Point-of-Care Testing in Diabetes Care

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Abstract: Assessing modifiable risk factors for metabolic and cardiovascular diseases prior to the onset of disease could allow effective prevention initiatives. Equally, monitoring in diabetic people glucose, haemoglobin A1c, ketones, lipid profiles, and urinary microalbumin concentrations allows the prevention, early detection, and treatment of diabetes-related acute and chronic complications and has a positive impact on the process of care in the management of patients with diabetes. The point-of-care testing (PoCT) technology offers convenient aspects: immediate results, decision-making without the need for repeated visits, use of fingerstick blood samples. More patients could be identified at early stages of their disease/complication provided that pre-analytical, analytical, and post-analytical errors are minimised. Indeed, prediction requires instruments with proved precision, accuracy, validity, and reliability. Reference laboratory services are now available to manufacturers so to confirm PoCT results. There are several PoC devices on the market that may allow for "real time" screening, diagnosis, and monitoring in diabetes care. Tight glucose control has a key role in long-term health of diabetic people and in the primary prevention of diabetic chronic complications. Diabetic patients are currently educated to control capillary glucose levels daily in order to maintain them within target limits. Blood glucose meters are widely used not only by diabetic patients to self-manage their disease but also by physicians to monitor critically ill patients. Glycated haemoglobin A1c can now be measured with fast and easy automated PoCT instruments to monitor long-term serum glucose regulation. Urinalysis dipsticks and blood betahydroxybutyrate meter allow measuring urine and blood ketones to prevent ketoacidosis. Since the routine measurement of urinary albumin has been suggested in diabetes mellitus as a predictor of overt diabetic nephropathy, semi-quantitative visual dipsticks and quantitative automated methods of urine testing became available for bedside detection of urine albumin at low concentrations and for the determination of the microalbumin creatinine ratio. While the National Cholesterol Education Program recommends that all adults aged 20 years and over have their blood cholesterol checked at least once every 5 years, adult diabetic patients should measure fasting lipid profile at least annually or every two years in case of low-risk lipid values. There are PoCT devices on the market that provide a full lipid panel (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides). The overview summarises current state-of-the-art of PoCT in diabetes care.

Keywords: Point of care systems, diabetes mellitus, blood glucose self-monitoring, HbA1c, ketones, lipids, urinary albumin, quality control.

POINT OF CARE TESTING: PRELIMINARY REMARKS ABOUT THE QUALITY OF WAIVED TESTS

The term point of care testing (PoCT) refers to any test that is performed near the patient with the intent to assist caregivers in the quick formulation of diagnosis and/or clinical interventions by providing immediate results [1]. Primary requirement in the PoCT context is error prevention to avoid inappropriate care. The rates of PoCT preanalytical, analytical, and postanalytical errors are unknown but surveillance of quality testing is regulated by the Centers for Medicare and Medicaid Services (CMS) through the Clinical Laboratory Improvement Amendments, CLIA (http://www.cms.gov/clia/). CLIA established three categories of tests. *Moderate complexity and high complexity* (non-waived) test methods are subject to regulations setting analyst qualifications, adherence to established testing protocols, and participation to approved proficiency testing programs. Laboratories must meet CLIA quality control (QC) requirements either by testing external QC materials (at least two levels per test procedure per day) and/or using equivalent QC procedures (internal monitoring systems). *Waived complexity* tests, on the contrary, are considered simple, accurate, and usable at home with no requirements for trained analysts, internal or external QC assessment. To receive a certificate of waiver (COW) under CLIA, laboratories must meet only three requirements: enrol in the CLIA program, pay certificate fees, and follow manufacturer's instructions. The list of waived tests includes several test systems (Table **1**) most of which have few basic formats: lateral-flow, flow-through, agglutination, or solid-phase (the so-called dipstick included) (http://www.rapid-diagnostics.org). Rapid diagnostic tests are principally useful in primary care settings or low-resource settings. Thus, they should be truly accurate, simple to use, low-cost, easily interpretable and stable when stored under adverse environmental conditions, yet no many of these requirements have been proved to be met. Notwithstanding the assumed simplicity of waived tests, erroneous results are possible and also frequent. Sources and amplifiers of PoCT testing error have been identified, classified, and successively revised [2, 3]. Due to the increasing types of tests waived, the growing number of laboratories without

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1389-5575/11 $58.00+.00

Table 1. CLIA List of Waived Tests (Adapted from http://www.cms.gov/clia/). The Original List Carries the Name of the Specific Test System Along with Manufacturer and Approved CPT Code. Rapid Diagnostic Tests that may be Useful in Diabetology are Evidenced (in Bold)

