HbA1c POCT IN DIABETES MANAGEMENT

POINT-OF-CARE TESTING FOR HbA1c – A POSSIBILITY FOR IMPROVED DIABETES CARE

DIABETES IS A MAJOR HEALTH CONCERN BUT CAN BE MANAGED

The prevalence of diabetes is rising rapidly worldwide. In 1980, 108 million people suffered from diabetes. In 2017, the number had increased almost four-fold to 425 million and by 2045, 629 million people are estimated to be diabetic. It is a serious and life-long condition that, if not properly managed, increases the risk for diabetes related complications. In 2016, 1.6 million deaths worldwide were directly caused by diabetes. An additional number of deaths are associated with the complications. In 2012 this accounted for 2.2 million deaths. In addition to the suffering from poor health, diabetes places a tremendous financial burden on both patients and health care system.

Type 2 diabetes is by far the most common type of diabetes, accounting for around 90% of all cases. Traditionally type 2 diabetes is diagnosed in older adults, but is now seen more often also in younger adults and even in children. Being overweight or obese are strong risk factors, as is physical inactivity. An growing number of people adopt to a western lifestyle increasing their exposure to these risk factors. Diabetes prevalence is now rising more rapidly in middle- and low-income countries.

Long-term hyperglycemia is a significant risk for developing diabetes complications. These include loss of vision, renal failure, cardiovascular events, sensory neuropathy and microvascular complications. Diabetes is now a leading cause of blindness, kidney failure, heart attack, stroke and lower limb amputation. There are thus strong reasons to efficiently diagnose and monitor diabetes. With long term follow-up and compliance to treatment goals, diabetes can be controlled and its consequences avoided or delayed.

A growing number of people are diagnosed with diabetes. Prevalence is now increasing more rapidly in middle- and low-income countries. There is thus a need for efficient methods for diagnosis and monitoring of diabetes. With good glycemic control the serious complications and associated suffering and costs, can be delayed or avoided.

HbA1c IS THE RECOMMENDED BIOMARKER FOR DIAGNOSIS AND MONITORING OF DIABETES

Traditionally, diabetes has been diagnosed by measuring fasting plasma glucose. In 2009, however, an International Expert Committee stated that highly standardized assays for glycosylated hemoglobin (HbA1c) were available, and they instead recommended HbA1c testing for diabetes diagnosis with a threshold of $\geq$ 6,5% (International Expert Committee, 2009). HbA1c has several advantages over fasting plasma glucose. One is that it reflects the average blood glucose levels over the past 2 to 3 months and is therefore not sensitive to day-to-day variations caused by stress

or illness. Another advantage is that it does not require fasting prior to testing.

HbA1c has played a key role as biomarker for long term glycemic control in diabetes management since it was introduced in clinical practice in the 1970s. In addition to its advantages over fasting plasma glucose it also correlates well with the risk for diabetes complications. In a prospective observational study on patients with diabetes type 2 it was shown that for each 1% reduction in mean HbA1c there are risk reductions of 21% for any endpoint or death related to diabetes. The risk reduction for microvascular complication was even greater: 37%. No threshold was found meaning the lower the blood glucose, the lower the risk for complications. The authors conclude that any reduction in HbA1c is likely to decrease the risk for complications with the lowest risk in those with HbA1c in the normal range < 6.0% (Stratton et al, 2000). There is thus a lot to gain to keep blood sugar levels at an appropriate level. However, that seems easier said than done.

HbA1c is the recommended biomarker for diagnosing diabetes. It does not require fasting and is insensitive to day-to-day variations caused by stress or illness. It reflects glycemic levels over the past 2 to 3 months.

GLYCEMIC CONTROL IS A MAJOR CHALLENGE IN DIABETES

Glycemic control in diabetes patients has been shown to be a major challenge. Only six of ten patients meet their individual target for HbA1c (Ali et al, 2014). There are probably several reasons for this. The patient may for example not adhere to his or her diabetes care plan or the treatment is not aggressive enough to reach glycemic control. Given the importance of long term glycemic control in preventing complications HbA1c testing on a regular basis is recommended. The American Diabetes Association recommends that HbA1c testing should be performed at least twice a year in patients who meet treatment goals and have a stable glycemic control. For patients who are not meeting glycemic goals or have had a change in their therapy HbA1c testing is recommended quarterly (ADA, 2016).

