CME

Glucose monitoring as a guide to diabetes management

Critical subject review

BERND KOCH, MD, FRCPC, MSC

PURPOSE To encourage a balanced approach to blood glucose monitoring in diabetes by a critical review of the history, power, and cost of glucose testing.

DATA SOURCES The Cambridge Data Base was searched and was supplemented by a random review of other relevant sources, including textbooks, company pamphlets, and laboratory manuals.

STUDY SELECTION Keywords used were "glucosuria diagnosis," "blood glucose self-monitoring," "glycosylated hemoglobin," and "fructosamine" for the 10-year period ending 1992, restricted to English language and human.

DATA EXTRACTION About 200 titles were retrieved and reviewed according to the author's judgment of relevance.

FINDINGS "Snapshot tests" (venous and capillary blood glucose) and "memory tests" (urine glucose, glycated hemoglobin fractions and fructosamine) must be employed according to individual patient treatment goals. Day-to-day metabolic guidance is facilitated by capillary blood glucose testing for patients receiving insulin and by urine glucose testing for others. Capillary blood glucose testing is mandatory in cases of hypoglycemia unawareness (inability to sense hypoglycemia because of neuropathy) but is not a substitute for a knowledge of clinical hypoglycemia self-care. Criteria by reason (clinical judgment and cost effectiveness) must be separated from criteria by emotion (preoccupation with technology and marketing).
No randomized studies show that any of these tests consistently improve clinical outcome. Optimal metabolic control and cost savings can be expected from a rational selection of tests.

OBJECTIF Favoriser une approche objective à la surveillance de la glycémie chez les diabétiques par une analyse critique de l'histoire, de la puissance et du coût des diverses méthodes de mesure de la glycémie.

SOURCES DES DONNÉES Recension de la base de données Cambridge complétée par une revue aléatoire d'autres sources pertinentes, notamment des volumes de référence, des dépliants fournis par les entreprises et des volumes de laboratoire.

SÉLECTION DES ÉTUDES Les mots clés utilisés furent « diagnostic de la glycosurie », « autosurveillance de la glycémie », « hémoglobine glycosylée » et « fructosamine ». La recension couvrait une période de dix ans se terminant en 1992 et se limitait aux articles de langue anglaise et aux études faites chez les humains.

EXTRACTION DES DONNÉES Environ 200 articles furent recensés et analysés en fonction de leur degré de pertinence telle que jugée par l'auteur.

RÉSULTATS Les tests « instantanés » (glycémie veineuse et capillaire) et les tests « mémoire » (glucose urinaire, hémoglobine glycosylée et fructosamine) doivent être individualisés en fonction des objectifs thérapeutiques de chaque patient. Chez les diabétiques insulinodépendants, la surveillance métabolique quotidienne est facilitée par la glycémie capillaire alors que la mesure du glucose urinaire suffit pour les autres. La glycémie capillaire est essentielle dans les cas où le patient n'a pas conscience de son hypoglycémie (présence d'une neuropathie qui empêche le patient de ressentir son hypoglycémie) mais elle n'est pas un substitut pour éviter d'en apprendre davantage sur la maîtrise personnelle des signes cliniques de l'hypoglycémie. Il faut séparer les critères « raisonnables » (jugement clinique et coefficient coût-efficacité) des critères « émotifs » (préoccupations techniques et de mise en marché). Aucune étude randomisée n'a démontré que l'un ou l'autre de ces tests contribuait à améliorer les résultats cliniques. À partir d'une sélection rationnelle de ces tests, on peut s'attendre à une maîtrise métabolique optimale et à des coûts moindres.

Dr Koch *is a medical consultant and is affiliated with several hospitals in Ottawa.*

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IN 1841 TROMMER NOTED THE COLOUR change from blue to red when divalent copper sulfate in an alkaline medium is reduced by glucose. In modifications by Fehling (1848) and Benedict (1908), and as Clinitest tablets (Ames 1941), this principle has been used successfully for urine glucose testing to guide diabetes care.[1] However these tests measure "total reducing substances" and has therefore been replaced by enzymatic dipstick urine glucose (DSUG) methods to test for "true glucose," marketed as TesTape (Ely Lilly 1956), Clinistix and Diastix (Ames), and Chemstrip uG 5000 (Boehringer Mannheim).