Adenovirus	**Ethanol**	**Mononucleosis**
Aerobic/anaerobic organisms – vaginal	Fern test (saliva for ovulation)	Nicotine
Albumin	Follicle stimulating hormone (FSH)	Occult blood
Alanine amino-transferase (ALT)	**Fructosamine**	Ovulation tests
Alkaline phosphatase (ALK)	Gammaglutamyltransferase (GGT)	pH
Amylase	**Glucose**	Platelet aggregation
Aspartate amino-transferase (AST)	**Glycosylated HGB**	Potassium
B-type natriuretic peptide (BNP)	**HDL cholesterol**	Pregnancy test (urine)
Bilirubin, total	Helicobacter pylori	Protime
Bladder tumor associated antigen	Hematocrit	Protein, total
Blood urea nitrogen (BUN)	Hemoglobin	Respiratory Syncytial Virus
Calcium	HIV	Semen
Calcium-ionized	Influenza	Sodium
Carbon dioxide (CO_2)	**Ketones (blood)**	Strept antigen test
Chloride	**Lactic acid**	Trichomonas
Catalase	**LDL cholesterol**	**Triglycerides**
Cholesterol	Lead	TSH
Creatinine	**Lipid profile**	**Uric acid**
Drugs of abuse	Lithium	**Urinalysis**
Erythrocyte sedimentation rate (ESR)	Luteinizing hormone (LH)	
Esterone-3-glucuronide	**Microalbumin**	

oversight, and the findings of serious quality problems in investigations of the waived laboratories, CMS initiated a pilot study consisting of on-site inspections. The results of expanded pilot study confirmed that: a) 32% of these laboratories failed to have current manufacturer's instructions, b) 32% didn't perform QC as required, and c) 16% failed to follow current manufacturer's instructions (CSM fact sheet, Visiting CLIA, Certificate of Waiver Laboratories). Strategies for error prevention and error monitoring have been developed [3]. The National Academy of Clinical Biochemistry together with the College of American Pathologists and the American Society for Microbiology has developed evidence-based guidelines for PoCT [4, 5]. The European Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for ensuring that medicines and medical devices work, and are acceptably safe (http://www.mhra.gov.uk/). MHRA's Guidance on the vigilance system for CE-marked medical devices is supplementary to the European Commission Guidelines on a Medical Device Vigilance System (http://ec.europa.eu/consumers/medical_devices/meddev/) and the MHRA's Directives Bulletin 3 – Guidance on the operation of the EU vigilance system in the UK. Indeed, PoCT can improve prognosis and decrease mortality when performed correctly according to guidelines [6]. The effect of PoCT on length of stay in the emergency departments varied between settings, particularly contributed by brain-to-brain time, i.e. the time from the physician order of a laboratory test until the time the physician receives and interprets the results [7]. Other requirements in the PoCT context that are doubtfully satisfied also include test low-cost, stability during storage, and lot-to-lot reproducibility of results. Few studies have systematically analysed cost effectiveness of PoCT with contrasting results probably due to the fact that it varies according to the disease group and the type of test [6, 8-9]. An Australian randomised controlled trial (PoCT Trial) has been funded to determine the safety, clinical effectiveness, cost effectiveness and satisfaction of PoCT in a general practice setting [10]. The effect of adverse storage conditions on PoCT test systems and reagent strips as well as variability among lots have been evaluated and can contribute to poor analytical quality [11, 12]. In conclusion, the literature does not consistently confirm many of the presumed qualities and benefits of PoCT. However, some evidence supports its role in improving glycaemic control, lipid levels, and oral anticoagulant therapy safety (in this case, as long as continuity of INR estimation by location and method is maintained for individual patients) [6, 8, 13-18].

POINT OF CARE TESTING FOR THE SCREENING AND MANAGEMENT OF DIABETES MELLITUS

Prevention and management strategies are crucial to address the problem of chronic diseases: the population-based

approach focuses on health promotion activities, while the individual approach focuses on high-risk (primary prevention) or affected (secondary prevention) individuals through direct interventions (www.paho.org/english/gov/ce/ce142-09-e.pdf). PoCT may have a useful role in primary and secondary prevention of chronic metabolic diseases, such as in screening for diabetes risk, screening or monitoring treatment of dyslipidemias. PoCT is even more useful in the prevention, detection, and treatment of diabetes-related acute and chronic complications through monitoring glucose, haemoglobin A1c, ketones, lipid profiles, and urinary microalbumin concentrations [19]. Moreover, PoCT has been found to have a positive impact on the process of care in the management of patients with diabetes. Immediacy and convenience promote face-to-face communication between patients and health care providers so to reinforce patient education [20]. Below is an overview of current state-of-the-art of PoCT technology in diabetes care, recommendations and limitations for its clinical application.

Portable Glucose and A1c Meters

Diabetes mellitus is a chronic disease requiring a multidisciplinary and integrated team approach to reduce the risk of long-term complications. One of treatment goal is maintaining a tight glycaemic control through continuing medical care and patient self-monitoring/management [21]. Self-monitoring of blood glucose (SMBG) and A1c measurement are the primary techniques available to assess the effectiveness of the management plan on glycaemic control. SMGB has replaced semiquantitative urine glucose testing that is no more recommended for routine care of subjects with diabetes mellitus [22]. SMGB frequency and timing should be dictated by patient's needs and goals. Recommended glycaemic targets for adults with diabetes are the following: preprandial capillary plasma glucose 70-130 mg/dL and peak postprandial capillary plasma glucose <180 mg/dL in accordance with the American Diabetes Association (ADA) [21], whereas <110 mg/dL and <140 mg/dL, respectively, in accordance with the International Diabetes Federation (IDF) (http://www.idf.org/). According to guidelines [22], the imprecision of glucometers together with the substantial differences among meters precludes their use in the diagnosis of diabetes and limits their usefulness in screening for diabetes and monitoring of blood glucose [13]. Indeed, even though SMBG is instrument and user dependent [22], it is considered a component of effective therapy, especially in insulin-treated diabetic patients. Most presently marketed glucose meters work with electro-chemical methods (rather than reflectance technology) where glucose-oxidase (GOx) measurements are converted into electrical signals. The GOx enzyme (EC 1.1.3.4) catalyses the oxidation of β-D-glucose to D-glucono-1,5-lactone in the presence of the cofactor flavin adenine dinucleotide (FAD). FAD is reduced to $FADH_2$ that is then oxidised by molecular oxygen to final hydrogen peroxide. A GOx electrode detector measures the charge resulting from the electrons passed through the enzyme.

