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Clinical correlation between a point-of-care testing system and laboratory automation for lipid profile

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ABSTRACT

Background: We evaluated the clinical correlation between the CardioChek PA analyzer and a clinical laboratory reference method to use for screening program purposes.
Methods: Fasting blood samples were collected on 516 patients (age 20–85 y). One venous sample was collected using a serum tube for the evaluation on a COBAS reference analyzer. A second venous sample was collected in a lithium heparin tube and was evaluated on the CardioChek PA analyzer (CCPA venous). A fingerstick sample (CCPA fingerstick) was evaluated only on the CardioChek PA analyzer. Linear regression analyses were performed for each measured analyte, total cholesterol, HDL-cholesterol and triglycerides.
Results: The correlation between the CCPA fingerstick and CCPA venous was extremely high for HDL-C and triglycerides, and good for total cholesterol. Our results demonstrated a good clinical agreement for total cholesterol, HDL-C and triglycerides between 97.7% and 94.6% in the comparison of the CCPA to the reference analyzer.
Conclusions: We identified the pre-analytic phase as an important step to guarantee the quality of results and indicate that the CardioChek PA is a reliable lipid point-of-care testing system that can be used for the application of clinical screening anywhere.

1. Introduction

Cardiovascular disease (CVD) is the most frequent cause of morbidity and mortality in the contemporary world. Reducing serum lipid concentrations can decrease atherosclerotic plaques, thus contributing to prevention of CVD. Population screening for the detection of dyslipidemias aims at early identification of individuals at high risk of developing CVD [1].

Point-of-care testing (POCT) provides fast results, with easy operation, making it highly suitable for population screening tests. The clinical application of POCT has been demonstrated to be efficient in raising awareness about the importance of lipid levels to prevent future CVD and stroke events [2].

The CardioChek PA analyzer (PTS Diagnostics) is a portable whole blood test system that uses a single test strip to measure total cholesterol (TC), HDL cholesterol (HDL-C) and triglycerides (TG) [3]. The use of the CardioChek PA analyzer by health professional workers is highly recommended for the proposed screening programs in Brazil; the analytical performance is suitable for use as part of national health services, providing fast and reliable results.

In general, POCT devices may have greater variability compared to large equipment found in the clinical laboratory. These analytical differences could be due to a combination of environmental variations (temperature, humidity, the use of a whole blood sample, and training of individual operators) [4].

2. Methods

2.1. Study design and patients

In this study, 516 fasting blood samples (12 h) were collected from patients (age between 20–85 y) at the outpatient department of the University Medical Center UNIFESP/EPM, Brazil. The study was submitted to the local ethics and research committee; the patient participation was voluntary upon completion of the consent form, according to the Helsinki Declaration. From each outpatient presenting at the medical center, two venous whole blood samples were collected from a single venipuncture and an additional single, whole blood fingerstick sample was collected with a lithium heparin coated capillary pipette.

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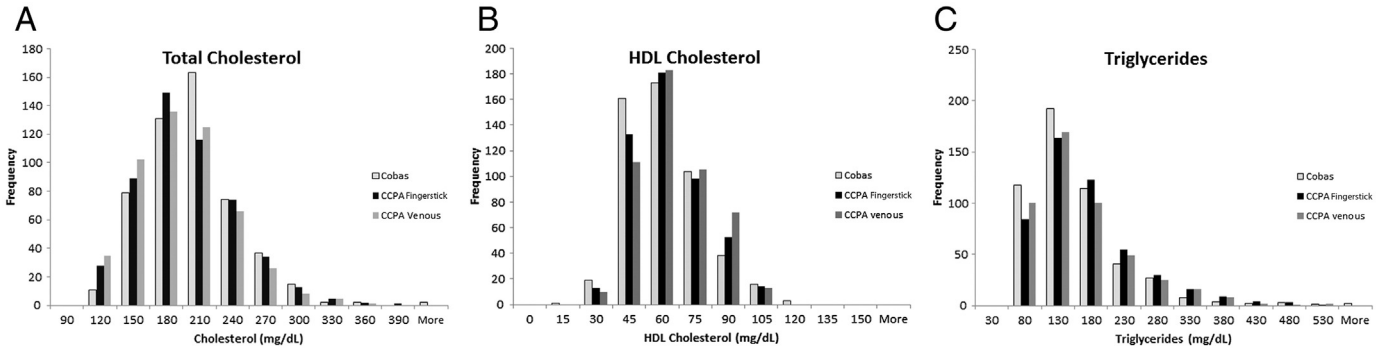

Fig. 1. Distribution of each specific test (Cobas, CCPA Fingerstick and CCPA venous) in the population studied. A: Total cholesterol, B: HDL cholesterol; C: triglycerides.