Enzymatic laboratory venous blood glucose (LVBG) methods have prevailed since the 1960s. The Dextrostix (Ames 1963) allowed visual test strip capillary glucose (TSCG) monitoring and was complemented 6 years later by the first reflectance meter for digital reading. Countless additional test systems for TSCG have since been introduced. Glycated hemoglobin fractions have been used since 1971 and glycated serum proteins (as fructosamine) since 1985.

The LVBG and TSCG tests are a "snapshot" of blood glucose and aim at sensing the nadir of the blood glucose curve before the three main meals and at bedtime. They allow therapeutic titration to the endpoint of normoglycemia by adjusting the insulin that is most active at that particular time. The worth of these tests is restricted by an element of chance in their timing and by atypical patient behaviour in anticipation of the test.

Glycated hemoglobin fractions and fructosamine are "memory tests." They permit assessment of the overall blood glucose control of the previous 8 and 3 weeks, respectively, but are not useful for day-to-day insulin adjustment.

The DSUG measures the amount of glucose fuel spilled (and wasted) since the last previous voiding and as such is a short memory test. Done on a second-void urine sample, it is almost a snapshot.

Glucose monitoring merits a review for three reasons:

- Millions of diabetics are involved.
- Huge public funds are required.
- Objective criteria, such as clinical judgment and cost effectiveness, but also preoccupation with high technology and marketing forces determine rates of utilization.

Reviewing the literature

The Cambridge Data Base was entered with the keywords "glucosuria diagnosis," "blood glucose self-monitoring," "glycosylated hemoglobin," and "fructosamine" for the 10-year period ending 1992. About 200 titles were retrieved and reviewed. This systematic search was supplemented by a random review of other relevant sources, including textbooks, company pamphlets, and laboratory manuals. Cost figures are based on 1992 sources.[2,3]

Hypoglycemia

An elevated blood glucose level is caused by the disease diabetes. Upper limits are a matter of definition.[4] In contrast, a low blood glucose level in the context of diabetes is iatrogenic. Lower limits are not clearly defined, and figures and symptoms correlate poorly in clinical practice.[5] For patients with insulin-treated diabetes, mild hypoglycemia in a controlled setting could be an inevitable and acceptable price to pay for good control of blood glucose. It is mandatory that patients be thoroughly familiar with the clinical triad of iatrogenic hypoglycemia management:

- Know the setting for hypoglycemia: exertion, a late meal, or alcohol.
- Know individual symptoms: moodiness, sweating, palpitation, etc.

Definitions

DSUG – Enzymatic dipstick urine glucose

LVBG – Enzymatic laboratory venous blood glucose

TSCG – Test strip capillary glucose

Accuracy – Ability to obtain true values

Precision – Ability to obtain reproducible values

Reliability – Predictable operator behaviour

Sensitivity – Ability to exclude false negatives

Specificity – Ability to exclude false positives

- Eat promptly; diagnosis is confirmed if the patient feels better quickly.

All patients taking hypoglycemic medication and their caregivers must be familiar with this practical algorithm for hypoglycemia. Blood glucose testing is not a substitute for that knowledge. Patients receiving insulin or sulfonylureas, notably those who develop hypoglycemia without warning, must test for hypoglycemia by TSCG or by laboratory venous blood glucose if in hospital. Patients not receiving hypoglycemic medication need not fear or test for hypoglycemia.

Dipstick urine glucose testing

Clinistix can merely distinguish between "light," "medium," and "dark" (as on the product label). The remaining three products can *detect urine glucose* concentrations from 5.5 to 111 (Diastix, read exactly at 30 s), above 111 (TesTape, read at 60 s, or at 120 s if higher than 28) and up to 280 mmol/L (Chemstrip uG 5000, read at 120 s).