As detailed in MHRA's sheet "Blood glucose meters" and documented in literature [23-31], there are many contraindications and interferences that may affect the near patient glucose analysis, such as dialysis treatment, peripheral circulatory failure, severe dehydration, variations in blood oxygen tension, high concentrations of non-glucose reducing substances in the blood (ascorbic acid), high bilirubin values, extremes of haematocrit, hyperlipidaemia, improper application, timing, environmental temperature and humidity. Moreover, accuracy decreases at very high or very low glucose concentrations. Correlation to plasma hexokinase values and haematocrit interference are the main variables that differentiate glucose meters (Fig. (**1**)). Meters that correlate with plasma glucose measured by a reference method over a wide range of glucose concentrations and minimize the effects of haematocrit will allow better glycemic control for critically ill patients [23]. Between-lot differences ranging from 0.7% to 18.2% have been observed and may result in differences between day-to-day results. Therefore, the validation of new lots of reagent strips with a laboratory method is recommended [24]. Although some glucose meters have substantial systematic bias when compared with a hexokinase method, the majority of commonly used meters are sufficiently precise. However, precision varies at extremely high or low glucose concentrations. Since analytical performance varied over the physiological range of glucose values, separate accuracy and precision goals should be defined for hypoglycemic, normoglycemic, and hyperglycemic ranges [29]. Environmental conditions may affect the precision and accuracy of glucose meters. Thus, elevation, temperature, and relative humidity affect blood glucose meter performance, and elevated glucose levels are more greatly underestimated at higher elevations [30].

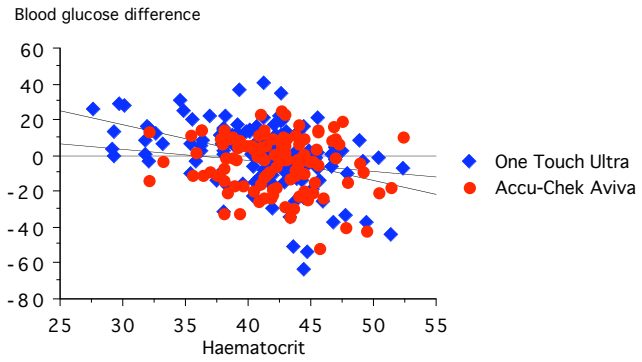

Fig. (1). Impact of haematocrit (x axis) on the absolute difference between blood glucose measurements made using two glucose meters (One Touch Ultra, Lifescan, and Accu-Chek Aviva, Roche Diagnostics) on the market and the reference laboratory method.

Among the multiple analytical goals proposed for the performance of glucose meters, following the Diabetes Control and Complications Trial (DCCT), the ADA recommended a hardly achievable goal for total error of <5%. None of four new fast acting devices reached the ADA criteria of a 100% of readings within a 5% deviation limit [25]. Obviously, testing of blood glycaemia under controlled conditions does not necessarily reflect the quality of the measurements obtained in the hands of ordinary patients. Indeed, the analytical quality of SMBG among patients was poorer than, and could not be predicted from, the performance of the meters in the hands of a technician [31]. Optical and

electric technologies for noninvasive glycaemia monitoring would have a great impact on diabetes management and are rapidly evolving, but need further assessment [32]. The combination of results of SMBG testing and the A1c best judge glycaemic control [21]. Measurement of glycated haemoglobin is an index of long-term (120 days) glycaemic status and a measure of risk for the development of diabetes complications. ADA standards of medical care in diabetes recommend a treatment goal of HbA1c less than 7% for adults with diabetes, while target level <6.5% has been set by IDF. The frequency of HbA1c testing is dependent on the clinical situation and can vary from twice per year to every 2-3 months. Laboratories should use only assay methods certified by the National Glycohemoglobin Standardization Program (NGSP) and participate in proficiency-testing programs [22]. Laboratory methods quantify glycated haemoglobin based either on charge differences (cation-exchange chromatography) or on structural differences (boronate affinity chromatography and immunoassay) between glycated and nonglycated components. Intereassay coefficient of variation (CV) should be lower than 5%; ideally intralaboratory CV should be <3% and interlaboratory <5%. PoCT A1c testing platforms use various technologies: boronate affinity chromatography, immunoassay, or micro-optical detection methods (MODM). MODM technology incorporates immunoassay and chemistry technology to measure A1c and total haemoglobin by using a hand held monitor and single-use test cartridge; it received NGSP certification and external control materials are available. Small bench top A1c analysers have achieved a performance comparable with the HPLC assay [14] with a minimum within-site imprecision [33] (Fig. (**2**)). Hand held devices provided average A1c values in agreement with corresponding central laboratory values but with a large dispersion of individual determinations [34]. The repeatability for HbA1c was within 59% CV [35]. A large, retrospective cross-sectional study evidenced that availability of PoCT A1c improves patient's glycaemic control not only in the short term, but also in the longer term with a strong time-by-site interaction in favour of specialised centers [14-15].

