

OBSERVATIONS

Cost-Effectiveness of Two Screening Programs for Microalbuminuria in Type 2 Diabetes

The presence of microalbuminuria is associated with an increased risk for developing nephropathy and cardiovascular diseases in both type 1 and type 2 diabetes (1–3). A proper pharmacological treatment can reduce urinary albumin excretion rate (AER) and prevent clinical nephropathy. Consequently, the screening for microalbuminuria should be an essential tool of the care for diabetic patients.

Controversy still exists regarding the type of urine specimen to be used to evaluate microalbuminuria. AER determined in timed urine collections (24 h or overnight) is the most direct measure of urinary albumin excretion (4,5). However, due to the demand of the protocol and frequent imperfect patient adherence, the AER is not practical for epidemiological studies or clinical settings. For these reasons, the measurement of the albumin-to-creatinine ratio (ACR) in a random spot urine has become a widely accepted clinical tool for assessing urinary albumin excretion (6–8). Recently, several semiquantitative office tests for detecting abnormal albuminuria have been developed (9).

The aim of our study was to identify the easiest and most cost-effective screening program for microalbuminuria in an outpatient clinic. We evaluated specificity, sensitivity, and positive (PPV) and negative (NPV) predictive values of measurement of microalbuminuria by using ACR or by an immunological semiquantitative test in a first-morning spot urine sample in comparison with AER measured in three timed overnight urine collections.

Urinary albumin concentration was determined by using an immunological semiquantitative test (Micral-test; Roche Diagnostics, Mannheim, Germany) and the ACR by using DCA 2000 Analyzer

(Bayer, München, Germany) in a first-morning urine specimen of 1,712 type 2 diabetic patients consecutively admitted to our outpatient clinic. AER was then measured using three timed overnight urine collections that were performed at home a month after the screening evaluation. Albuminuria was detected by immunoturbidimetric method (Image; Beckman). Sensitivity, specificity, PPV, and NPV were calculated to determine the diagnostic properties of Micral and ACR. The AER, calculated as the median of three timed overnight urine collections, was used as the reference indicator. Microalbuminuria was defined as Micral-test ≥ 20 mg/l or ACR > 2.8 g/mol for women and > 1.9 g/mol for men (10) or AER between 20 and 200 $\mu\text{g}/\text{min}$. Patients with urinary tract infections, acetonuria, hematuria, or leucocyturia ($n = 56$) were excluded from the study.

In the remaining 1,656 patients eligible for evaluation, the median of AER revealed that 1,273 patients were normoalbuminuric (76.8%), 338 microalbuminuric (20.4%) and 45 macroalbuminuric (2.7%). These figures are similar to those already found in an Italian population (11). Macroalbuminuric patients were excluded from the subsequent analysis.

Of the remaining 1,611 patients, 516 patients were classified as microalbuminuric by using Micral-test (194 false-positive test results and 16 false-negative tests compared with the AER method). According to the ACR, 420 patients were microalbuminuric (95 false-positive tests and 13 false-negative tests). The correlation coefficient between ACR and AER levels was 0.858.

For the Micral-test, a sensitivity of 95.2%, a specificity of 84.7%, a PPV of 62.4%, and a NPV of 98.5% were calculated; for the ACR, a sensitivity of 96.1%, a specificity of 92.5%, a PPV of 77.3%, and an NPV of 98.9% were found.

Although the semiquantitative measurement (Micral-test) and ACR measurement in a first-morning urine specimen were easy methods, acceptable for patients, and convenient to be carried out in an office setting because of a fast reading time, both determinations had a very high sensitivity but a lower specificity. Particularly, 194 of 516 patients with Micral ≥ 20 mg/l were determined to be normoalbuminuric with AER; 95 of 420 patients who were determined to be