Hydrogen peroxide and bleaches can cause false-positive results with all three. Ascorbic acid, levodopa, and salicylates can cause false-negative results. Adding iodate to the reagent mixture of Chemstrip uG 5000 has lessened that problem with respect to ascorbic acid.

The ability of the DSUG to *predict blood glucose* is limited for three reasons: DSUG is a memory test while blood glucose tests are snapshots; healthy kidneys can concentrate or dilute the glomerular filtrate by a factor of 20; and the renal threshold for glucose is the result of complex mechanisms that vary in time and between individuals.[6] Owing to the heterogeneity of the nephron population, even a healthy adult excretes 0.1 to 0.7 mM of glucose in the 24-hour urine collection,[7] and more under a modest glucose load.[8] Ignoring these facts has prompted misleading conclusions.[9]

A high renal threshold for glucose is sometimes perceived as an obstacle to DSUG. In practice this is uncommon but could impose limits to ambitious efforts at metabolic control among patients with impaired renal function. Postprandial urine testing can offset such threshold problems.

A low renal threshold for glucose leads to false-positive urine tests and is caused either by a rise in glomerular filtered load without a proportional rise in tubular reabsorption (as in pregnancy, early diabetes, and sickle cell disease) or by reduced tubular reabsorption without proportional fall in filtered load (as in renal glucosuria or in any osmotic diuresis).

As recently as April 1992, the American Diabetes Association stated that "the development of... blood glucose meters has made urine glucose testing obsolete for most patients."[10] Numerous experts, however, continue to use DSUG successfully for non–insulin-dependent diabetes mellitus; Scott and Tattersall[11,12] in a 1986 review of self-monitoring, concluded that "urine testing for glucose can be a useful way of monitoring diabetes."[11] Villinger[12] in 1986 recommended DSUG for type II diabetics with near normal renal glucose thresholds and for stable type I diabetics. Allan et al[13] in a randomized, controlled study of type II diabetics in 1990, showed that TSCG was no better in achieving control but eight to 10 times more expensive than DSUG. Zimmerman and Service[14] in a 1988 review stated, "an inexpensive urine test... with instructions to promptly report any positive results... may prevent serious complications more quickly than a poorly done fingerstick blood glucose test." Jörgens and Grüsser[15] in 1991 reported a large outreach program in Germany where patients with diabetes type II were taught only DSUG, and Alberti[16] in the UK in 1992 stated that, for non–insulin-dependent diabetes mellitus, DSUG was a good alternative to TSCG.

Even for insulin-dependent diabetes mellitus, several investigators have concluded that DSUG remains a useful tool for self-care. Ludvigsson[17] in 1984 found good correlation between DSUG and TSCG among juvenile diabetics and concluded that DSUG has a place in the management of juvenile diabetes. Nearly all of his patients preferred daily DSUG and a sporadic blood test to regular TSCG. Daneman et al[18] in a double-crossover study noted that 69% of 16 diabetic children preferred TSCG, but there was no difference in glycated hemoglobin levels

between patients monitored with TSCG and DSUG over corresponding 3-month periods. Hermansson et al[19] in 1986 studied 32 diabetic children and found that DSUG correlated with glycated hemoglobin levels as well as TSCG did and that only 6.4% of patients preferred TSCG. The authors concluded that TSCG was a complement rather than a substitute for DSUG. Worth et al,[20] in a 1982 randomized, crossover study of 38 patients receiving insulin twice daily, found that TSCG offered no improvement in control over intensive attention and conventional urine glucose monitoring.

In 1959 the author treated 20 boys aged 8 to 18 years who had insulin-dependent diabetes mellitus of 5 to 14 years' duration in the Elliot P. Joslin Camp for diabetic boys in Massachusetts. Day-to-day care was guided by DSUG (Benedict) alone, tested four times daily. At the end of a 10-day period, each boy had a true whole venous blood glucose measurement before each meal and at bedtime. The mean of all blood tests was 7.9 mmol/L. There were 1.7 reactions per boy per period (unpublished data).