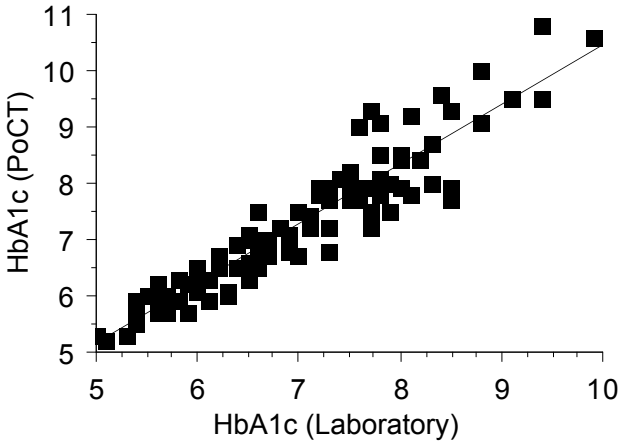

Fig. (2). Comparison between HbA1c levels measured by a PoCT system (Metrika A1c Now) and the laboratory ion-exchange chromatography on HLC-723 G7 analyser, TOSOH Bioscience.

Ketone Bodies Determination

Total serum ketone bodies are usually less than 0.5 mMol/L: β-hydroxybutyrate (βHBA) and acetoacetate (AcAc) are present in equimolar amounts, whereas acetone - derived from AcAc decarboxylation -is present in small quantities. βHBA increases in those conditions that affect the redox equilibrium of hepatic mitochondria, such as diabetic ketoacidosis. Since ketoacidosis is a cause of mortality and morbidity associated with diabetes, its prevention must be pursued. People with type 1 diabetes are advised to measure urine or blood ketones in the presence of hyperglycaemia before beginning vigorous activity as well as in any intercurrent illness leading to deterioration of glycaemic control [21]. It has been proposed that a diabetic patient with capillary blood glucose > 250 mg/dL and capillary blood ketone bodies exceeding 0.5 mmol/L requires therapeutic management; for values greater than 3 mmol/L or in case of more serious clinical symptoms, hospitalisation is indicated [36]. In the hospital setting, health care providers should measure ketones in all cases of combined hyperglycaemia and acute clinical conditions. Moreover, ketone determinations should be used to diagnose and monitor the course of ketoacidosis, when capillary blood βHBA should fall by 1 mMol/L per hour with optimal treatment [37]. Common dipsticks and tablets to measure ketones in the urine or blood are based on the reaction between ketones and nitroprusside that provides a semi-quantitative estimate only of AcAc or AcAc plus acetone (if the reagent contains glycine), but do not register the presence of βHBA. Hand held meters use dry-chemistry test strips to measure enzymatically blood concentration of βHBA. In the presence of NAD , β-hydroxybutyrate dehydrogenase converts βHBA to AcAc and NADH, which is reoxidised to NAD by a redox mediator and the current generated was proportional to the βHBA concentration [22]. Urinary tests with nitroprusside carry a lower cost than electrochemical strips for capillary blood ketone body determination whose use has been limited to populations at specific risk of ketoacidosis.

Hand held ketone sensor gave accurate and precise results comparable with the reference method [38]. In diagnosing diabetic ketoacidosis among uncomplicated cases, serum ketone measured by nitroprusside reaction and blood βHBA measured by blood ketone meter had similar sensitivity and specificity [39]. Capillary blood βHBA determination is not subject to interference from sulfhydryl-containing drugs or ascorbic acid [22].

Fasting Lipid Profile

The National Cholesterol Education Program (NCEP) recommends that all adults aged 20 years and over have their blood cholesterol checked at least once every 5 years (http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm). The risk of cardiovascular disease (CVD) is heightened in diabetic population, but primary and secondary prevention of CVD events and coronary hearth deaths by lipid-lowering therapy has been demonstrated to be effective. A comprehensive diabetes evaluation includes fasting lipid profile, i.e. total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol and triglycerides. In most adult diabetic patients, fasting lipid profile should be measured at