microalbuminuric with ACR were considered normoalbuminuric with AER. Although the use of ACR reduces the influence of variations in urinary flow rate, it is considerably more expensive than Micral-test (€4.64 vs. €1.54 per test), because the former needs the additional measurement of creatinine at the expense of extra costs. In our population, an initial screening to identify microalbuminuric patients carried out with ACR rather than Micral-test would have determined a much higher final cost (€7,684 vs. €2,250). However, this extra cost could still be acceptable if the results obtained were comparable to those found with a standard measurement of AER in a timed urine collection. Although in the past decade numerous reports evaluated the use of ACR in first-morning specimens as an alternative to AER (12), in our study, compared with AER, the good sensitivity of ACR (96.1%) was associated with a PPV of only 77.3%. Therefore, by using the determination of ACR rather than AER in our population to identify patients with microalbuminuria, ~6% of our normoalbuminuric type 2 diabetic patients would have received an inappropriate therapeutic intervention for microalbuminuria. On the other hand it remains to be established whether a repeated determination of ACR as for AER (in three first-morning spot urine samples) would have improved the specificity of ACR, thereby reducing the percentage of false-positive tests.

In conclusion, our results demonstrate that the detection of urinary albumin concentration in a first-morning urine sample by a semiquantitative test (Micral) is the easiest and most cost-effective screening procedure to identify microalbuminuric subjects in an outpatient type 2 diabetic population. The ACR, because of its low PPV, cannot substitute the determination of AER in timed overnight urine collections for the confirmation and the initiation of a therapeutic intervention for microalbuminuria in type 2 diabetic patients.

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Editor's Comment—I interpret these results to support the recommendation of both the American Kidney Foundation and the American Diabetes Association that ACR can be used instead of a timed collection. Timed collections, 24 h or otherwise, are very inconvenient and often not collected accurately. Since albumin excretion is highly variable from day to day (up to 25%), a repeat ACR to fulfill the criterion of two of three positive values within a 3- to 6-month period as recommended for the diagnosis of microalbuminuria would very likely have reduced the false-positive rate of 6%.

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Self-Monitored Blood Glucose in Pregnant Women Without Gestational Diabetes Mellitus

The Fourth Workshop-Conference on Gestational Diabetes Mellitus (GDM) recommended to lower maternal blood glucose (BG) goals (1). However, data on glucose values in non-diabetic pregnant women are scant and targets have not been derived from clinical trials (1). In addition, the regression line between laboratory and capillary BG measurements deviates from the origin with differences between meters (2).

We aimed to assess the BG range in pregnant women without GDM using self-monitoring of blood glucose (SMBG) with three reflectance meters (Accutrend Sensor, One Touch, and Precision). Universal GDM screening was performed using criteria from the first Workshop-Conference at three periods during pregnancy (before 24 weeks, at 24–28 weeks, and at 32–35 weeks). A total of 36 pregnant women were studied shortly after a normal screening/oral glucose tolerance test (12 subjects per period). Within each period, permuted-block randomization was performed and then separated into six groups (2 reflectance meters, sequence of use). Women were asked to perform SMBG before and 1 h after each main meal while maintaining their usual diet and activity. At each time two BG measurements were performed, one with each meter.

Maternal age was 30.2 years (24–38), BMI was 24.1 kg/m² (18.6–33.0), the gestational age at second screening was 26.0 weeks (24–29), and plasma glucose 1 h after challenge was 112.0 mg/dl (77–

174), without differences between groups (Kruskall-Wallis ANOVA). Women who were tested after the first period performed monitoring at a gestational age of 16 weeks (12–23), those who were tested after the second period performed monitoring at 27.5 weeks (24–30), and those who were tested after the third period performed monitoring at 36 weeks (32–39). Differences for capillary BG (mg/dl) in the three periods were tested with ANOVA and adjusted for the meter. Fasting BG decreased (first period 88.0 ± 9.4, second period 87.5 ± 14.0, and third period 78.8 ± 15.8) and 1-h postprandial BG increased in the third period (105.9 ± 21.6, 109.5 ± 15.5, and 117.5 ± 21.4), whereas no change was observed for preprandial (lunch/dinner) BG (85.9 ± 14.1, 87.7 ± 15.2, and 80.9 ± 17.7) and no influence for the meter was observed.

