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REVIEW OF TESTS USED BY PATIENTS IN MONITORING DIABETES MELLITUS

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Abstract

Tests used in monitoring diabetes by patients have been reviewed to enable patients make the right choice of tests. Most diabetic patients who take insulin injections or are treated with sulphonylureas should follow intensive treatment programmes that include frequent self-monitoring of blood glucose (SMBG) at home. This is aimed at achieving preprandial plasma glucose levels of 5.0 – 7.2 mmol l^{-1} and peak postprandial plasma glucose levels of < 10.0 mmol $^{-}$1. Glycated haemoglobin (HbA_{1C}) should be tested by patients at home or by a doctor every 3 months to access glycaemic control and quality of diabetic care. Management plan should achieve normal or near-normal glycaemia of < 7.0 per cent to reduce diabetic complications. Routine laboratory blood glucose testing by laboratory personnel should be used to test the accuracy of SMBG and all portable capillary blood testing devices, and not access glycaemic control, except when adjusting oral medications in a patient not taking insulin. Home tests for blood â-hydroxybutyrate for diagnosing and monitoring ketoacidosis are available for use by diabetic patients. Urine glucose and ketone tests used by patients are unreliable. Government, non-governmental organizations and individuals should strive to make SMBG and HbA_{1C} testing accessible and affordable to diabetics to improve diabetic care in Ghana.

Introduction

Diabetes mellitus is a metabolic disorder of multiple aetiology characterized by defects in insulin secretion, insulin action, or both. This leads to characteristic deficiency of insulin or its inadequate function, resulting in disturbances of carbohydrate, lipid and protein metabolism, which manifests as chronic hyperglycaemia. Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, dehydration, weight loss and blurring of vision. The long term effects of diabetes mellitus include progressive development of specific complications such as retinopathy with potential blindness, nephropathy that may lead to renal failure and, or neuropathy with risk of foot ulcers, amputation charcot joints, including sexual dysfunction (Stratton *et al.*, 2000). Diabetic patients are at increased risk of cardiovascular, peripheral vascular and cerebrovascular diseases. Diabetes mellitus may be caused by a defect in the immune system, a flaw that may compromise other disease-fighting mechanism.

The main aetiological classes of diabetes mellitus are type 1 diabetes, type 2 diabetes and 'other types' diabetes mellitus. In type 1 diabetes, there is absolute deficiency of insulin. Approximately 5-10 per cent of all cases of diabetes are in this class. In type 2 diabetes, insulin levels may be normal, decreased or increased .The main defects in type 2 diabetes include predominantly insulin resistance, that is, decreased ability of insulin to act on peripheral tissues and also impaired insulin secretion due to â-cell defect. The specific aetiology of type 2 diabetes is unknown. Type 2 diabetes comprises approximately 90 per cent of all cases of

diagnosed diabetes mellitus. "Other types" diabetes mellitus is a less common form. It may be due to genetic defects of â-cell function or insulin action, diseases of the exocrine pancreas, endocrinopathies, drug-or chemical induced and infections (WHO, 1999).

Tests used in monitoring diabetes mellitus include urine glucose and urine ketones and blood glucose and blood glycated proteins (haemoglobin and serum proteins). Since hyperglycaemia is the defining hallmark of the diabetes state and because glucose is relatively easy to quantify, glucose determination is the first choice in selecting a test for monitoring diabetes mellitus. However, diabetes mellitus is characterized not only by hyperglycaemia, but also by other metabolic derangements involving carbohydrates, lipids and proteins. Hence, the use of the additional tests of ketones and glycated proteins are also used in monitoring diabetes mellitus. All these tests allow us to describe the metabolic control of the diabetic state. Results of these tests are used to assess the efficacy of therapy and to make adjustments in medical netrition therapy (MNT), exercise, and medications in order to achieve the best possible blood glucose control.