least annually or every 2 years in case of low risk profile (LDL cholesterol <100 mg/dL, HDL cholesterol >50 mg/dL, and triglycerides <150 mg/dL) [21]. The Cholesterol Reference Method Laboratory Network (CRMLN) certifies manufacturers or clinical diagnostic products that measure total cholesterol, HDL cholesterol, and LDL cholesterol according to the NCEP guidelines [40]. Total error is calculated as the sum of percent bias and 1.96 total CV; percent bias is the mean difference between measured value and reference value, expressed as a percent of the reference value, and total CV includes within-run and among run variation. Analytical goals for the total error of lipid measurements are as follows: ≤8.9% for total cholesterol, ≤12% for LDL cholesterol, ≤13% for HDL cholesterol, and ≤15% for triglycerides. The CRMLN laboratories use reference methods or designated comparison methods that are standardised to the Centers for Disease Control and Prevention reference methods (http://www.cdc.gov/labstandards/crmln.html). PoCT technology is becoming popular for lipid profiling and screening. Portable devices usually combine enzymatic methodology and solid-phase technology. Cholesterol and its fatty acid esters in blood can be quantified using dry analytical elements with co-immobilised enzymes. The enzyme cholesterol esterase catalyses the hydrolysis of cholesterol ester to cholesterol and fatty acid anion. In turn, cholesterol oxidase catalyses the oxidation of cholesterol to cholesterol-4-en-3-one and hydrogen peroxide [41]. Finally, a peroxidase-mediated reaction converts a chromogen into a dye that is read by the analyser using reflectance photometry; alternatively, amperometric biosensors are based on electrochemical entrapment technique and measurement of the amperometric response. The same enzymatic reaction measures HDL cholesterol using dry analytical elements that comprise one or more reagent layers containing a non-HDL lipoprotein precipitant and/or a HDL selective surfactant, which confer HDL selectivity on the assay [42]. Multi-chemistry diagnostic test strips usually calculate LDL cholesterol using the Friedewald formula: LDL cholesterol = total cholesterol – HDL cholesterol – triglycerides/5. However, whole-blood direct quantitative determination of LDL cholesterol is also possible taking advantage of surfactant-lipoprotein interactions and differing surface charge density of the LDL and non-LDL lipoproteins in a sample [43]. The enzyme lipoprotein lipase catalyses the hydrolysis of tryglycerides to glycerol and three fatty acids; glycerol kinase catalyses the transfer of a phosphate from ATP to glycerol thus forming glycerol-3-phosphate that, in turn, is converted by the enzyme glycerophosphate oxidase to dihydroxyacetone-phosphate and hydrogen peroxide for the final colour reaction. Unfortunately, both bench top analysers and hand held single use devices do not meet all of the NCEP guidelines [13, 44-47]. Haematocrit still interferes with analysis by PoCT systems (Fig. (**3**)). The Cholestech LDX met the NCEP goals for total error for all analytes except LDL cholesterol [47]; the significant variability in lipid determinations limited the clinical usefulness of this desktop analyser especially because 2 SD of the mean bias between the laboratory and the portable determinations of LDL cholesterol exceeded the cut off that defines treatment goals [44]. Although the Reflotron met most of the NCEP guidelines for accuracy, the portable analyser provided clinically relevant underestimations of total cholesterol values, especially for the lower and upper values [46]. The portable CardioCheck PA system met the NCEP goals for total error for triglyceride but not for other lipid analytes [47]. Thus, lipid values obtained from portable lipid analysers cannot be used to make clinical decisions regarding the diagnosis and management of lipid disorders in individual patients [13, 44-47].

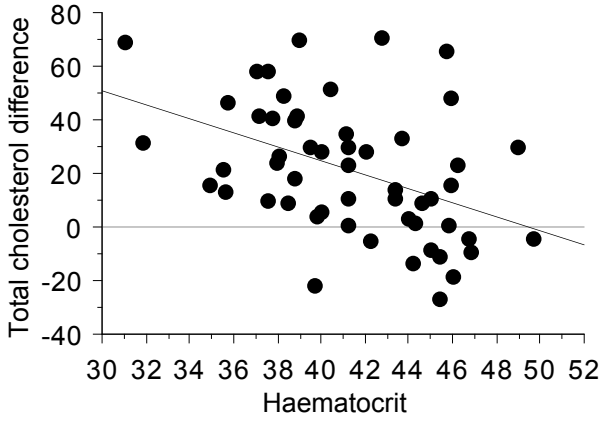

Fig. (3). Impact of haematocrit (x axis) on the absolute difference between blood total cholesterol measurements made using one commercial PoCT device (the PTS PANELS Lipid Panel Strips run on the CardioChek PA system) and the laboratory method.

Urinary Albumin

Diabetic nephropathy is the single leading cause of end-stage renal disease and occurs in up to 40% of patients with diabetes. However, optimised glucose and blood pressure control can reduce the risk and slow the progression of diabetic nephropathy. Small increases in urinary albumin excretion, undetectable by conventional qualitative tests, have been recognised as an early sign of diabetic nephropathy. Microalbuminuria is defined as a urinary albumin excretion rate (UAER) of 20-200 μg/min on two of three consecutive timed urine collections (or a spot urinary albumin/creatinine ratio, ACR, of 30-300 μg/mg creatinine). Overt nephropathy or macroalbuminuria corresponds to UAER >200 μg/min (or a ratio >300 μg/mg). Because of variability in urine albumin excretion, the diagnosis requires that two of three specimens collected within a 3-to 6-month period are abnormal. Testing for serum creatinine and urine albumin excretion with spot urine ACR should be performed at least annually in type 1 diabetic patients with diabetes duration of ≥5 years and in all type 2 diabetic patients, starting at diagnosis [21]. Screening for microalbuminuria can be performed by measurement of the albumin-to-creatinine ratio in a random spot collection (preferred method). Measurement of a spot urine for albumin only, whether by immunoassay or by using a dipstick test specific for microalbumin, without simultaneously measuring urine creatinine, is susceptible to false-negative and positive determinations [21]. Taking into account the large within-person day-to-day variation of albumin excretion, the analytical CV of methods to assay microalbuminuria has been proposed <15%. Guidelines recommend that semiquantitative or qualitative screening tests for microalbuminuria should have a high clinical sensitivity (being positive in