After we translated these results into practice, the first conclusion is that different meters do not seem to be a main determinant of SMBG values. Knowledge of SMBG values in healthy pregnant women can be used to establish glycemic goals for diabetic pregnant women. Recently, the maximal value for mean 1-h postprandial BG in healthy pregnant women (105.2 mg/dl) has been proposed as the target for diabetic pregnant women (3,4). This can be considered too tight because half of the pregnant population would be over the target, and to decrease BG implies risk (5). A range between mean and +1 SD or +1 SD and +2 SD would be safer. In this study, mean to +2 SD would translate into fasting BG 88–111 mg/dl before 30 pregnancy weeks and 79–110 mg/dl afterward, preprandial BG (lunch/dinner) 85–116 mg/dl throughout pregnancy, and 1-h postprandial BG 108–145 mg/dl before 30 weeks and 118–160 mg/dl afterward. In the aforementioned study (3), mean +2 SD for 1-h postprandial BG is <115 mg/dl, a figure remarkably lower. We have no clear explanation for the difference; it cannot be attributed to obesity (data not shown), and we can only speculate on the influence of reagent storage and meter calibration. This underscores the importance of additional information on SMBG values in healthy pregnant women.

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Pulmonary Mucormycosis in a Diabetic Patient with HIV

In 1994, a 43-year-old woman was admitted to the hospital for acute lung infection and was subsequently diagnosed with HIV without any opportunistic infection. One month before admission, she developed fever, asthenia, cough, and polyuro-polydipsic syndrome with a 10-kg weight loss. The chest X-ray was normal. Clinical assessment showed hyperthermia (38.4°C), permanent cough, hemoptysis, anterior chest pain, and crackles in the right upper field. The chest X-ray revealed a systematic opacity in the right upper lobe. A computed tomographic scan showed a voluminous cavitation (56 × 64 mm) with a bronchus of drainage. The laboratory tests revealed type 2 diabetes (glycemia 28 mmol/l; se-

rum HCO₃ 22 mmol/l; anti-GAD antibodies 0.51 units/ml [<1]; and C-peptide 2.3 ng/ml [0.9–4]). Her C-reactive protein level was 248 mg/l, and her blood cell count and electrolytes were in the normal range. Immunodeficiency was not severe (CD4 370/mm³) and her viral load was low (1,700 copies/ml). A bronchoscopy showed a diffuse mucosis thickening with congestion. Mycobacteriological culture from a transbronchial biopsy carried out a final diagnosis of mucormycosis. No other localization of mucormycosis was found.

Treatment involved systemic amphotericin B, surgical resection of the right upper lobe, and the strict glycemic control. One month later, the patient was afebrile and asymptomatic.

Mucormycosis is an opportunistic fungal infection commonly found in patients with neutropenia (immunosuppressive agents) and diabetes. Mucormycosis seldom occurs in AIDS patients, except in those with neutropenia or additional risk factors (1). Because of the aerobic nature of fungi, the rhinocerebral form is the most frequent (55%), followed by pulmonary localization (30%) (2). The disease is severe with vascular invasion, thrombosis, and necrosis. Diabetic subjects are predisposed to rhinocerebral location, whereas neutropenic subjects are susceptible to pulmonary or disseminated infections (3). Only 225 cases of pulmonary mucormycosis were reported, 56% of which were found in patients with diabetes (2). In neutropenic patients, the clinical presentation mimics pulmonary aspergillosis, a rapidly progressive pneumonia with diffuse infiltrates. Conversely, diabetic subjects develop a localized endobronchial form (4). In diabetic patients, the mechanisms of the disease involve the combined effects of hyperglycemia, ketosis, and acidosis. The fungistatic activity of serum is due to the transferrin, which reduces the free-iron available to the fungus for growth. Acidosis temporarily disrupts the ability of transferrin to bind iron. Since ketoreductase is available in the fungi, they can use ketone bodies in their metabolism (1). The mechanism is different in poorly controlled diabetes, owing to impaired chemotaxis and phagocytosis of neutrophils (1).

The diagnosis is difficult. The mucormycosis is usually fulminant and mostly discovered at autopsy (5). Overall mortal-

ity rate of pulmonary mucormycosis is ~80%, depending on underlying disease, delay to diagnosis, and extent of the lesion. Mortality is lower in surgical compared with medical treatment (11 vs. 68%) (2). Optimal therapy requires control of the underlying disease, surgical resection, and systemic antifungal therapy (1,2,4).