Considering the difficulty in achieving good glycemic control in diabetic patients, efforts should be made to overcome any avoidable obstacles on the path to reaching the treatment goals. One thing to look into is the testing procedure. With traditional laboratory testing, the physician decides what tests to be taken when seeing the patient and sends him or her to the laboratory to be tested. It is only when the results are sent to the doctor's office that the decision to make any treatment changes can be taken. In many clinics the "new" HbA1c result is reviewed only when the patient comes for the next revision 1 to 6 months later (Pillay et al, 2019). If testing is instead done point of care (POCT) this delay is avoided.

POCT is defined as laboratory testing performed by non-laboratory personnel outside the clinical laboratory at the bedside or near the site of clinical care delivery. HbA1c POCT in diabetes management is now recommended by the American Diabetes Association since it provides the opportunity for more timely treatment changes (ADA, 2016).

Only six out of ten diabetes patients meet their individual target for HbA1c. One reason may be a delay in treatment escalation while waiting for the patient's next appointment at the office. The American Diabetes Association recommends HbA1c POCT in diabetes management.

STRONG EVIDENCE FOR POSITIVE EFFECTS ON GLYCEMIC CONTROL WITH POCT

Rust et al (2008) identified at least nine discretionary steps in the traditional care process with laboratory testing where a failure by any participant, patient or

care provider, could result in a missed opportunity to improve glycemic control. Reducing the number of steps before the physician has the opportunity to sit face-to-face with a patient whose HbA1c levels are elevated is desirable and has been shown to significantly decrease HbA1c levels. When testing is performed point of care, any changes in treatment can be taken and discussed with the patient within minutes after the test result has become available.

A positive effect on glycemic control has been shown in several studies in different settings (Schnell et al, 2017). In one primary care setting there was a significant mean decrease in HbA1c levels 6 months post implementation of POCT as compared to 6 months pre implementation (Eigbunke and Gerard, 2013). Similarly, patients with type 2 diabetes attending a diabetes clinic at a regional-level hospital in South Africa, significantly improved their glycemic control from baseline to follow-up three months later when they were tested point of care. No such improvement was seen in the group tested at the laboratory (Pillay et al, 2019). In patients with type 1 or 2 diabetes attending the Massachusetts General Hospital Diabetes Center, a group tested point of care had significantly lowered their HbA1c levels at the 6 month-follow up, with the effect persisting at 12 months. The patients who had had traditional laboratory testing did not change their HbA1c levels (Cagliero et al, 1999). Even after 3.5 years, an effect of POCT on improved HbA1c levels, was detected in a large, retrospective cross-sectional study on 16 000 patients attending a diabetes centre in Texas, US (Petersen et al, 2007).

The introduction of POCT has been shown to be associated with more appropriate diabetes management. Documentation and adherence to guideline compliant testing frequency by health care providers increased significantly (Eigbunke and Gerard, 2013), as well as frequency of treatment intensification (Miller et al, 2003). Another important aspect of diabetes management has been observed. Patients with good glycemic control, HbA1c levels ≤ 7%, were identified and inappropriate treatment escalation potentially leading to risks of hypoglycemia could be avoided (Thaler et al, 1999).

The introduction of HbA1c POCT has been shown to have a significantly positive effect on glycemic control. This has been attributed to more appropriate treatment intensification, improved adherence to guidelines concerning testing frequency as well as increased patient and provider motivation.

PATIENT SATISFACTION AND BENEFITS IN DIABETES CARE WITH POCT

Patient satisfaction and an improved doctor-patient dialogue has been reported in several studies comparing POCT with traditional laboratory testing (Schnell et al, 2017 and references therein). Patients have reported a higher satisfaction with the sample collection, an increased confidence in the process and an enhanced relationship with their physician. Health care providers regard the improved opportunity for immediate management decisions made possible with rapid HbA1c values an important advantage of POCT. It is also regarded as an excellent opportunity to enhance patient's diabetes education and motivation.