more than 95% of patients with microalbuminuria) to be useful for screening. Accredited laboratories using quantitative methods must confirm positive results. The ability of PoCT devices to detect microalbuminuria with the required clinical sensitivity has not been confirmed by published studies and resulted user-dependent [22]. Bench top analysers measure urine creatinine by colorimetry and urine albumin using an immunoturbidimetric reaction with anti-albumin antibodies; the turbidity created by the antigen-antibody complex is measured photometrically. Sensitivity and specificity for microalbuminuria diagnosis were found 92% and 98%, respectively (positive and negative predictive values 92 and 98%, respectively) [48]. Some semi-quantitative reagent strips for determining albumin and creatinine in urine are based on chemical principles. Albumin test may be based on dye binding using a high affinity sulfonephthalein dye; creatinine test is based on the peroxidase-like activity of a copper-creatinine complex that catalyses the reaction of diisopropylbenzene dihydroperoxide and 3,3',5,5'-tetramethylbenzidine. In large studies, this type of strips showed a sensitivity of 79% and a specificity of 81% (poor positive predictive value of 46%, excellent negative predictive value of 95%) [49]. Other qualitative dipsticks are optically read immunoassays using a conjugate of albumin antibody and β-galactosidase. These dipsticks gave a sensitivity of 88% and a specificity of 80% (positive predictive value 69%, negative predictive value 92%) [50].

CONCLUDING REMARKS

Assessing modifiable risk factors for metabolic and cardiovascular diseases prior to the onset of disease could allow effective prevention initiatives. The PoCT technology offers convenient aspects: immediate results, decision-making without the need for repeated visits, use of fingerstick blood samples. Thus, easily accessible PoCT could help screening, diagnosis, and monitoring efforts in several clinical settings. However, PoCT devices did not achieve optimum performance; their accuracy and precision are often not sufficient to ensure reliable measurements so to recommend their large-scale use in the absence of effective strategies for error prevention.

REFERENCES

[1] Ehrmeyer, S.S.; Laessig, R.H. Point-of-care testing, medical error, and patient safety: a 2007 assessment. *Clin. Chem. Lab. Med*., **2007**, *45*, 766-73.

[2] Kost, G.J.; Louie, R.F.; Tang, Z.; Lee, J.H.; Somsanith, K.J.; Tran, N.K. Reducing potential medical errors in point-ofcare testing. Clinical effects of heparin and EDTA on handled glucose meter results. *Point Care*. **2002**, *1*, 2-8.

[3] Meier, F.A.; Jones, B.A. Point-of-care testing error: sources and amplifiers, taxonomy, prevention strategies, and detection monitors. *Arch. Pathol. Lab. Med*., **2005**, *129*, 1262-7.

[4] Nichols, J.H.; Christenson, R.H.; Clarke, W.; Gronowski, A.; Hammett-Stabler, C.A.; Jacobs, E.; Kazmierczak, S.; Lewandrowski, K.; Price, C.; Sacks, D.B.; Sautter, R.L.; Shipp, G.; Sokoll, L.; Watson, I.D.; Winter, W.; Zucker, M.L.; National Academy of Clinical Biochemistry. Executive summary. The National Academy of Clinical Biochemistry Laboratory Medicine Practice Guideline: evidence-based practice for point-of-care testing. *Clin. Chim. Acta*, **2007**, *379*, 14-28.

[5] Sautter, R.L.; Lipford, E.H. Point-of-Care testing: guidelines and challenges. *N.C. Med. J.*, **2007**, *68*, 132-5.

[6] Price, C.P. Point of care testing. *Br. Med. J.*, **2001**, *322*, 1285-8.

[7] Ryan, R.J.; Lindsell, C.J.; Hollander, J.E.; O'Neil, B.; Jackson, R.; Schreiber, D.; Christenson, R.; Gibler, W.B. A multicenter randomized controlled trial comparing central laboratory and point-of-care cardiac marker testing strategies: the Disposition Impacted by Serial Point of Care Markers in Acute Coronary Syndromes (DISPO-ACS) trial. *Ann. Emerg. Med*., **2009**, *53*, 321-8.

[8] Grieve, R.; Beech, R.; Vincent, J.; Mazurkiewicz, J. Near patient testing in diabetes clinics: appraising the costs and outcomes. *Health Technol. Assess.*, **1999**, *3*, 1-74.

[9] Parry, D.; Fitzmaurice, D.; Raftery, J. Anticoagulation management in primary care: a trial-based economic evaluation. *Br. J. Haematol*., **2000**, *111*, 530-3.

[10] Laurence, C.; Gialamas, A.; Yelland, L.; Bubner, T.; Ryan, P.; Willson, K.; Glastonbury, B.; Gill, J.; Shephard, M.; Beilby, J. for members of the PoCT Trial Management Committee. A pragmatic cluster randomised controlled trial to evaluate the safety, clinical effectiveness, cost effectiveness and satisfaction with point of care testing in a general practice setting -rationale, design and baseline characteristics. *Trials*, **2008**, *9*, 50.