Monitoring of glycaemic status, as performed by patients and health care providers, is considered the cornerstone of diabetic management. A major objective in the management of diabetes mellitus is to achieve fasting and post-prandial plasma glucose concentration as close as possible to physiological levels. The aim is to prevent chronic tissue exposure to hyperglycaemia and reduce the risk of microvascular complications whilst avoiding iatrogenic hypoglycaemia (Williams, 1994). The management of type 2 diabetes should also include efforts to reduce the risk of atherosclerosis which is the major cause of mortality in type 2 diabetes.

The review provides current knowledge on the purpose of tests used in monitoring diabetes mellitus by patients. The advantages and disadvantages of each test are emphasized to allow the right choice to be made and the implications of the tests to perform. The review also shows the increasing roles to be played by patients in home testing to control diabetes mellitus.

Historical background

Historically, before 1975, routine patient monitoring consisted of urine sugar/glucose and ketone determination whilst blood glucose determination was done occasionally (Service, Molnar & Taylor, 1972). At that time, the primary purpose of monitoring was to provide information to guide therapy aimed at relieving symptoms of hyperglycaemia including polyuria, polydipsia and nocturia, rather than to achieve a specific glycaemic status. Since 1975, dramatic changes have taken place in the methods and goals of monitoring. By the mid-1980s, patient monitoring of capillary blood glucose had replaced urine glucose testing as the recommended method of day-to-day testing. At the same time, determinations of glycated proteins were found to be clinically useful measures of average glycaemia over weeks and months, and gradually became part of routine monitoring.

Urine glucose testing by patients

Urine glucose testing by patients in the home setting typically consists of semiquantitative measurements based on single voiding or, less often, by more quantitative "blocks" collected over 4 – 24 h. The rationale is that urinary glucose values reflect mean blood glucose during the period of urine collection, and that, single-voided specimen reflect blood glucose at the time of voiding (Service, Molnar & Taylor, 1972). Second voided specimens do not appear to offer any significant advantage over first voided specimens (Guthrie, Hinnen & Grthrie, 1979). Commercially available testing methods include glucose reagents strips (clinistix) and glucose reagent

tablets (clinitest). Both are based on the glucose oxidase and peroxidase reaction. Urine glucose testing provides only a rough estimate of prevailing blood glucose levels (Hayford, Weydert &Thompson, 1983). Further, as indicated by the American Diabetes Association (2004), urine glucose test provides no information about blood glucose levels below the renal threshold, which for many patients today is the target range for blood glucose control.

There are other reasons why the use of urine glucose test in estimating blood glucose concentration in diabetes management is undesirable (Sacks *et al.,* 2003; Singer *et al.*, 1989). The renal threshold for glucose in healthy adults corresponds to a plasma glucose concentration of about 10 mmol l^{-1}. There is wide individual variation that results in under estimation of urine glucose when the renal threshold is increased and over estimation when the renal threshold is low. Fluid intake and urine concentration affect urine test results. The urine glucose value reflects an average level of blood glucose during the interval since the last voiding and not the level at the time of the test (Sacks *et al*., 2003; Singer *et al*., 1989).

Negative urine glucose test does not distinguish between hypoglycaemia, euglycaemia, and mild or moderate hyperglycaemia. Thus, urine glucose testing is of limited value in preventing hypoglycaemia and hyperglycaemia. Urine glucose testing, which uses a colour chart with which the test strip colour is compared, is less accurate than capillary blood glucose monitoring, which typically uses a digital readout from a reflectance meter. Some drugs interfere with urine glucose determinations. Evaluation of urine dipsticks reveals high imprecision at low glucose concentrations.