In depth interviews with health care professionals revealed the perception that POCT has many benefits including face-to-face encounters with immediate feedback, proactive patient education, increased collaboration between patient and provider as well as improved patient adherence. However, the respondents also felt some concern about cost factors and possible issues regarding accuracy of the POCT devices (Brown et al, 2004). In a survey among general practitioners in the UK to establish clinical needs, the ability to measure HbA1c point of care was on their top 3 wish list in all surveyed areas: diagnosis, reducing referrals and monitoring (Turner et al, 2016). The results are similar in a survey of current and future use of POCT in four European countries and the US. Respondents in all five countries included diabetes in the top ten conditions they would like to be able to diagnose with POCT. The current use of POCT varied with the most frequent use reported in the UK and the US. Generally, desired use was higher

than actual use suggesting a demand for POCT (Howick et al, 2014).

Both patients and health care professionals express a high satisfaction with HbA1c POCT. The possibility for face-to-face encounters with the patient with immediate feedback on test results is perceived as the main advantage by physicians. The desired use of POCT is higher than actual use suggesting a demand for POCT.

IS POCT MORE EXPENSIVE THAN LABORATORY TESTING?

Compared to the number of scientific papers reporting a positive impact on glycemic control with POCT, there are only a few studies evaluating practice efficiency. The cost-effectiveness of POCT in primary care has therefore been questioned. The concerns mentioned earlier that it may increase cost for testing may be relevant if not looking at the bigger picture. If the direct cost for a test performed point of care is compared with a laboratory performed test the cost could be higher. If, on the other hand, also indirect costs are taken into account, the comparison turns out quite differently. In Massachusetts General Hospital, US, the practice efficiency was studied before and after the implementation of POCT for HbA1c. Following POCT there was a 21% decrease in total number of tests ordered per visit, an 89% decrease in the number of telephone calls to patients, an 85% decrease in the number of result letters sent to patients, and a 61% reduction in the number of follow-up visits for an abnormal laboratory result. All these changes were significant. The potential cost savings from improved efficiency were $24.64 per patient (Crocker et al, 2014). The authors then conducted a confirmatory study in a more typical general internal medicine primary care practice. They found a 90% reduction in the number of letters sent to patients and a 50% reduction in the number of follow-up tests as a result of an abnormal result. These reductions were statistically significant. There were also reductions in number of telephone calls and follow-up visits due to abnormal laboratory results but these did not reach statistical significance due to the relatively low numbers of calls and follow-up visits. The authors found that the benefits were similar albeit not as strong as in the previous study. Also in this study, there was an overall financial benefit, but it was not as great per patient. In conclusion, the study demonstrated the expanded generalizability of potential benefits of POCT in the primary care setting.

If the direct cost for a test performed by a laboratory reference method is compared with the cost for a test performed point of care, the latter will probably be higher. However, when all costs are included, both direct and indirect ones, significant cost savings can be achieved with POCT. When POCT is successfully implemented it changes patient work substantially and that is where money can be saved.

ANALYTICAL PERFORMANCE TODAY IS EQUIVALENT TO REFERENCE METHODS

An important issue regarding POCT for HbA1c has been the analytical accuracy of the different POCT devices available. In 2009 instruments for POCT of HbA1c were compared to hospital laboratories. Of the eight devices tested, only two passed the criteria for imprecision (≤ 3%). In addition, the reagent lot-to-lot variation was an issue of concern (Lenters-Westra and Slingerland, 2010, Little et al, 2011). Despite the fact that all the devices studied were certified according to the National Glycohemoglobin Standardization Program (NGSP), the majority of them did not meet the standards in the study. The authors speculate that the varying results could be explained by the fact that analytical performance in the field may differ from that during certification which is performed by experienced technologists under ideal circumstances.

However, both hardware and software of the POCT technology has undergone major technical development in recent years, and requirements

for measuring performance have become tighter. According to the present NGSP requirements 92.5% of results should fall within ± 6% variation relative to a standard reference laboratory measurement with a desirable imprecision of no more than 2%, but accepting 3%. In a recent study in two different primary care clinics in Sweden, nondiabetic and prediabetic patients as well as patients diagnosed with type 1 or 2 diabetes were tested for HbA1c values both with POCT and a reference laboratory method. 96% of the results from the POCT device fell within 6% variation with a total imprecision of less than 2%. The authors conclude that the POCT device tested is accurate and easy to use for the intended user (Andersson et al, 2017).

In Norway, where 3 out of 4 general practice offices have instruments for HbA1c POCT, a review of an external quality assurance survey in general practice offices and hospital laboratories showed that over the course of 6 years 60-90% of general practice offices met the quality specification for accuracy (≤ 6%) and imprecision (≤ 3%) in diabetes diagnosis. The corresponding figure for hospital laboratories was actually slightly lower: 54-84% (Sølvik et al, 2013).