In this particular case, diabetes was probably the underlying disease and the HIV status was an additional risk factor. Moreover, the HIV infection favored a misleading diagnosis such as opportunistic infection (tuberculosis, aspergillus, etc.) or neoplasia.

In conclusion, mucormycosis should be considered in nonimmunodeficient diabetic patients with acute lung disease with cavitation, because early diagnosis and aggressive management maximize the chances for cure.

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A Mitochondrial Genotype Associated With the Development of Autoimmune-Related Type 1 Diabetes

Oxidative stress has been demonstrated to play an essential role in the destruction of pancreatic β -cells without infiltrating inflammatory cells in mice with type 1 diabetes (1). Recently, it was reported that a nucleotide substitution in mitochondrial DNA, a C-to-A transversion at nucleotide position 5178 within the NADH dehydrogenase subunit 2 gene, resulting in a Leu \rightarrow Met substitution (Mt5178A), is related to longevity and that individuals with Mt5178C are more susceptible to adult-onset diseases than those with Mt5178A (2). Mt5178C/A genotype may influence oxidative damage to mitochondrial DNA. Myers et al. (3) recently reported that the specific inhibition of mitochondrial oxidative phosphorylation induced hyperexpression of GAD in pancreatic β -cells. Inhibitors of NADH-ubiquinone oxidoreductase (complex I) seemed to be particularly effective in increasing the expression of GAD. Therefore, we hypothesized that the Mt5178C genotype is related to type 1 diabetes, especially autoimmune-related diabetes.

A total of 385 patients with type 1 diabetes (154 males, 231 females; current mean age 30.7 ± 5.5 years; onset age 14.4 ± 6.8 years; mean \pm SD) diagnosed under the age of 30 were randomly recruited from outpatients attending the Diabetes Center at Tokyo Women's Medical University. The subjects were diagnosed with type 1 diabetes according to the guideline of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (4). At the time of this study, all patients were ketosis-prone, and insulin treatment had been started immediately after the onset of type 1 diabetes. The

mean BMI was 21.1 ± 0.5 kg/m². The mean daily insulin dose was 1.01 ± 0.23 IU \cdot kg⁻¹ \cdot day⁻¹. A total of 469 healthy people (276 males, 193 females; current age 35.4 ± 6.4 years) who had no abnormality in glucose or lipid metabolism served as control subjects. The Mt5178A/C genotype was analyzed by use of PCR and restriction fragment-length polymorphism with *AluI* digestion (2).

The frequency of Mt5178C among patients with type 1 diabetes (264 of 385, 68.6%) was significantly higher than that among healthy control subjects (285 of 469, 60.8%) ($P = 0.017$; odds ratio 1.409; 95% CI 1.060–1.871). This finding suggests that Mt5178C is associated with genetic susceptibility to type 1 diabetes. There was no association of Mt5178C with HLA-DR4, -DR9, -DQ3, or -DQ4 as representative HLA class II molecules in Japanese patients with type 1 diabetes (5).

Next, the relation of mitochondrial genotype to the presence of pancreatic β -cell-specific autoantibodies was examined. Antibodies to GAD and to a receptor-type protein tyrosine phosphatase, designated IA-2, were assayed in a total of 180 subjects within 3 months after the onset of the disease. Sera within 2 weeks after the onset were tested for insulin autoantibody (IAA). The ratio of C-to-A was significantly higher in the patients who were positive for GAD antibody, IA-2 antibody, or IAA (Abs+) than in the patients who were negative for all three (Abs-) (Table 1).

Our present observation suggests that mitochondria with the Mt5178C genotype are susceptible to enhanced oxidative stress to pancreatic β -cells, resulting in activation of autoimmune mechanisms leading to the development of type 1 diabetes.

