Monitoring of Diabetes Mellitus - the role of HbA1c

Terminology:
DM Diabetes Mellitus GH Glycated haemoglobin HbA1c Haemoglobin A1c DCCT Diabetes Control and Complications Trial NGSP National Glycohemoglobin Standardization Program HPLC High Performance Liquid Chromatography

Introduction:
Diabetes Mellitus (DM) is a chronic, systemic disease characterised by disturbed carbohydrate metabolism, micro vascular complications (retina and kidney) and macro vascular complications (coronary and carotid arteries). To put the costs associated with DM into perspective, it has been reported that the annual per capita healthcare cost for a diabetic is 4 times higher than for a non-diabetic person. The costs attributable to DM arise because of both acute and chronic complications. It has been conclusively established that micro vascular complications can be decreased in diabetics who are intensively managed, compared to a control group who are less well controlled.

Glycated haemoglobin is established as the laboratory parameter that reflects the degree of control of a diabetic person. Although glycated haemoglobin (GH) and Haemoglobin A1c (HbA1c) are often used interchangeably, it should be pointed out that HbA1c is a component of GH. The HbA1c level in a person reflects an integrated assessment of the mean glycaemic control over the average red cell life span for an individual.

HbA1c was the main laboratory parameter used to reflect glycaemic control in the DCCT1 study. Subsequently HbA1c levels exceeding 8.1% was shown to be associated with a dramatic rise in microalbuminuria and it was recommended that by controlling HbA1c levels below 8.1%, the incidence of diabetic nephropathy could be reduced. Recently exiting evidence that macro vascular complications are reduced in well-controlled diabetics compared to poorly controlled diabetics was published . The thickness of the carotid artery intima-media, a reflection of atherosclerosis, was related to HbA1c level. Good control of DM (measured by normal HbA1c levels) led to a reduced progression of disease.

Laboratory aspects of measuring glycated haemoglobin:
The irreversible binding of glucose molecules to haemoglobin molecules causes an alteration of the charge, chemical binding property and immunological characteristics of the haemoglobin molecule. Ion exchange chromatography, affinity chromatography and immuno-assay methodology can be used to separate the glycated haemoglobin from the non-glycated haemoglobin. The results of the GH are expressed as a percentage of total haemoglobin. HbA1c refers to a particular fraction of GH and most assays reports are standardised to HbA1c irrespective of whether the total GH or HbA1c fraction is measured directly.

The degree of glycation of haemoglobin is a function of the average glucose concentration and the life span of the red cells. In haemolytic conditions the red cell life span is shortened and the GH is lower for any integrated glucose concentration than in a comparable individual with normal (120 days) red cell survival.

In a comprehensive review on laboratory monitoring of diabetic patients, under the auspices of the National Association of Clinical Biochemistry and the American Diabetes Association, it is strongly recommended that assays for GH (HbA1c) must be approved by a special task group (NGSP) and that the results must be related to DCCT equivalent results. Diagnostic manufacturers submit their assays on a yearly basis for approval and the results are published (http://www.missouri.edu/~diabetes/ngsp.html) - a copy of a list of NGSP certified methods are attached as a supplement to this document)

The bulk of methodologies approved by the NGSP are chromatographical and immunological methods. The chromatographical methods are mostly performed on dedicated, automated high performance liquid chromatography (HPLC) analysers. The immunological assays are performed by turbidimetric methodology on

routine laboratory analysers. Comparative evaluations of methodology studies show no significant difference in the performance of automated HPLC and immunological assays.

Clinical aspects of measuring glycated haemoglobin5:
HbA1c measurements are the recommended assay for monitoring glycaemic control. Other glycated proteins such as Fructosamine (glycated albumin) are not recommended for routine monitoring.

HbA1c assays are recommended twice a year for well-controlled diabetics and quarterly (4 times a year) in poorly controlled diabetics.

HbA1c is not recommended for screening or diagnosis of diabetes mellitus. Plasma glucose is the sole diagnostic criterion for diabetes mellitus.

In persons with decreased red cell survival (acute blood loss or abnormal haemoglobin) the HbA1c values will be falsely lowered regardless of the method used to measure HbA1c (HPLC or immunological). In populations with a high incidence of abnormal haemoglobins an alternative glycated protein assay such as Fructosamine should be considered .

Discussion:
The assertion that HPLC represents the "gold standard" for measuring HbA1c and therefore that HPLC should replace immunological assays for HbA1c is not apparent from a review of the literature. What is clear is that both HPLC and immunological methodologies should be standardised to a traceable international reference standard, such as NGSP certified methodology.

The immunological assays that feature in the NGSP certification list are in common use in South African laboratories. These assays are generally billed under code 4182 (Turbidimetric or nepeholometric methodology) at a 2004 NRPL tariff of R 55.10.

While the HPLC methodology is undoubtedly acceptable as an alternative to immunological assays on technical grounds, it is questionable whether the HPLC methodology should be reimbursed at a higher rate, as an acceptable alternative methodology at a lower price is available. If the principle of technological up coding is accepted by medical aid funders, it can be confidently predicted that this will be the start of an avalanche.

Recommendations:
1. HbA1c methods should be NGSP certified.
2. Reimbursement should be at the level of the lowest cost NGSP certified HbA1c method - in this case code 4182.
3. The principle of technological up coding should be resisted.

Technological up coding - where a more expensive methodology to measure an analyte is used although no clinical benefit is apparent.

1. American Diabetes Association. Economic consequences of diabetes mellitus in the US in 1997. Diabetes Care. 1998;21:296 - 308
2. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependant diabetes, NEJM. 1993; 329;977 – 986
3. Krolewski SA et al. Glycoslated hem