Urine and blood ketone testing by patients

The ketone bodies which are breakdown products of fatty acids include â-hydroxybutyrate, acetoacetate and acetone. Ketone testing is an important part of monitoring in type 1 diabetic patients, in pregnancy with pre-existing diabetes, and in gestational diabetes (American Diabetic Association, 1992, 2004a). The presence of ketones may indicate impending or even established ketoacidosis, a condition that requires immediate medical attention. Patients with type 1 diabetes are required to test for ketones during acute illness or stress or when blood glucose levels are consistently elevated (e.g. > 16.7mmol l^{-1}), during pregnancy, or when any symptoms of ketoacidosis, such as nausea, vomiting, or abdominal pain, are present. Ketones are normally present in the urine but concentrations are usually below the limit of detectability with routine testing methods. However, positive ketone readings are found in normal individuals during fasting and in up to 30 per cent of first morning urine specimens from pregnant women (Jovanovic-Peterson & Peterson, 1991). Urine ketone levels are proportional to blood levels but, like urine glucose, are affected by urine volume and concentration.

All the commercially available urine testing methods rely on nitroprusside reaction to produce a purple colour in the presence of ketone bodies. Acetone is detected only if the reagent contains glycine in addition to sodium nitroprusside, and none of the tests detect â-hydroxybutyric acid. Urine ketone tests using nitroprisside containing reagents can give false-positive results in the presence of several sulphydryl drugs, including the antihypertensive drug captopril (Csako, 1990). False negative readings have been reported when test strips have been exposed to air for an extended period of time or when urine specimens have been highly acidic, such as after large intakes of ascorbic acid (Rosenbloom & Malone, 1978).

Urine ketone testing materials should be available in the clinic or laboratory, though, urine ketone tests are not reliable for diagnosing or monitoring treatment of ketoacidosis (Foster & McGarry, 1983). This is because despite the

limitations mentioned, the final concentrations of acetoacetate and â-hydroxybutyrate in urine usually exceed those in blood despite their reabsorption by the renal tubules. Blood ketone testing methods that quantify â-hydroxybutyrate, the predominant ketone body, are available (Kuch & Feldbruegge, 1987) and are preferred over urine ketone testing for diagnosing and monitoring ketoacidosis. Home tests for blood â-hydroxybutyrate are also available.

Blood glucose testing by patients

In recent years, self-monitoring of blood glucose (SMBG) by patients has revolutionalized management of diabetes mellitus. The results of the Diabetes Control and Complications Trial (DCCT) Research Group (1993) showed that patients with type 1 diabetes who maintained near-normal blood glucose levels for up to nine years had dramatic reductions in the risk of developing retinopathy, nephropathy and neuropathic complications. Almost identical risk reductions with improved glycaemic control were demonstrated in patients with type 2 diabetes who participated in UK. Prospective Diabetes Study (UKPDS) (1998a, 1998b). Based principally on the DCCT and UKPDS results, it has been recommended by the American Diabetes Association (2004a) that treatment of individuals with diabetes should be aimed at lowering blood glucose to normal or near-normal levels. To achieve normal or near-normal blood glucose levels, most patients with diabetes who take insulin injections or are treated with sulphonylureas, have to follow intensive treatment programmes that include frequent SMBG monitoring.

The frequency and timing of glucose monitoring should be dictated by the needs and goals of the individual patient, but for most patients with type 1 diabetes, SMBG is recommended three or more times daily. The optimal frequency of SMBG for patients with type 2 diabetes is unknown, but should be sufficient to facilitate reaching normal or near normal glucose goals. Thus, the frequency of surveillance for both type 1and 2 diabetes should be such that the risk for both hyper- and hypoglycaemic episodes are minimized. When adding to or modifying therapy, type 1 and 2 diabetic patients should test more often than usual. The role of SMBG in stable diet-treated patients with type 2 diabetes is not known.

Data indicate that only a minority of patients in both developed and developing countries perform SMBG. Barriers to increasing use of SMBG include cost of testing, inadequate understanding by both health care personnel and patients about the health benefits and proper use of SMBG results, patient psychological and physical discomfort associated with finger-prick blood sampling, and complexity of the technique. Thus, efforts should be made to substantially increase appropriate use of SMBG. In Ghana, the introduction in 2005 of the 'ONE TOUCH HORIZON', a blood glucose monitoring system, is aimed at stepping up the use of SMBG. Given the importance of SMBG to diabetes care, government, non-governmental organizations and individuals should strive to make the procedure readily accessible and affordable for all patients who require it.