One venous sample was collected in a tube without additives for the separation of serum and was evaluated on a Cobas 6000® (COBAS) from Roche Diagnostics at the Central Laboratory within 1 h of collection. Specimens that demonstrated hemolyzed serum after centrifugation in the Laboratory were discarded from the study. The Central Laboratory has a proficiency-testing program in place that guarantees the quality of lipid profile results (Controllab proficiency-testing program). A coefficient of variation (CV) of ±5% for lipid profile has been consistently achieved. The Central Laboratory performed the measurement of total cholesterol (TC) and triglycerides (TG) by standard enzymatic colorimetric assay (Roche Diagnostics) methods. The HDL cholesterol (HDL-C) was measured by a homogenous enzymatic colorimetric test, (Roche HDL-C plus 3rd generation (HDLC3)). This assay uses magnesium ions and dextran sulfate to selectively react with LDL, VLDL and chylomicrons which are resistant to polyethylene glycol (PEG)-modified enzymes. The cholesterol concentration of HDL is determined enzymatically by cholesterol esterase and cholesterol oxidase coupled with PEG.

The second venous sample (collected in a lithium heparin coated tube) was evaluated on a CardioChek PA analyzer (CCPA venous). The fingerstick sample (CCPA fingerstick) was also evaluated on the CardioChek PA analyzer. The use of both venous and capillary samples on the CardioChek PA allows the clinician confidence in the interchangeability of sample types. CCPA uses dry-chemical testing for measurement of TC, HDL-C and TG in whole blood using PTS Diagnostics lipid panel test strips. A membrane removes the red blood cells, and via horizontal flow the test strip analyzes plasma lipid concentrations. The evaluations of total cholesterol and HDL-C use the same enzymatic reaction. The HDL lipoproteins are separated from lipoproteins LDL and VLDL using phosphotungstic acid and a magnesium salt layer above the membrane fractionation layer. The resulting HDL fraction in plasma reacts with surfactants and enzymes for measuring cholesterol concentration. The evaluation of TG is carried out by a colorimetric enzymatic method using lipoprotein lipase, glycerol kinase, glycerol phosphate oxidase and peroxidase. The CCPA analyzer uses reflectance photometry [3].

The sample collection location was temperature controlled (23–24 °C) and humidity controlled (40–50%) and the procedure was conducted under aseptic conditions using traditional methods of antecubital venipuncture. The time of tourniquet used did not exceed 1 min, as recommended in the Clinical and Laboratory Standards Institute Guidelines [5].

The fingerstick was performed according to the CardioChek PA manufacturer's instructions. The temperature of the testing environment was between 20–27 °C and the humidity < 80%. The site temperature was recorded before, during and after the test. The individuals responsible for the collection of venous and capillary samples are technicians and running of the CCPA was trained following routine manufacturer's instructional procedures.

The lipid panel test strips from PTS Diagnostics were tested using the CardioChek PA quality control level 1 and level 2. ChekMate™ Strips were also used to verify that the optics of the analyzer are functioning properly in all wavelengths used by the equipment. The ChekMate MEMo Chip was inserted in the analyzer, followed by the ChekMate, levels 1 and 2. Manufacturer's instructions recommend the use of ChekMate Strips on a daily basis as well as testing liquid quality controls with each new lot of test strips, each new shipment of test strips, for troubleshooting the analyser or to comply with each facility's quality control requirements. In this study, more stringent quality control was performed by running the liquid controls each day of testing and running the ChekMate Strips only at the initiation of the evaluation. Each test result was associated with a sequential number and the name of the operator. All data was recorded in a data collection sheet and later transferred to a Microsoft Excel file.

2.2. Statistical analysis

Data analyses were performed using Microsoft Excel (2010). The difference between the CardioChek PA results and the laboratory results was calculated in a pair-wise fashion. The average differences were calculated. Linear regression was used to analyze paired data, describing the relationship between the two methods. Statistical significance was defined as a $p < 0.05$.

Table 1
Linear regression analyses.

	Total cholesterol		HDL cholesterol		Triglycerides	
	Fingerstick	Venous	Fingerstick	Venous	Fingerstick	Venous
n[a]	511	504	492	494	489	472
Slope	0.92	0.87	1.01	1.00	1.16	1.06
Offset	9.4	11.8	3.0	5.5	−4.0	−2.6
Correlation coefficient (R)	0.854	0.856	0.936	0.923	0.969	0.953
Sample range (mg/dl)	101–370	101–339	20–97	21–100	50–498	50–486

[a] Samples beyond the reporting range of the CardioChek PA were excluded.