Albisser et al[21] showed in 1990 that DSUG and TSCG allowed comparable control of glycemia in computer-based algorithms.

Visual impairment can limit a patient's ability to read urine glucose strips.[22] If the problem is colour blindness, digital readout devices help; if it is blindness, audible signals have been used.[23]

One secret to the success of metabolic control is frequent testing, as facilitated by low cost and simplicity. Dipstick urine glucose measurement meets both these criteria. One DSUG costs between $0.08 and $0.12, requires a minimum of equipment, and takes 1 to 2 minutes to perform.

Laboratory venous blood glucose determination

Standard blood glucose values refer to true glucose in whole venous blood. Plasma values are about 12% higher and capillary blood values can be 15% to 25% higher depending on the time since the last meal. Tests for total reducing substances read 15% higher.

Laboratory venous blood glucose determination is accurate with a correlation coefficient of 0.98 or more of the reference method and a linear relation up to 25 mmol/L. Higher concentrations can be read accurately by diluting. Laboratory venous blood glucose is precise below a coefficient of variance of 0.02.[24]

Patients should use laboratory services wisely. There is no sense going to the laboratory if hypoglycemia is obvious. The required action is immediate nourishment. There is also little sense going to the laboratory if DSUG or TSCG indicate hyperglycemia when a patient has not followed dietary guidelines. Patients should measure their own DSUG or TSCG when they have LVBG and should record the date and results for later comparison. This will quickly uncover those with prohibitively high or low renal thresholds and will serve as quality control. A fasting venous blood sample should include glycated hemoglobin measurement every 8 weeks or fructosamine measurement every 2 weeks, as indicated.

The cost of one LVBG in a highly efficient, largely automated modern laboratory setting is about $2.70.

Glycated hemoglobin fractions and fructosamine

When glucose and proteins are combined in solution, complex reactions take place that are referred to as nonenzymic glycation yielding ketoamine compounds, in their turn called glycated proteins. These reactions are partly irreversible, and the products are proportional to the glucose concentration. These glycated proteins have long been suspected as pivotal to the pathogenesis of the late complications of diabetes.[25]

Glycated hemoglobin fractions also reflect the quality of diabetes care. Critical reviews of this subject have been published.[26,27]

Glycated hemoglobin fractions comprise several hemoglobin fractions that differ from one another depending on the assay method used. They correlate with the average blood glucose of the previous 2 to 3 months[28-30] (a 1% rise reflects a rise of the average blood glucose of 1.7 mM/L) and are considered superior to clinical judgment

in assessing metabolic control in diabetes.[31] Lack of a reference method and of a single laboratory standard have compromised quality control.

Numerous reviews of the methodology of glycated hemoglobin determinations have been published.[32] Two methods, hemoglobin A_{Ic} and total glycated hemoglobin levels, can be briefly described as follows.

Hemoglobin A_{Ic}, measured by cation-exchange chromatography, has a reference range of 4.0% to 6.0% (acceptable diabetic control up to 8.6%). Prolonged storage, ambient temperature above 4°C, hemoglobinopathies with Hb G, Hb H, -Wayne, and Hb F, β-lactam antibiotics, methemoglobin, high blood levels of bilirubin and triglycerides, opiate addiction, lead poisoning, alcoholism, uremia, treatment with high doses of acetylsalicylic acid, and recent elevation of blood glucose level cause false high readings. Hemoglobin S, Hb C, and Hb E and conditions associated with shortened red cell life, such as hemorrhage, hemolysis, and hepatic cirrhosis, lead to false low results.

