

## **Quality Specifications for Clinical Chemical Analyses Used to Monitor Patients with Diabetes Mellitus**

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### INTRODUCTION

The goal for treatment of patients with diabetes mellitus is to achieve the best possible quality of life and to minimize the risk of acute and late complications of the disease. The risk of acute complications, such as ketoacidosis and hyperosmolar, non-ketotic coma is highly dependent on the capacity of the patient to handle the metabolic control in critical situations such as acute illness. The risk of diabetic late complications is determined by a number of factors, among which diabetes-duration and long-term glycaemic control emerge as the two most important. Therefore, monitoring of metabolic control and adjustment of the treatment according to the outcome of the test results is one of the most important objectives for the diabetic clinics.

Today, the late complications of diabetes mellitus are accessible to prevention or active treatment. One example is photocoagulation of diabetic retinopathy, which has been shown to halt the progression of diabetic eye disease also in a long-term perspective (5). Another example, highly dependent on clinical laboratory methods, is the identification of patients with moderate albuminuria - "microalbuminuria". An aggressive treatment of blood pressure at this early stage of diabetic nephropathy has been shown to prevent further deterioration of renal function and even lead to regression of microalbuminuria (2).

Thus, monitoring of diabetic control and diabetic complications, as a basis for prevention or treatment are major objectives for modern management of patients with diabetes mellitus. This increasingly important role for disease monitoring in

diabetic patients has made the analytical precision of the clinical chemistry methods more important. The quality specifications for the chemical analyses utilized in diabetes care may therefore need to be re-assessed against the back-ground of recent developments in the treatment of diabetes mellitus.

#### MONITORING OF DIABETIC CONTROL

Home monitoring of blood glucose using tests strips forms the basis of the patients' management of diabetes under everyday conditions. This permits the patient to take measures to avoid hypoglycaemia and handle problems with acute and long-term hyperglycaemia. In insulin-dependent diabetic patients urine tests for ketones is a necessary complement to blood testing in situations with hyperglycaemia and acute illness. Urine tests for glucose are used less frequently today and has largely been replaced by the blood tests. In children and under certain conditions in adult patients urine testing may still be employed for diabetes monitoring.

#### BLOOD GLUCOSE

When tested in the laboratory all the commercially available test strips for blood glucose measurements have been shown to have an adequate reliability and the correlation between wet chemistry and the dry methods is close to 1.0 (1).

The reliability of the blood glucose measurements is highly dependent on the patient's ability to read the strips visually and to perform the analytical procedure correctly and finally to register the data without cheating.

An unresolved problem of analytical precision is the rapidly expanded use of reflectometers for test strip reading at home. An inquiry among the major manufacturers in October 1990 showed that from 1985 till today approximately 25.000 reflectometers have been distributed to Swedish patients. It is essential that the capacity of these reflectometers to provide correct readings is secured. There is no clear cut line of responsibility for this quality control since the patients buy the meters individually. It may be desirable, however, for routine clinical

chemistry laboratories to be engaged in the quality control of home blood glucose measurements. Recent studies in hospital wards, with many individuals in the staff involved, have shown that the agreement between reading of test strips and wet laboratory methods is poor in a considerable number of the tests performed (4).

For blood glucose measurements a good analytical precision is desirable in the range above normoglycaemia but absolutely essential in the low blood glucose range (2.0-5.0 mmol/L). For the patient reliable readings in the hypoglycaemic and near--hypoglycaemic range is imperative in order to permit actions to avoid hypoglycaemia to be taken in time. This requirement is valid both for the test strips and for wet chemistry in the laboratory. The coefficient of variation for laboratory systems should be around 3 %, whereas 5-8 % would be possible to obtain with dry chemistry (1). The values for the latter is likely to exceed that figure considerably in many situations, particularly for home blood glucose monitoring.

#### HEMOGLOBIN A<sub>1c</sub>

During the last decade hemoglobin A<sub>1c</sub> has evolved as the gold standard for the assessment of long-term glycaemic control in diabetic patients. Hemoglobin A<sub>1c</sub> is occupying a dominating position in scientific studies as well as in clinical practice. The introduction of serum fructosamine, which has the advantage of a simpler analytical procedure suitable for adaptation to multianalyzers, has not been able to change this position. Fructosamine, mirrors a shorter time period of metabolic control than hemoglobin A<sub>1c</sub> and is also influenced by other factors than the plasma glucose levels, which may cause confusion in the interpretation of the results.

There are several methods in use for the assessment of hemoglobin A<sub>1c</sub> such as iso-electric focusing, column chromatography and fast performance liquid chromatography. A development of the analytical techniques has lead to the analysis of stable HbA<sub>1c</sub>, recently. However, a certain variability has been found between the routine laboratories (6). Both for reasons of quality control of diabetes care between hospitals and to secure a proper

interpretation of data of metabolic control for patients moving between hospitals, it is critical that the work for standardization of hemoglobin A<sub>1C</sub> measurements continues.

Another development which would facilitate the management of diabetes is methods for hemoglobin A<sub>1C</sub> measurements, which allows the patient to post a dried capillary blood sample taken at home to the clinic. Analysis prior to the hospital visit will provide the patient, the physician or diabetes nurse with a good measure of long-term metabolic control when he/she meets the patient.

Hemoglobin A<sub>1C</sub> serves both as a measure of long-term glycaemic control and is part of a bio-feed back system involving the patient. Therefore, the long-term stability of the method is imperative, since many patients adjust their daily life and treatment to the hemoglobin A<sub>1C</sub> levels in agreement with the diabetes team. Today, therapeutic action is taken if hemoglobin A<sub>1C</sub> changes exceeds 1 %. The quality specifications for the methods should be made with this in mind.

#### TESTS FOR EARLY DIABETIC NEPHROPATHY

Routine assessment of microalbuminuria in diabetic patients has become an important tool for early detection of diabetic nephropathy. Microalbuminuria which has been defined as urinary albumin excretion between 30 - 300 mg/24 h, represents a partly reversible state of nephropathy (3). The therapeutic actions taken when microalbuminuria is first detected in a patient with type 1 diabetes mellitus are efforts to improve glycaemic control and treatment of even minor elevations of blood pressure. Aggressive treatment of more severe forms of diabetic nephropathy have been shown to improve prognosis in patients with insulin-dependent diabetes mellitus (2), whereas the prognostic implications for renal function is less clear in non-insulin-dependent diabetes mellitus. In the latter category microalbuminuria seems to predict macrovascular disease manifestations.

The last few years we have witnessed a large output of laboratory methods for microalbuminuria testing. Since important clinical decisions are based on the results of the tests one can easily identify a number of factors of importance for analytical

quality which has to be studied in more detail. The analytical precision of the techniques, timing of the urine collections, the biological variability, which has been shown to be great, preservation of albumin in urine collections are some of these factors. The results vary considerable and today the precision of the microalbuminuria testing is low. Therefore it is wise to use repeated tests to underlie the clinical decision. It remains to be established if a better analytical precision can be achieved by improvement of laboratory methods or if the biological variations prevent a substantially better precision than what is available today.

#### CONCLUDING REMARKS

From the diabetologist's point of view it is clear that much can be gained by efforts to secure a excellent quality control of clinical chemistry methods. Problems with the analytical precision still exist both for the monitoring of glycaemic control at home, in the hospital setting and for the long-term assessment of glucose control with hemoglobin A<sub>1c</sub>. Therapeutic advances in the field of diabetic complications has focussed the interest on the qualitative monitoring of small amounts of albumin in the urine, which is still hampered by severe problems with analytical precision.

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