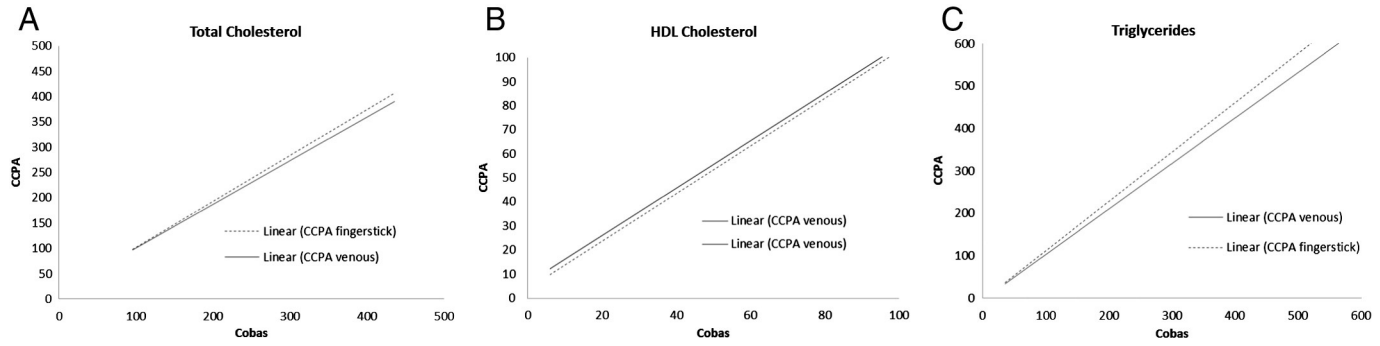

Fig. 2. Correlation between Cobas and CCPA. A: Total cholesterol, B: HDL cholesterol; C: triglycerides. Statistics are shown in Table 1. Correlation between CCPA fingerstick and CCPA venous was extremely high for HDL-C (r = 0.953) and TG (r = 0.953), and good for TC (r = 0.879).

2.3. Clinical agreement

The data were analyzed by risk classification according to the US National Cholesterol Education Program (NCEP) ATPIII guidelines (NIH Publication No. 01-3305 May 2001) the American College of Cardiology/American Heart Association Guideline (2014) [6] and the V Brazilian Dyslipidemias Guidelines (2013) [7]. Each individual test was classified based on traditional risk categories for each of the analytes. The categories are as follows (in mg/dl): Total cholesterol has 3 categories; <200, 200–239 and ≥240. HDL cholesterol falls into 3 categories; <40, 40–60 and >60. Triglycerides has 4 categories; <150, 150–199, 200–499 and ≥500. Clinical agreement was defined as the CardioChek PA and the laboratory results being in the same category. In an effort to avoid overestimation of clinical differences (for example a laboratory TC value of 201 can be categorized differently than a result of 199 mg/dl), any result within 5% of a category boundary could be classified as either side of that boundary.

In this study, performance of the CardioChek PA system was considered acceptable if the average difference of all paired results ((CardioChek PA-COBAS)/COBAS * 100) was ±10% for total cholesterol, ±12% for HDL-C and ±15% triglycerides. These average bias levels were considered challenging as the US Clinical Laboratory Improvement Amendments (CLIA) proficiency testing criteria's recommendations for acceptable analytical performance are: ±10% for total cholesterol, ±30% for HDL-C and ±25% triglycerides.

The range of CardioChek PA analyzer for TC is 100 to 400 mg/dl, for HDL-C is 15 to 100 mg/dl and for TG is 50 to 500 mg/dl. All results presented outside the range of CCPA analyzer, were documented as "less than" or "greater than" in the print results and were excluded from linear regression analyses. This explains why the total numbers of samples differ slightly at each table.

3. Results

We evaluated the POCT and laboratory measurements from 516 patients. Fig. 1 demonstrates the distribution of values for each specific test in the population studied. Linear regression analyses were performed for each measured analyte, total cholesterol, HDL-cholesterol and triglycerides. The results of these analyses are shown in Table 1 and Fig. 2.

The control behaviors were: Multichem Control L1 — cholesterol: package insert range (110 to 220 mg/dl), mean (SD) = 161 (10), CV = 6%; triglycerides package insert range (50 to 200 mg/dl), mean (SD) = 131 (22), CV = 16%; HDL package insert range (20–45 mg/dl), mean (SD) = 31 (2), CV = 8%. Multichem Control L2 — cholesterol: package insert range (170 to 340 mg/dl), mean (SD) = 231 (15), CV = 6%; triglycerides package insert range (110 to 340 mg/dl), mean (SD) = 222 (28), CV = 13%; HDL package insert range (30–70 mg/dl), mean (SD) = 50 (3), CV = 5%.

We estimated the bias that might be expected between the CardioChek PA analyzer and the laboratory in 2 ways. First, the bias between paired results was calculated as [(CardioChek PA — Lab)/Lab] * 100 for each patient sample. The average observed bias for each analyte was then calculated (Table 2).

Predicted biases were also calculated at clinically relevant decision points for each analyte using the linear regression equations and calculating the average of these biases. The results are shown in Table 2.