Total glycated hemoglobin levels, measured by affinity chromatography, have a reference range of 4.3% to 7.7% (acceptable diabetic control up to 9.0%). Storage conditions are less critical. Hepatic cirrhosis as well can cause false low readings, but hemoglobinopathies do not interfere. Total glycated hemoglobin level measurement is favoured for its better differentiation of glucose control.[30]

Glycated serum protein, measured as fructosamine, has a reference range of 205 to 285 μM/L. Albumin with a half-life of 21 days and IgG with a half-life of 22 to 25 days make up 80% of the quantity. Results should be corrected for abnormal serum proteins using the equation[33]:

Corrected fructosamine = Measured fructosamine/Total protein (g/L) x 72

Fructosamine correlates with the average blood glucose level of the previous 2 to 3 weeks and can detect shorter or more recent fluctuations of blood glucose.[34] It is, therefore, the preferred memory test during pregnancy.[35,36] Fructosamine correlates with retinopathy and adds to clinical assessment of glucose control.[37] Fructosamine is superior to plasma glucose determination in screening for diabetes with its added risk in acute myocardial infarction.[38] Unlike tests for glycated hemoglobin levels, a standardized fructosamine test is available, making results from different laboratories comparable. High blood levels of methyldopa, bilirubin (above 35 μM/L), hemoglobin (above 1000 mg/L), and triglycerides (above 10.2 mM/L) can cause false high results. Storage longer than 2 days should be at <4°C.

Glycated hemoglobin costs about $11.50 and fructosamine about $4.70; ie, they are more expensive tests. Considering their power to reflect a prolonged period, however, they are emerging as the most cost-effective methods of diabetes control.

Test strip capillary blood glucose

Test strip capillary blood glucose serves to guide diabetes care, not diagnosis.[39] It is not considered suitable for diagnostic testing of high-risk neonates.[40] The accuracy (correlation coefficient upward of 0.98 of the reference method) and precision (coefficient of variance of below 0.045) of TSCG approach the values of LVBG.[41,42] Vallera and colleagues[43] in 1991 showed good correlation of TSCG with venous plasma glucose. The Glucoscan 2000 meter had a positive bias and was influenced by the prandial state, whereas the AccuChek II meter was more accurate in the range below 5.6 mmol/L.[43] Umpierrez and associates[44] have shown that dilution is feasible to accommodate high values in decompensated diabetics. Hematocrit values below 35% and above 55% cause false high and low readings, respectively.

Carney et al[45] in 1983 noted improved glycated hemoglobin levels in diabetic children monitored by TSCG as compared to DSUG. Test strip capillary glucose measurement in clinical practice is not as reliable as its potential accuracy and precision and is not always predictable in individual patients. Inappropriate blood application to the test strip; incorrect timing; inadequate meter service (strips, meter, battery, standard);

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and lack of training, of trainability, or of motivation impose limits.[46-48]

Gonder-Frederick et al[49] in 1988 found that 25% of all TSCG data were fabricated, albeit without evil intent. Ziegler et al[50] studying insulin pump patients found in 1989 that nine in 14 omitted one sixth of test results and eight in 14 invented one third of test results. Educational level did not predict reliability. Mazze et al[51] in 1984 studied 19 patients with insulin-dependent diabetes mellitus who were given meters with a secret memory. Underreporting or omissions in the respective logbook averaged 10%, whereas overreporting or addition of phantom values averaged 40%. An average of 26% of logbook entries were not identical with the meter readings.[51]

Lawrence et al[52] in 1989 found that 19% of nurse-operated TSCG deviated from simultaneuous LVBG by more than 20%. Burritt et al[53] in an evaluation of the One Touch glucose meter used by a phlebotomy team in 1990 showed differences greater than 15% from the laboratory reference in 7.5% (split sample) and 7.2% (blind sample). Ting and Nanji[54] in 1988 studied the quality of TSCG done by 39 nurses in a teaching hospital: 24% of TSCG on wards and 62% of those done in intensive care units deviated by more than 20% from the reference values. Of 85 patients tested, 12 (14%) would have received different insulin doses had the reference value been available.

