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CLINICAL RESEARCH

Application of a Nanotechnology-Based, Point-of-Care Diagnostic Device in Diabetic Kidney Disease

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Introduction: Early detection of diabetes mellitus (DM) and diabetic kidney disease (DKD) is important for preventing end-stage renal failure and reducing cardiovascular complications. Availability of a validated point-of-care (PoC) device that can measure various DKD markers would be useful in this respect, especially in resource-poor parts of the world.

Methods: We validated a novel nanotechnology-based multianalyte PoC device (minimally invasive and does not require trained medical personnel) against laboratory gold standard tests for the detection of 5 biomarkers related to management of DM and DKD. The prospective study was funded by an ISN ANIO grant in 2 phases: (i) proof of concept: random samples were tested for the analytes with the PoC device and correlated with the laboratory gold standard; and (ii) clinical validation in a well-characterized cohort of patients. A nonenzymatic- and nonantibody-based electrochemical PoC device for quantitative measurement of markers—glycosylated hemoglobin (HbA_{1c}), hemoglobin, serum albumin, microalbuminuria, urine creatinine, and albumin-to-creatinine ratio—was developed and used in this study. The disposable strips were interfaced with a multipotentiostat hand-held PoC device (3.7-V rechargeable lithium battery, 5-inch touch screen, Bluetooth enabled) working in amperometry mode, which provided the results in <1 minute. Data were analyzed using linearity plots and Bland-Altman difference plot analysis.

Results: A total of 4717 individuals were screened during the study (phase 1: 2576 and phase 2: 2141.) In phase 2, samples were tested in 529 subjects (346 females)—120 subjects with type 1 DM, 255 subjects with type 2 DM, 54 subjects without DM, 400 subjects with stage 2 chronic kidney disease, and 30 subjects with stage 3 chronic kidney disease.

Conclusion: A nanotechnology-based PoC device for quantitative measurement of HbA_{1c}, hemoglobin, serum albumin, microalbuminuria, and the urine albumin-to-creatinine ratio was developed for detection of early DKD and showed excellent correlation between the device and laboratory results. This device has the potential for early detection of DM and/or DKD, especially in remote communities in underserved areas of the world where prevalence of diabetes is rapidly increasing.

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Chronic kidney disease (CKD) is increasingly being recognized as a public health problem in developing countries like India and rest of the world.[1,2] Approximately 10% of the world population is affected by CKD, and millions die each year because of the lack of diagnostic tools and timely treatment.[3] Diabetes mellitus (DM) is the major risk factor for CKD worldwide. Both experimental and cohort studies support the pathogenetic role of hyperglycemia and CKD.[4] This problem is particularly of major importance in India where there is an epidemic of patients with new-onset type 2 DM, and where diabetic nephropathy has

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been shown to be the most important cause of end-stage renal disease.[5,6] The delivery of care to these patients, especially in the rural areas of India, is woefully inadequate.[7] There is an acute need for comprehensive, continuous, and cost-effective healthcare delivery for these underserved people.[8] Early detection and strategies for prevention of progression to diabetic kidney disease (DKD) would make a major difference for these patients and would also be economically beneficial for a resource-constrained country.[9] Early diagnostics in remote and resource-challenged settings is difficult without access to costly well-equipped clinical laboratories and trained medical personnel. Consequently, developing cost-effective and easy-to-implement diagnostic tools remains an important goal in global health. One promising approach to achieve this goal is to detect disease biomarkers from accessible body fluids with point-of-care (PoC) biosensors. PoC biosensors can potentially improve patient care through real-time and remote health monitoring. We report the use of a multianalyte PoC device based on novel electrochemical sensing technology. This device quantitatively tests for glycosylated hemoglobin (HbA_{1c}), hemoglobin, serum, and urine albumin and urine creatinine. Realizing the importance of anemia in diabetes, especially in DKD, we believe that this device will be extremely useful in detection of early DKD in most of the rural population of not only India, but the rest of the world.

MATERIALS AND METHODS

The PoC device technology was developed at the Indian Institute of Science, Bangalore, over the last 5 years, and it is based on nonenzymatic- and nonantibody-based electrochemical biosensing technology.[10–14] The PoC measurement is done on electrochemical disposable test strips that contain a membrane impregnated with patented sensing chemistries. This device, unlike many other devices, performs quantitative measurement of the analytes in question, at any remote area, with absolutely no infrastructure requirements.

For the first time, the single hand-held device tests for 5 different biomarkers (hemoglobin, HbA_{1c}, serum albumin, urine microalbumin, and urine creatinine) and will be extendable to other markers (glycated albumin, serum creatinine, serum bilirubin, and so on) in the future. The range of analytes measured in this device are HbA_{1c} (5.0%−15%), hemoglobin (2−25 g/dl), serum albumin (1−6.0 g/dl), microalbuminuria (2 mg/l−1 g/l), and urine creatinine (50 mg/l−2 g/l). The device is further being modified to extend the upper limit of detection, especially for urine analytes. The device is shown in Figure 1.

This study was done in 2 phases. The first phase was the clinical proof-of-concept phase, in which samples were tested with the PoC device and compared with laboratory gold standard methodologies. During the clinical validation phase, the technology was verified in the clinical setting. (Samatvam Endocrinology Diabetes Centre – Jnana Sanjeevini Diabetes Hospital and Medical Centre, Bangalore, India). All the samples (blood and urine) that were tested by the PoC device were simultaneously tested at a reference laboratory. Laboratory methods used for urine albumin, urine creatinine, hemoglobin, serum albumin, and HbA_{1c} were immunoturbidimetry, the Jaffe method, the SLS colorimetric Q5 method, the BCG method, high-performance liquid chromatography, and the Bio-Rad method, respectively. The albumin-to-creatinine ratio (ACR) values were calculated from the measured urinary albumin and creatinine. The PoC device can store the test data of 60,000 patients, which can be transferred to a computer and/or mobile device via Bluetooth. All the samples were tested on the same day for microalbuminuria, urine creatinine, ACR, HbA_{1c}, hemoglobin, and serum albumin using the multianalyte PoC device. The same

Figure 1. anuPath multianalyte diagnostic device. Q14

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