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Point-of-care Testing of HbA1c, Renal Function and Lipids in Remote or Disadvantaged Regions

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and Dr Clarita Cadiz (Philippines) and (Medtronic supported) diabetes educators Kelly Goodlet, Marina Spence, Katy Dyson and Sara Albano, who volunteered for the Philippines programs. We thank Sherilyn Goldstone for editorial assistance.

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Abstract (50 words)

For optimal diabetes management HbA1c, lipid and renal function measurements are key. Suitable point-of-care systems can provide such data in remote areas, diabetes camps, disaster relief, small community hospitals and in community screening days in disadvantaged regions. Some systems are currently used in Australian rural, remote and Indigenous health services.

Key Words

Diabetes, HbA1c, diabetes complications, point-of-care testing

Glycated haemoglobin (HbA1c) is the gold standard reflecting average glycaemia in diabetes,[1] and in many countries HbA1c (>6.5%, 48 mmol/mol) is now approved for diabetes diagnosis as an alternative to fasting, random or oral glucose tolerance test blood glucose measurements.[2] High HbA1c levels are associated with increased risk of chronic complications in Type 1 (T1D)[3] and Type 2 diabetes (T2D)[4] and with adverse outcomes in gestational diabetes.[5] Good diabetes management targeting HbA1c to levels as close to 7% (53 mmol/mol) as possible is associated with reduced chronic complications, but can increase risk of hypoglycaemia.[3-5] Ideally, to optimise glycaemia in people with known diabetes, HbA1c testing is recommended four times per year, as recognised in

several national diabetes guidelines.[6-9] Analytical methods for HbA1c include cation exchange chromatography, boronate affinity chromatography and enzymatic and immunoassays,[9] which require HPLC or the large instrumentation used in clinical chemistry laboratories. Point-of-care (POC) instruments, using either boronate affinity or immunoassay methods for HbA1c, are portable and offer a range of additional tests usually only available with large, expensive equipment in pathology practices and major hospitals.[10] The accuracy of selected, but not all, POC HbA1c assays is sufficient to achieve (Australian) National Association of Testing Authorities (NATA) accreditation and a Medicare rebate for use in pathology laboratories and hospital outpatient clinics in Australia.[11-14] Improved analytical performance, a wider range of analytes offered and their portability has expanded system use in remote outpatient and community clinics, and as we describe herein, in response to disasters, at diabetes camps and diabetes community education or screening days in overseas disadvantaged regions. Currently available POC systems that meet Australian standards for accuracy requirements and laboratory accreditation requirements are the Alere AS100/Alere 2 (Abbott, Australia) and Siemens DCA Vantage (Siemens, Bayswater, VIC, Australia), the features of which are summarised in Supplementary Table 1.

Various artefacts and assay limits of detection can affect biochemical analytes. For both POC and full-sized pathology service instruments clinical conditions that can lead to a mismatch between HbA1c and blood glucose levels include haemoglobinopathies (such as thalassemia and sickle cell disease), haemolysis, anaemia and renal failure.[15] The National Glycohaemoglobin Standardisation Program (NGSP) website has a comprehensive list of the effects of haemoglobinopathies and other interferences in various HbA1c methods.[15] Several common clinical issues can reduce the accuracy of POC HbA1c methods. These include HbA1c levels that exceed the instrument and assay detection

range and severe hypertriglyceridaemia (usually >15.7 mmol/l).[16] Marked hypertriglyceridaemia can be the result of diabetic ketoacidosis, poor glycaemic control and/or aggravation of underlying genetic dyslipidaemia by acquired diabetes, obesity, renal disease, liver disease, pregnancy or by triglyceride elevating drugs (e.g., corticosteroids, thiazides or oestrogens).[17]