[11] Bamberg, R.; Schulman, K.; MacKenzie, M.; Moore, J.; Olchesky, S. Effect of adverse storage conditions on performance of glucometer test strips. *Clin. Lab. Sci*., **2005**, *18*, 203-9.

[12] Kristensen, G.B.B.; Christensen, N.G.; Thue, G.; Sandberg, S. Between-lot variation in external quality assessment of glucose: clinical importance and effect on participant performance evaluation. *Clin. Chem*., **2005**, *51*, 1632-6.

[13] Shephard M.D.; Mazzachi, B.C.; Shephard, A.K.; McLaughlin, K.J.; Denner, B.; Barnes, G. The impact of point of care testing on diabetes services along Victoria's Mallee Track: results of a community-based diabetes risk assessment and management program. *Rural Remote Health*., **2005**, *5*, 371.

[14] Cagliero, E.; Levina, E.V.; Nathan, D.M. Immediate feedback of HbA1c levels improves glycemic control in type 1 and insulin-treated type 2 diabetic patients. *Diabetes Care*, **1999**, *22*, 1785-9.

[15] Petersen, J.R.; Finley, J.B.; Okorodudu, A.O.; Mohammad, A.A.; Grady, J.J.; Bajaj, M. Effect of point-of-care on maintenance of glycemic control as measured by A1C. *Diabetes. Care*, **2007**, *30*, 713-5.

[16] Rink, E.; Hilton, S.; Szczepura, A.; Fletcher, J.; Sibbald, B.; Davies, C.; Freeling, P.; Stilwell, J. Impact of introducing near patient testing for standard investigations in general practice. *Br. Med. J*, **1993**, *307*, 775-8.

[17] Fitzmaurice, D.A.; Hobbs, F.D.R.; Murray, E.T.; Holder, R.L.; Allan, T.F.; Rose, P.E. Oral anticoagulation management in primary care with the use of computerized decision support and near-patient testing: a randomized, controlled trial. *Arch. Int. Med*., **2000**, *160*, 2343-8.

[18] Fitzmaurice, D.A.; Murray, E.T.; Allan, T.F.; Holder, R.L.; Hobbs, F.D.R.; Rose, P.E.; Hobbs, F.D.R. A comparison of international normalised ratio (INR) measurement in hospital and general practice settings: evidence for lack of standardisation. *J. Clin. Pathol*., **2000**, *53*, 803-6.

[19] Krentz, A.J.; Olufadi, R.; Byrne, C.D. In *Point of care testing*, second edition; Price C.P.; St. John, A.; Hicks, J.M., Eds.; AACC Press: Washington, D.C., **1999**; pp. 309-22.

[20] Brown, J.B.; Harris, S.B.; Webster-Bogaert, S. Point-of-Care Testing in Diabetes Management: What Role Does It Play? *Diabetes Spectrum*, **2004**, *17*, 244-8.

[21] American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*, **2011**, *34*, S11-S61.

[22] Sacks, D.B.; Bruns, D.E.; Goldstein, D.E.; Maclaren, N.K.; McDonald, J.M.; Parrott, M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin. Chem.*, **2002**, *48*, 436-72.

[23] Karon, B.S.; Griesmann, L.; Scott, R.; Bryant, S.C.; Dubois, J.A.; Shirey, T.L.; Presti. S.; Santrach, P.J. Evaluation of the impact of hematocrit and other interference on the accuracy of hospital-based glucose meters. *Diabetes Technol. Ther*., **2008**, *10*, 111-20.

[24] Solnica, B.; Naskalski, J.; Gernand, W. Analytical evaluation of the Optium Xido blood glucose meter. *Clin. Chem. Lab. Med*., **2008**, *46*, 143-7.

[25] Weitgasser, R.; Hofmann, M.; Gappmayer, B.; Garstenauer, C. New, small, fast acting blood glucose meters--an analytical laboratory evaluation. *Swiss Med. Wkly*., **2007**, *137*, 536-40.

[26] Diabetes Research in Children Network (DirecNet) Study Group. Relative accuracy of the BD Logic and FreeStyle blood glucose meters. *Diab. Technol. Ther*., **2007**, *9*, 165-8.

[27] Bilen, H.; Kilicaslan, A.; Akcay, G.; Albayrak, F. Performance of glucose dehydrogenase (GDH) based and glucose oxidase (GOX) based blood glucose meter systems at moderately high altitude. *J. Med. Eng. Technol*., **2007**, *31*, 152-6.

[28] Arabadjief, D.; Nichols, J.H. Assessing glucose meter accuracy. *Curr. Med. Res. Opin*., **2006**, *22*, 2167-74.

[29] Chen, E.T.; Nichols, J.H.; Duh, S.H.; Hortin, G. Performance evaluation of blood glucose monitoring devices. *Diabetes Technol. Ther*., **2003**, *5*, 749-68.

[30] Fink, K.S.; Christensen, D.B.; Ellsworth, A. Effect of high altitude on blood glucose meter performance. *Diabetes Technol. Ther*., **2002**, *4*, 627-35.