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Cockcroft's Formula Underestimates Glomerular Filtration Rate in Diabetic Subjects Treated by Lipid-Lowering Drugs

Diabetic subjects are often dyslipemic and have to be treated by fibrates or statins. These drugs must be cautiously used (and sometimes withdrawn) when chronic renal failure is present. Accurate evaluation of glomerular filtration rate (GFR) is thus of crucial importance in diabetic patients to detect early renal impairment. The Cockcroft-Gault formula estimates glomerular func-

Table 1—Frequency of Mt5178C and Mt5178A in 180 patients who were tested for GAD and IA-2 antibodies and IAA

	Abs+	Abs-	Odds ratio (95% CI)	P
C:A	94:42	20:24	2.686 (1.339–5.389)	0.0046

Table 1—Utilisation and impact of AHT on attained SBP in a whole district diabetes population

AHT	SBP (mmHg)			Total
	<140	140–160	>160	
Yes	587 (9) Well treated	880 (14) Suboptimally treated	1,069 (16) Poorly treated	2,536 (39) Labelled hypertensive
No	1,697 (26) Not hypertensive	1,295 (20) Possibly hypertensive	957 (15) Probably hypertensive	3,949 (61) Not labelled hypertensive
Total	2,284 (35)	2,175 (34)	2,026 (31)	6,485 (100)

Data are n (%).

treated to target SBP <140 mmHg, and only 285 (4%) attained a target of <130 mmHg. Using 160 mmHg as the definition and treatment target, 54% were hypertensive (3,493 of 6,485), of whom 957 were untreated and 1,069 were suboptimally treated (i.e., overall, 31% had SBP >160 mmHg).

Our hypertension prevalence (74%), low treatment rates (2,536 of 4,788, 53%), and poor control rates (587 of 4,788, 12%) at SBP of 140 mmHg compare directly with another U.K. study (5). These data clearly imply a huge workload for resource-constrained services. The obligation to improve access, equity, and systematic health care will increase this workload. Priority setting may deprive some people of potential but small benefits. However, concepts of rationing and prioritization to maximize gains and improve the efficiency of delivery of health care overall (6) must consider the curvilinear relationship between SBP and vascular risk. High-risk groups may be defined by understanding event rates for all vascular/diabetes complications at different SBP thresholds (1) (40.4, 51.3, and 76.2 per 1,000 person-years at <130, <140, and >160 mmHg, respectively). Our data strongly suggest that service providers must embrace these questions, and a necessary debate should ensue regarding the need for pragmatic intervention targets and how best to achieve them.

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A Case of Recurrent and Fatal Hypothermia in a Man with Diabetic Neuropathy

Severe hypothermia most commonly results from accidental exposure to environmental cold temperatures. However, numerous medical conditions can contribute to or even cause hypothermia, including those that increase bodily heat loss (e.g., exfoliative dermatitis), those associated with deficient heat pro-

duction (e.g., hypothyroidism, liver failure, and malnutrition), and those causing abnormal thermoregulation (e.g., spinal chord injury and sepsis syndrome). Hypothermia in diabetic patients is well described, particularly in association with hypoglycemic episodes (1) and diabetic ketoacidosis (2). Hospital admissions for hypothermia are more frequent among patients with diabetes than among the general patient population (3). Diabetic patients with neuropathy may be at risk for clinical hypothermia because of impairment of physiologic thermoregulatory mechanisms. We report a case of recurrent and fatal hypothermia in a man with diabetes and neuropathy.

P.V., a 40-year-old man with insulin-treated diabetes, was admitted to the intensive care unit of our hospital in January 2001 with hypothermia (rectal temperature 31.5°C) and coma. The patient was found by his wife early on the morning of admission to be cold and unresponsive. The patient had been discharged from our hospital only 1 week prior, and he was known to have diabetes, renal insufficiency, and lower-extremity neuropathy with reduced sensation and deep tendon reflexes. The medical record notes that the patient was also hypothermic (temperature 33.9°C) upon presentation for his prior admission. In the emergency department, his blood pressure was 78/48 mmHg, and his heart rate was 43 bpm and regular. The patient had no focal neurological deficit and a computed tomography scan of his head revealed old lacunar infarct. There was no leukocytosis or gap-acidosis, and his blood area nitrogen, creatinine, and glucose were 16 mmol/l, 504 μmol/l, and 6.9 mmol/l, respectively. The patient was given warmed intravenous fluids and blankets, but had an episode of ventricular tachycardia requiring defibrillation. The patient was moved to intensive care where he quickly

recovered and returned to his baseline level of health. The patient's thyroid function and cortisol response to stimulation were both normal. The chest radiograph showed no infiltrate, and blood cultures and HIV antibody were negative. He had no further episodes of hypothermia or arrhythmia, and he was discharged from the hospital. In February 2001, we received notification that the patient had expired at a local hospital after again being found by his wife to be unresponsive and cold. The medical record notes that the patient's temperature was 33.9°C upon his arrival to the other facility, where he was resuscitated but subsequently expired of cardiac arrest.