With the major technical development of the POCT technology in recent years, there are now analyzers meeting the necessary requirements. Clinicians considering the introduction of HbA1c POCT should carefully select an analyzer based on clinical needs and acceptable levels of variation and precision. User-friendliness is also an important consideration to ensure intended test quality with the particular device.

References:

Ali MK, McKeever Bullard K, Gregg EW et al. A Cascade of Care for Diabetes in the United States: Visualizing the Gaps. *Ann Intern Med* 2014;161:681-689.

American Diabetes Association. Standards of Medical Care in Diabetes-2016. *Diabetes Care* 2016;39(Suppl 1):1-112.

Andersson A, Lindh J, Eriksson A. Evaluation of the HemoCue HbA1c 501 System in Primary care Settings. *Point of Care* 2017;16(3):128-130.

Brown JB, Harris SB, Webster-Bogaert S et al. Point-of-Care Testing in Diabetes Management: What Role Does It Play? *Diabetes Spectrum* 2004;17(4): 244-248.

Cagliero E, Levina EV, Nathan DM. Immediate feedback of HbA1c levels improves glycemic control in Type 1 and insulin-treated type 2 diabetic patients. *Diabetes Care* 1999;2(2) :1785–1789.

Crocker JB, Lee-Lewandrowski E, Lewandrowski N et al. Implementation of point-of-care testing in an ambulatory practice of an academic medical center. *Am J Clin Pathol.* 2014;1(42): 640-646.

Eigbunke V, Gerard S. The impact of point-of-care A1C testing on provider compliance and A1C levels in a primary setting. *Diabetes Educ.* 2013;3 9(2):66-73.

Howick J, Cals JWL, Jones C et al. Current and future use of point-of-care tests in primary care: an international survey in Australia, Belgium, The Netherlands, the UK and the USA. *BMJ Open* 2014;4:e005611. doi:10.1136/bmjopen-2014-005611.

The International Expert Committee. International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes. *Diabetes Care* 2009;32(7):1327-1334.

Lenters-Westra E and Slingerland RJ. Six of Eight Hemoglobin A1c Point-of-Care Instruments Do Not Meet the General Accepted Analytical Performance Criteria. *Clinical Chemistry* 2010;56(1):44–52.

Little RR, Lenters-Westra E, Rohlfing CL et al. Point-of-Care Assays for Hemoglobin A1c: Is Performance Adequate? *Clinical Chemistry* 2011;57(9):1333-1340.

Miller CD, Barnes CS, Phillips LS et al. Rapid A1c availability improves clinical decision-making in an urban primary care clinic. *Diabetes Care* 2003; 26:1158–1163.

Petersen JR, Finley JB, Okorodudu AO et al. Effect of Point-of-Care on Maintenance of Glycemic Control as Measured by A1C. *Diabetes Care* 2007;30(3):713-715.

Pillay S, Aldous CM, Singh D et al. Validation and effect on diabetes control of glycated haemoglobin (HbA1c) point-of-care testing. *S Afr Med J* 2019;109(2):112-115.

Rust G, Gailor M, Daniels E et al. Point of care testing to improve glycemic control. *International Journal of Health Care Quality Assurance.* 2008;21(3):325-335.

Schnell O, Crocker JB, Weng J. Impact of HbA1c testing at point of care on diabetes management. *Journal of Diabetes Science and Technology.* 2017;11(3) 611–617

Sølvik UØ, Røraas T, Christensen NG et al. Diagnosing Diabetes Mellitus: Performance of Hemoglobin A1c Point-of-Care Instruments in General Practice Offices. *Clinical Chemistry* 2013;59(12):1790–1801.

Stratton IM, Adler AI, Neil HAW et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405.

Thaler LM, Ziemer DC, Gallina DL et al. Diabetes in Urban African-Americans.XVII. Availability of Rapid HbA1c Measurements Enhances Clinical Decision-Making. *Diabetes Care* 1999;22:1415–1421.

Turner PJ, Van den Bruel A, Jones CHD et al. Point-of-care testing in UK primary care: a survey to establish clinical needs. *Family Practice* 2016;33(4):388-394.

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