[31] Skeie, S.; Thue, G.; Nerhus, K.; Sandberg, S. Instruments for self-monitoring of blood glucose: comparisons of testing quality achieved by patients and a technician. *Clin. Chem*., **2002**, *48*, 994-1003.

[32] Tura, A. Noninvasive glycaemia monitoring: background, traditional findings, and novelties in the recent clinical trials. *Curr. Opin. Clin. Nutr. Metab. Care*., **2008**, *11*, 607-12.

[33] Shephard, M.D.; Gill, J.P. The Analytical Quality of Point-of-Care Testing in the 'QAAMS' Model for Diabetes Management in Australian Aboriginal Medical Services. *Clin. Biochem. Rev*., **2006**, *27*, 185-90.

[34] Kennedy, L.; Herman, W.H.; GOAL A1C Study Team. Glycated hemoglobin assessment in clinical practice: comparison of the A1cNow point-of-care device with central laboratory testing (GOAL A1C Study). *Diabetes Technol. Ther*., **2005**, *7*, 907-12.

[35] Stivers, C.R.; Baddam, S.R.; Clark, A.L.; Ammirati, E.B.; Irvin, B.R.; Blatt, J.M. A miniaturized self-contained single-use disposable quantitatitve test for hemoglobin A1c in blood at the point of care. *Diabetes Technol. Ther*., **2000**, *2*, 51726.

[36] Guerci, B.; Tubiana-Rufi, N.; Bauduceau, B.; Bresson, R.; Cuperlier, A.; Delcroix, C.; Durain, D.; Fermon, C.; Le Floch, J.P.; Le Devehat, C.; Melki, V.; Monnier, L.; Mosnier-Pudar, H.; Taboulet, P.; Hanaire-Broutin, H. Advantages to using capillary blood beta-hydroxybutyrate determination for the detection and treatment of diabetic ketosis. *Diabetes Metab*., **2005**, *31*, 401-6.

[37] Wallace, T.M.; Matthews, T.R. Recent advances in the monitoring and management of diabetic ketoacidosis. *Q. J. Med*., **2004**, *97*, 773-80.

[38] Byrne, H.A.; Tieszen, K.L.; Hollis, S.; Dornan, T.L.; New, J.P. Evaluation of an electrochemical sensor for measuring blood ketones. *Diabetes Care*, **2000**, *23*, 500-3.

[39] Tantiwong, P.; Puavilai, G.; Ongphiphadhanakul, B.; Bunnag, P.; Ngarmukos, C. Capillary blood beta-hydroxybutyrate measurement by reagent strip in diagnosing diabetic ketoacidosis. *Clin. Lab. Sci*., **2005**, *18*, 139-44.

[40] National Cholesterol Education Program. Recommendations on lipoprotein measurement. *NIH Publication No. 953044*, **1995**.

[41] Singh, S.; Chaubey, A.; Malhotra, B.D. Amperometric cholesterol biosensor based on immobilized cholesterol esterase on conducting polypyrrole films. *Anal. Chim. Acta*, **2004**, *502*, 229-34.

[42] Yamada, T.; Nishino, S.; Takubo, T.; Hino, M.; Kitagawa, S.; Tatsumi, N. Simple high-density lipoprotein cholesterol assay based on dry chemistry. *Clin. Chim. Acta*, **2002**, *320*, 78-88.

[43] Okada, M.; Matsui, H.; Ito, Y.; Fujiwara, A.; Inano, K. Low-density lipoprotein cholesterol can be chemically measured: a new superior method. *J. Lab. Clin. Med*., **1998**, *132*, 195-201.

[44] Stein, J.H.; Carlsson, C.M.; Papcke-Benson, K.; Einerson, J.A.; McBride, P.E.; Wiebe, D.A. Inaccuracy of lipid measurements with the portable Cholestech L.D.X analyzer in patients with hypercholesterolemia. *Clin Chem*., **2002**, *48*, 284-90.

[45] Taylor, J.R.; Lopez, L.M. Cholesterol: point-of-care testing. *Ann. Pharmacother*., **2004**, *38*, 1252-7.

[46] Bowden, R.G.; Kingery, P.M., Long, L. Precision of a dry-chemistry method of lipid screening. *Public Health*., **2006**, *120*, 572-6.

[47] Shephard M.D.; Mazzachi, B.C.; Shephard, A.K. Comparative performance of two point-of-care analysers for lipid testing. *Clin. Lab*., **2007**, *53*, 561-6.

[48] Sarafidis, P.A.; Riehle, J.; Bogojevic, Z.; Basta, E.; Chugh, A.; Bakris, G.L. A comparative evaluation of various methods for microalbuminuria screening. *Am. J. Nephrol*., **2008**, *28*, 324-9.

[49] Le Floch, J.P.; Marre, M.; Rodier, M.; Passa, P.H. Interest of Clinitek Microalbumin in screening for microalbuminuria: results of a multicentre study in 302 diabetic patients. *Diabetes Metab*., **2001**, *27*, 36-9.

[50] Parikh, C.R.; Fischer, M.J.; Estacio, R.; Schrier, R.W. Rapid microalbuminuria screening in type 2 diabetes mellitus: simplified approach with Micral test strips and specific gravity. *Nephrol. Dial. Transplant.*, **2004**, *19*, 1881-5.

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