Clinical agreement was defined as indicated in Section 2.3 above. These results are shown in Table 3. Samples were classified as "agree", "1 category disagreement" (only 1 category scapes to the other range) and "two category disagreement" (2 categories scape to the other range). There were no samples that disagreed by 3 categories.

When evaluating total disagreement in clinical risk categorization, Table 3 demonstrates that total disagreement for all analytes was

Table 2
Bias analyses.

	Total cholesterol[a]		HDL cholesterol[a]		Triglycerides[a]	
	Fingerstick	Venous	Fingerstick	Venous	Fingerstick	Venous
Average observed bias	−3.3%	−6.1%	7.5%	11.5%	12.7%	4.1%
Predicted bias	−3.7%	−7.0%	5.9%	9.0%	13.7%	4.5%

[a] Clinical relevant decision points used to calculate the predicted bias. CT = 160, 200, 240, 280 mg/dl; HDL-C = 40, 60, 80, 100 mg/dl; TG = 100, 150, 200, 250 mg/dl.

Table 3
Clinical agreement (using 5% from limit).

	Total cholesterol (N = 516)		HDL cholesterol (N = 514)		Triglycerides (N = 512)	
	Fingerstick	Venous	Fingerstick	Venous	Fingerstick	Venous
Agree	496/96.1%	499/96.7%	502/97.7%	486/94.6%	487/95.1%	493/96.3%
1-category disagree	19/3.7%	14/2.7%	12/2.3%	28/5.4%	23/4.5%	15/2.9%
2-category disagree	1/0.2%	3/0.6%	0	0	2 /0.4%	4/0.8%

Table 4
Linear regression analyses; venous vs. fingerstick.

	Total cholesterol	HDL cholesterol	Triglycerides
Slope	0.92	0.95	1.03
Correlation coefficient (R)	0.879	0.953	0.953
Average bias	4.0%	−3.3%	10.3%

≤5.4% whether venous or fingerstick samples are evaluated. Two category disagreement was only observed in less than 1% of the samples tested.

Correlation between CCPA fingerstick and CCPA venous were extremely high for HDL-C ($r = 0.953$) and TG ($r = 0.953$), and good for TC ($r = 0.879$) (Fig. 2). The average bias observed between paired venous and fingerstick samples was 4.0% for TC −3.3% for HDL-C and 10.3% for TG (Table 4). These results support the commutability of venous and fingerstick sample types.

4. Discussion

The use of POCT has the potential to reduce the incidence of undiagnosed and undertreated cardiovascular disease. Over the past 30 y, technology has allowed the development of more sophisticated and accurate equipment, bringing the patient closer to the testing site, particularly in primary and intensive care settings.

Despite these challenges, POCT tests can be a key factor in the change of service provision in health care, through disruptive innovation, radically changing the way healthcare professionals will treat their patients [8, 9]. The CardioChek PA analyzer was compared in laboratory technical validation studies and the results found were acceptable and adequate for its use in screening programs [3,10,11].

A critical point for assured quality in POCT devices is the pre-analytical phase. The effective operator training and compliance with all manufacturer's technical guidelines ensure better accuracy results [4].

Our results identified the pre-analytic phase as an important step to guarantee the quality of results. Simple hand washing is often not adequate to remove hand creams, lotions or environmental oils, therefore the punctured finger must be cleaned and wiped with a proper alcohol that can clean the finger adequately. Skin creams are frequently present on the individual's hands and they have the potential to interfere with the test strip's TG reactions.

As demonstrated in Table 3, the fingerstick samples did show an increased bias versus the laboratory for TG when compared to venous samples. This difference was clinically insignificant (Table 3) and is suspected to have been the result of insufficient cleaning of the finger prior to sampling.

Another important point that the CCPA has a calibrated pipette that ensures that the same blood volume is transferred to the test strip for every test. It has been demonstrated to minimize errors. It is important to emphasize that the observed variations are all considered satisfactory in accordance with CLIA requirements for precision. Failure to correctly perform these pre-analytical procedures may compromise the results and can be a limitation for the use of CCPA in lipid screening.

Our results also demonstrated good clinical agreement (94.6%–97.7%) to the reference for TC, HDL-C and TG allowing us to conclude that the CardioChek PA is a reliable lipid POCT system that can be used for the application of clinical screening anywhere. The benefits of use of POCT instruments in the workplace, in urban health screenings or in rural areas include not only the immediate feedback to the individual, but also the simplicity, ease and speed of testing, thus finger stick sampling with immediate testing is more appropriate. An advantage of the CardioChek analyzer is that, if venous blood is being drawn for other reasons, the venous blood can be used to measure the lipids with no clinical difference in the values compared to capillary (finger stick) blood.

As our results were clinically acceptable, we suggest that the CardioChek PA can be applied to monitor lipid levels of patients with dyslipidemias.

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