobin C; F: hemoglobin F; ß+: minor thalassemia ß°: major thalassemia

Labile fraction interference study (LA1c)

Labile fraction effect on HbA1c is displayed in Table 5. No significant change in HbA1c values was observed even at high glucose concentrations.

Sample to Sample carry over

We assayed a sample with a low HbA1c level (5.0 % equal to 31 mmol/mol) just after another sample with a high HbA1c level (20.0 % equal to 195 mmol/mol). There were no difference before or after the measurement of the second sample and similar results (5.0%) that obtained on the two automatons.

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Furthermore, the profiles obtained were identical eliminating any cross-sample contamination.

Discussion

The objective of our study is to evaluate the analytical performance of Capillarys 3 Octa® for HbA1c determination. The performances of this analyzer were compared to ADAMS HA 8180 V using HPLC and traceable to IFCC and NGSP measurement procedure.

The evaluation of the repeatability, studied on four samples with 2 levels of control, revealed CVs ranging from 1.0 to 3.2% which is in accordance with the criteria fixed by the FSBC in 2006 recommending CVs below 3% (11,12). In 2016, Rollborn et al. (13) have reported that among the two analyzers evaluated in their study, Capillarys 3 Tera® has the lowest CVs (0.8 to 2.2%) compared to the automaton based on the Roche Cobas 6000 immunological method (Tina -quant® Hemoglobin A1c Gen3).

The study of intermediate fidelity has shown that our analyzer gives CVs from 1.4 to 4.4% (2.2% for the NC; 1.4% for the PC; 4.4% for a HbA1c level equal to 5%; 2.7% for an HbA1c level equal to 6.4% and 2.8% for an HbA1c level equal to 8%), in agreement with the analytical objectives set by the Scientific Institute of Public Health recommending limits of CV lower than 4% (14).

According to the work of Herpol et al. (14), CVs found were equal to 1.07% and 0.80% for HbA1c levels of 5% and 9.5%, respectively.

Our linearity study was highly satisfying and showed an impressive level of linearity ranging from 4.4% up to 20.0% with measurement biases ranging from 2 to 5% which is lower than the CLT and recovery rates between 97 and 105%. An excellent correlation was proven between capillary electrophoresis and HPLC (r= 0,994 for samples without Hb abnormalities, r= 0,805 for samples with Hb abnormalities).

Urrechaga also found a good correlation for samples without Hb anomalies, between the two methods (r= 0.997) (15). Similarly Park et al. found similar results between these two methods for samples with Hb variants (16).

The interference of hematocrit (from 20 to 93%) was studied for both analyzers, and no effect was noted. The absence of hematocrit interference offers the possibility of HbA1c measurement on a globular pellet for a sample on which other plasma assays have been carried out.

No significant effect on HbA1c results was also observed for high triglycerides and total bilirubin levels (up to 25,5 mmol/L and 587 µmol/L, respectively), the deviations obtained compared to the test sample remain very insignificant. For the same technique, Wu et al. (17) and Herpol et al. (14) found no interference from triglycerides and total bilirubin on HbA1c measurement using C2FP and Capillarys 3 Tera®, respectively.

Studying the labile HbA1c fraction interference (LA1c), results did not show a significant variation in HbA1c even at high glucose values which is in agreement with the results found by Doggui et al. (18) on the C2FP automaton and those of Herpol et al. (14) with the Capillarys 3 Tera®.

Concerning the interference of Hb variants, our study was carried out on 107 whole blood samples, 44 of which have variants S and C and 63 have quantitative anomalies. The automaton allows the separation of S and C variants but the homozygous S/S and composite S/C forms are not detected. Indeed, the sensitivity was zero for homozygous S drepanocytosis and composite S/C hemoglobinosis. However, sensitivity is high for heterozygous forms (S and C). Capillarys 3 Octa® sensitivity of the quantification of HbA1c differs depending on the variant: it is 69 and 60% respectively for drepanocytosis heterozygous S and heterozygous hemoglobin C, while it is zero for homozygous S drepanocytosis and the S/C composite form.

In 2016, Rholfing et al. (19) did not note any interference either from HbS or from HbC on the results of HbA1c rendered by the same type of automaton.

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Conclusions

Throughout this evaluation, Capillarys 3 Octa® proved to be a precise and linear instrument for HbA1c measurement. Several clinical interferences such as LA1c, hematocrit, triglycerides, and total bilirubin for biomarkers in general and HbA1c in particular have had no effect on the results given by the automaton. In presence of Hb variants, in particular, Hb S and Hb C, this automaton provides reliable results for HbA1c. The study of the electrophoregram, in the presence of variants, helps to detect qualitative anomalies.

Furthermore, Capillarys 3 Octa® ability to separate the A2 fraction from the Hb would contribute to the diagnosis of thalassemia traits in diabetic patients during the monitoring of their diabetes.

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Conflict of Interest

There is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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