The accuracy of SMBG is instrument and user dependent, therefore, it is important for health care personnel to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. Plasma glucose values are 10 –15 per cent higher than whole blood glucose values. It is, therefore, crucial that people with diabetes know whether their monitor and strips provide whole blood or plasma results. In addition, because laboratory methods measure plasma glucose, most blood glucose monitors approved for home use and some test strips now calibrate blood glucose readings to plasma values. Optimal use of SMBG requires proper interpretation of the data. Diabetics should, therefore, be taught how to use the data to adjust medical nutrition therapy (MNT), exercise, or

pharmacological therapy to achieve specific glycaemic goals.

Health professionals should evaluate at regular intervals the patients ability to use SMBG data to guide treatment. Most importantly, based on the DCCT (1993) and UKPDS (1998a, 1998b) results, the American Diabetes Association (2004a) recommends that most adults with either type 1 or 2 diabetes aim at achieving preprandial plasma glucose levels of 5.0 – 7.2 mmol l^{-1} and peak postprandial plasma glucose levels of < 10.0 mmol l^{-1}. It is further recommended that plasma glucose targets be adjusted on an individual basis for the elderly, children, and patients with recurrent severe hypoglycaemia (American Diabeties Association, 2004a). With the availability of SMBG and glycated protein testing, routine laboratory blood glucose testing by health personnel should no longer be used to assess glycaemic control but to supplement information obtained from other testing methods and to test the accuracy of SMBG. Thus, comparisons between results from patient self-testing of blood glucose in the clinic and simultaneous laboratory testing are useful to assess the accuracy of patient results (Sacks *et al.*, 2003). Laboratory testing should also be used to assess the accuracy of testing performed by health personnel using portable capillary blood testing devices. When adjusting oral glucose-lowering medications in a patient not taking insulin, laboratory testing may be appropriate.

Glycated haemoglobin testing

Blood, urine glucose and urine ketone testing provide useful information for day-to-day management of diabetes. However, these tests cannot provide the patient and health care team with objective measure of glycaemia over an extended period of time. Measurements of glycated proteins, primarily haemoglobin and serum proteins, have added a new dimension to the assessment of glycaemia. With a single measurement, each of these tests can quantify average glycaemia over weeks and months, thereby, complementing day-to-day testing (Singer *et al.*, 1989) of blood urine glucose and urine ketones.

Glycated haemoglobin (GHb), also commonly referred to as glycosylated haemoglobin, glycohaemoglobin, HbA_{1C}, HbA1, or AIC, is a term used to describe a series of stable minor haemoglobin components formed slowly and non-enzymaticlly from haemoglobin and glucose. The rate of formation of GHb is directly proportional to the ambient glucose concentration (Rohlfing *et al.*, 2002). Since erythrocytes are freely permeable to glucose, the level of GHb in a blood sample provides a glycaemic history of the previous 120 days, the average erythrocyte lifespan. GHb accurately reflects the previous 2 – 3months of glycaemic control Little & Goldstein, 1992). It provides an additional advantage because GHb values are free of day-to-day glucose fluctuations and are unaffected by exercise or recent food ingestion.

GHb testing first became available to routine clinical laboratory in the late 1970s. Since then, use of the test for both research and patient care has increased steadily. Routine use of GHb testing in all patients with diabetes is recommended by the American Diabetes Association (2004a), first to document the degree of glycaemic control at initial assessment, then as part of continuing care. GHb is used both as an index of mean glycaemia and as a measure of risk for the development of micro- and macrovascular diabetic complications. The test is also being used increasingly by quality assurance programmes to assess the quality of diabetes care (Davidson, 1998). A multi-test system, considered the "gold standard" indicator of diabetic control, monitors AIC in diabetic patients, providing test results in only 5 min. The system has been cleared by the US Food and Drug Administration (FDA). HbA_{1C} can now be tested by patients at home, providing laboratory-quality results in minutes. The new test, called

Inview, requires only whole blood sample *via* a finger-prick top obtain results.