The concerted efforts of the industry to provide service have solved some of these problems, eg, meters with built-in memory[55] and hematocrit adjustment. A simple quality control system for TSCG in hospitals has been suggested.[56] Concurrent patient TSCG and LVBG must be encouraged. Because visual reading accuracy approaches meter reading, concurrent visual and meter reading is recommended,[57,58] and visual reading alone could be preferable for elderly patients.

The cost of TSCG is $0.70 to $0.90 for visual reading and $0.80 to $1.30 with a meter. Cutting strips lengthwise saves cost and gives valid results.[59] If a nurse measures glucose level, a few dollars must be added for her training, time, and quality control.

Clinical use of glucose monitoring

Selecting suitable methods for glucose monitoring for individual patients is a matter of clinical judgment.[60] Test strip capillary glucose is recommended for patients receiving insulin (and sometimes for those receiving oral hypoglycemic medication), in particular those who are:

- pregnant;
- on intensive insulin regimens, including insulin pumps;
- has hypoglycemia unawareness;
- working as commercial drivers, traveling for their occupation, or working shifts; and
- experiencing acute or active illness and facing surgery.

In addition, TSCG is justified for educational purposes, "seizing the teachable moment," and for expediency in institutions.

Dipstick urine glucose testing is recommended for those whose treatment goal is readily achieved by DSUG, who are unable to operate or read a meter or test strip or draw conclusions from them, and who do not meet minimum prerequisites for TSCG quality control.

The ability of DSUG to assess the postprandial glucose peak could soon lead to a new indication for DSUG. Acarbose, released in Canada in 1995, aims specifically to lower that peak.

Tests should usually be done before meals and at bedtime. Results should be charted in a diary, in columns for each period, and should be expressed periodically as average, percent normal, or percent negative for the column. The diary must be on hand at each office visit. Self-monitoring is enhanced if patients are capable of drawing conclusions from their tests: calling the doctor, self-adjusting diet and exercise, or self-adjusting insulin by a sliding scale.

Marketing in the industry and consumers' infatuation with technology tend to cause overuse of TSCG. Assuming a Canadian population of 27 million and a diabetes prevalence of 5%, omitting one unnecessary TSCG (about $1) daily per

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patient translates into a savings of around $0.5 billion yearly. It has been estimated that $1.5 billion (US) might be saved annually in the United States by refraining from using TSCG for type II diabetes.[13]

Diabetes is a worldwide public health problem. The cost of diabetes care increases constantly as the prevalence of diabetes rises with affluence and with world population growth. Diabetics in developing countries and indigent people in Western society expect to receive care that is comparable to that provided for affluent patients. They should be dissuaded from costly glucose testing (such as TSCG) unless it will be helpful.[61] Considerable physician time can be taken dissuading patients and caregivers from unwarranted use of TSCG.

A rapid capillary blood glucose method, using the Beckman Glucose II, is available for hospital use. It can be kept on the ward but is operated by a laboratory technologist during three half-hour periods before meals, thereby assuring laboratory-style quality control and replacing the very expensive nurse-operated TSCG.

Capillary blood glucose testing is occasionally depicted as a dramatic recent advance, implying that successful metabolic control was nonexistent before it became available. In fact, teaching diabetics self-care through glucose monitoring progressed hand in hand with the evolution of glucose testing in its various forms, and successful insulin treatment, guided by DSUG, was practised as early as 1922 at the Joslin Clinic.[62]

Randomized studies to show the superiority of any of the tests discussed in this paper have not been done.[63] Dipstick urine glucose testing is neither useless nor obsolete,[64] and TSCG should not be vaguely described as exact. Heeding these conclusions will save private and public funds and will save some patients awkward test procedures.

The Diabetes Control and Complications Trial has confirmed that good metabolic control is beneficial.[65] Glucose monitoring with an open mind about using any of the tests discussed in this paper can be expected to lead to optimal control and best possible clinical outcome. ■

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Correspondence to: *Dr Bernd Koch, 238 Argyle Ave, Ottawa, ON K2P 1B9*

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