To compare POC HbA1c, lipid and renal function tests by a POC system and a chemical pathology laboratory autoanalyser, blood samples from 30 Australians were analysed for HbA1c using the POC system (Alere AS100, Abbott Diagnostics Australia) used in our overseas field testing and a laboratory-based Bio-Rad D100 analyser at the Royal Prince Alfred Hospital, Sydney. Urine samples from 25 patients were compared for creatinine and albumin using the POC device and the Immulite 2000 (microalbumin) and Roche Cobas 602 (creatinine) systems (Table 1, Supplementary Figure 1). Twenty subjects' plasma samples were compared for total and HDL-cholesterol and triglyceride levels using the Alere POC and Roche Cobas 602 instruments, and the LDL-cholesterol levels were calculated. Excellent linear correlations were seen for all parameters measured (Figure 1), with r values ranging 0.92–0.99; excellent agreement of absolute values, and no statistical difference in levels by instrument types when analysed by Bland-Altman analysis.

We also compared quality control (QC) values obtained pre-departure and post-return from field testing trips, with 30 hours air travel and transit time and suboptimal storage conditions over two weeks between air travel. Values before and after suboptimal handling of reagents and QC materials were very comparable (Supplementary Table 2), though of course we do not recommend suboptimal QC and reagent handling. The within-day and between-day variations were remarkably similar to the report on properly handled reagents by Jain et al.[18]

As part of humanitarian aid by Insulin for Life (IFL, www.insulinforlife.org), HbA1c levels were measured in capillary blood samples using a POC system (Alere AS100, Abbott Diagnostics Australia) in five international settings during 2016–2018. POC hardware and consumables were carried to Ecuador and the Philippines as hand or checked luggage by IFL volunteers. HbA1c tests were performed on capillary blood from consenting participants by a retired endocrinologist/chemical pathologist (ET, 2016), a medical student (LH, 2017) and a nurse diabetes educator (SA, 2018). Assay controls were the company's control cartridges and finger-prick blood HbA1c levels from non-diabetic IFL volunteers. The clinical significance of their HbA1c result was explained to each person with diabetes, and their results provided to their treating clinician. In this report, the recommended target HbA1c levels are <7.5% (58 mmol/mol) for subjects <18 years old and <7% (53 mmol/mol) for those aged ≥18 years.

In Ecuador in 2016, three months after a major earthquake, HbA1c was quantifiable in 91 of 93 tested subjects with known diabetes from five affected cities. Mean (range) HbA1c was 8.4% (4.9–14.3%) (68 (30–133) mmol/mol), with 28% of subjects having HbA1c levels at target and 19% having a HbA1c ≥10% (86 mmol/mol).

In a 2017 T1D education camp for 15 young people in Cebu, the Philippines, mean (range) HbA1c levels were 9.8% (8.4–11.8%) (84 (68–105) mmol/mol), with 7% achieving target HbA1c levels and 47% with a HbA1c ≥10% (86 mmol/mol). At a community screening day (Dumaguete, Philippines) 47 people with known diabetes were tested, with unmeasurable results in three. For 36 adults, mean (range) HbA1c levels were 9.4% (5.5–14.1%) (79 (37–131) mmol/mol), with 25% reaching target

and 44% >10% (86 mmol/mol); for eight children mean (range) HbA1c levels were 9.8% (range 8.5–11.8) (84(69–105) mmol/mol), with none achieving target levels and 38% having HbA1c ≥10% (86 mmol/mol).

In a 2018 youth and adult T1D camp in the Philippines, 34 subjects were tested, with all being quantifiable. Mean (range) HbA1c levels were 8.6% (4.2–14.5%) (70 (22–135) mmol/mol), with 44% reaching target and 35% being ≥10% (86 mmol/mol). In a hospital for the poor (Dipolog City, Philippines) 36 adults with, or suspected of having, diabetes were tested, with results available for 34. Mean (range) HbA1c levels were 9.2% (5.2–14.2%) (77 (33–132) mmol/mol), with 24% at target and 39% ≥10% (86 mmol/mol).

Discussion

POC use in challenging sites was feasible. The presence of relatively low HbA1c levels (<6.5% or 48 mmol/mol) was noted in several subjects, which may indicate very tight glucose control, which would be challenging to achieve in the settings visited as most subjects did not have regular access to home glucose monitoring or to affordable diabetes care drugs. Alternate explanations may be frequent episodes of hypoglycaemia and/or misdiagnosis of diabetes in non-diabetic subjects or subjects with pre-diabetes.