In the absence of a definite testing protocol, expert opinion recommends AIC testing at least two times a year in patients who are meeting treatment goals (stable glycaemic control) and more frequently (quarterly assessment) in patients whose therapy has changed or who are not meeting glycaemic goals (American Diabetes Association, 2004a , 2004b). Since the AIC test reflects mean glycaemia over the preceding 2–3 months, measurement every 3 months is required to determine whether a patient's metabolic control has been reached and maintained within the target range. Thus, regular performance of the AIC test permits timely detection of departures from the target. For any individual patient, the frequency of AIC testing should be dependent on the clinical situation, the treatment regimen, and the judgments of the clinician (American Diabetes Association, 2005).

In clinical trials (DCCT 1993; UKPDS, 1998a, 1998b.), treatment regimens that reduced average A1C to about 7 per cent (1% above the upper limit of normal) were associated with fewer long-term retinopathy, nephropathy and neuropathy (DCCT, 2000). However, intensive control was found to increase the risk of severe hypoglycaemia and weight gain (Lawson *et al.*, 1999; Stratton *et al.*, 2000). The potential of intensive glycaemic control to reduce cardiovascular disease (CVD) is supported by epidemiological studies (Stratton *et al.*, 2000; UKPDS, 1998a) and a recent meta-analysis (Selvin *et al.*, 2004), but this potential benefit on CVD events has not yet been demonstrated in a randomized clinical trial. More stringent goals (i.e., a normal AIC < 6%) can be considered in individual patients and in pregnancy.

Conclusion

At present, it is recommended that all patients with diabetes, especially those who use insulin, should monitor their blood, not urine glucose levels. Urine glucose testing should be considered only if patients are unable to perform SMBG. Such patients should bear in mind that urine glucose testing provides only a rough estimate of prevailing blood glucose levels, and provides no information about blood glucose levels below the renal threshold, which, for many patients is the target range for blood glucose.

Blood ketone testing methods that quantify â-hydroxybutyric acid, the predominant ketone body, are available and are preferred to urine ketone testing for diagnosing and monitoring ketoacidosis. Home tests for blood â-hydroxybutyric acid are available for use by diabetics. Available urine ketone tests are not reliable for diagnosing or monitoring treatment of ketoacidosis. However, all diabetics who are, unable to perform blood ketones should test their urine ketones during acute illness or stress when blood glucose levels are consistently > 16.7 mmol l^{-1}, during pregnancy, or when any symptoms of ketoacidosis, such as nausea, vomiting or abdominal pain, are present.

It is further recommended that most adults with type 1 or 2 diabetes should aim at achieving preprandial plasma glucose levels of 5.0 – 7.2 mmol l^{-1} and peak postprandial plasma glucose levels of < 10.0 mmol l^{-1}. To achieve these levels, most diabetics, who take insulin injections or are treated with sulphonylureas, have to follow intensive treatment programmes that include frequent self-monitoring of blood glucose (SMBG). The frequency should be dictated by the needs and goals of the individual patient. Self-monitoring of blood glucose has no role in stable diet-treated type 2 diabetics. It is important for the laboratory and other health personnel to evaluate each patient's monitoring technique and all portable capillary blood testing devices by laboratory tests, both initially and at regular intervals thereafter, and the patient's ability to use SMBG data to guide treatment.

When adjusting oral medications in a patient not taking insulin, laboratory testing may be

appropriate. HbA_{1C} can now be tested by patients at home or at the clinic every 3 months to access glycaemic control and quality of diabetic care. Management plan is to be adjusted to achieve normal or near-normal glycaemia with an HbA_{1C} goal of < 7 per cent to reduce diabetic complications. However, more stringent levels (i.e. a normal AIC, < 6%) can be considered in individual patients and in pregnancy. Less stringent treatment goals may be appropriate for patients with a history of severe hypoglycaemia, patients with limited life expectancies, very young children or older adults and individuals with comorbid conditions.

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