There were several challenges with field use. POC HbA1c levels were not recordable in nine of 222 (4.1%) subjects, likely due to severe hypertriglyceridaemia or very high (>15% or 140 mmol/mol) HbA1c levels.[16] During the very hot and humid outdoors community education days in the Philippines in 2017 and 2018, the POC system overheated. When returned to operating temperature,

after packing in ice-filled plastic bags and fanning, QC testing was acceptable and clinical testing resumed. It is recognised that POC hardware and consumables costs may be beyond the resources of some disadvantaged services that may otherwise benefit. The technical capacity to maintain such a system may also be limited.

In remote regions of Australia, access to full pathology services can be limited and may require patient or blood sample travel, which can increase costs and reduce the timeliness of results and related clinical decisions and care.[17] POC tests are user-friendly and if performed with suitable instruments and skilled personnel, are practical, accurate and can be used for diabetes screening and care, increasing case detection and improving clinical care.[17-19] The Quality Assurance for Aboriginal Medical Services (QAAMS) Program provides a guideline for POC HbA1c use.[20]

The Afinion Alere AS100 POC instrument meets the requirements for clinical accuracy when in the field and under extreme climatic conditions. The reagents are stable to transport and the instrument can provide clinically useful data on patients that would not normally be able to access this type of pathology for their diabetes care. A wide range of HbA1c levels, with poor control being common, were identified in people with diabetes in disadvantaged regions overseas. POC system use in sometimes challenging field conditions is feasible and can assist diabetes diagnosis and care of people in remote or disadvantaged regions.

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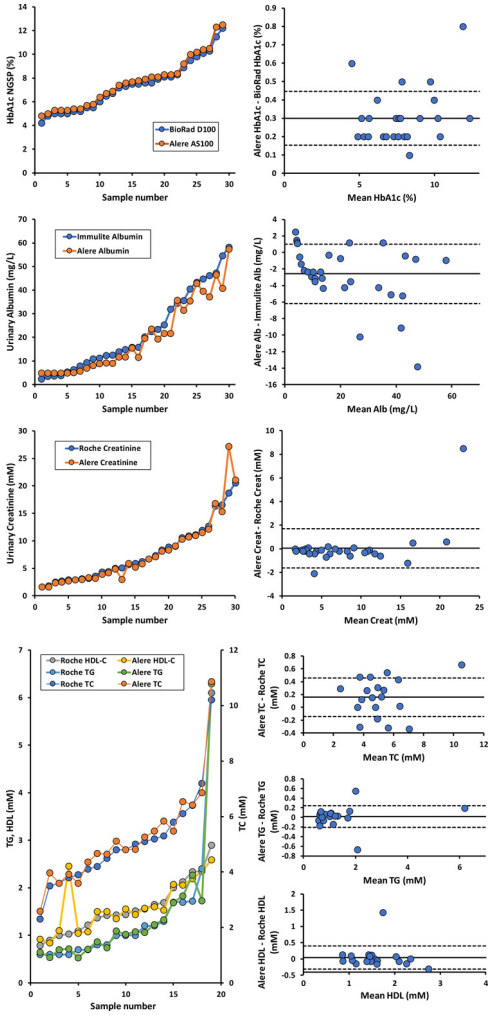
Supplementary Figure and Table Legends

Figure 1: Agreement between HbA1c, lipid and urine albumin and creatinine tests performed on a POC system (Alere AS100) and in the pathology laboratory (Siemens Immulite and Roche Cobas 602).

Supplementary Table 1: Characteristics of POC HbA1c systems that meet Australian (NATA) standards for clinical use.

Supplementary Table 2: Comparison of assays results before and after suboptimal handling of reagents and QC materials.

Supplementary Table 3: QC sample (low and high) values (C1 and C2, respectively) pre- and post-travel under non-ideal storage conditions during travel. Each QC sample was tested in triplicate (n=3) and a T-test for the difference between pre-and post-travel levels evaluated.



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