Diabetic patients with autonomic neuropathy may be predisposed to hypothermia by alteration of normal thermoregulatory mechanisms. Peripheral arterial vasomotion as measured with laser Doppler is impaired in diabetic patients with autonomic neuropathy (4), and these patients are at increased risk for intraoperative hypothermia (5). When exposed to external cooling, diabetic patients with autonomic neuropathy demonstrate impaired peripheral vasoconstriction and do not transiently increase their core temperature like nondiabetic patients (6). This case of recurrent and fatal hypothermia was due to the impairment of thermoregulatory mechanisms associated with diabetes and autonomic neuropathy. It is important to counsel diabetic patients, especially those who are elderly and have neuropathy, to guard against accidental cold exposure. Tests of autonomic function (e.g., heart rate variability testing) may identify diabetic patients at increased risk for hypothermia.

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Incidence and Costs of Severe Hypoglycemia

Hypoglycemia is a significant cause of morbidity and mortality and is the limiting factor in the successful metabolic control of diabetes. Severe hypoglycemic episodes can be life-threatening and are particularly feared by diabetic patients and their relatives.

In a prospective population-based study with sensitive screening for hypoglycemia, we determined the incidence and direct medical costs of severe hypoglycemia (SH) in a nonselected German population with 200,000 inhabitants (Detmold, East Westphalia) between 1997 and 2000. SH was defined as a symptomatic event requiring intravenous glucose or glucagon injection and was confirmed by a blood glucose measurement. To also detect atypical manifestations of SH, an initial blood glucose test from venous whole blood was performed in all 30,768 patients presenting to the medical emergency department of the region's central hospital and in 6,631 (85%) of all 7,804 patients attended by the emergency medical service in the region. The diabetes prevalence in Germany on the basis of pooled epidemiological data is 5%. Of these, 90% have type 2 diabetes, while 6% have type 1 diabetes (1). Therefore, in the investigated region with a population of 200,000 there will have been ~9,000 type 2 and 600 type 1 diabetic patients. During the 4-year period, 264 cases of SH (blood glucose 33 ± 17 mg/dl [SD]) were registered, comprising 14 (5%) cases of spontaneous hypoglycemia,

92 (35%) cases in type 1, 146 (56%) in type 2, and 10 (4%) in nonclassified insulin-treated diabetic patients. This corresponds to a rate of SH of 3.8/100 patients/year in type 1 diabetic patients and 0.4/100 patients/year in type 2 diabetic patients. These figures do not include the nonclassified insulin-treated diabetic patients. SH in type 1 diabetic patients was probably underreported because in some cases appropriately trained family members or carers would have been able to effectively treat SH by administration of glucagon without calling a doctor. Whereas 60% (55 of 92) of hypoglycemic patients with type 1 diabetes were treated only at the scene of the emergency by an emergency physician or in the hospital emergency department, hospitalization of patients with type 2 diabetes was usually unavoidable (95% [141 of 148]). Factors that contributed to inpatient treatment were poor general condition, concomitant disease requiring treatment, fractures and injuries sustained in connection with the hypoglycemia, and the need for monitoring in the 70 patients with sulfonylurea-induced hypoglycemia. Due to advanced age (76 ± 12 vs. 44 ± 17 years; $P < 0.0001$) and comorbidity (comedication 3.6 ± 2.6 vs. 1.0 ± 2.1 drugs; $P < 0.0001$), hypoglycemic individuals with type 2 diabetes spent considerably more time in hospital than type 1 diabetic patients (9.5 ± 10.6 vs. 2.3 ± 5.3 days; $P < 0.0001$). The total annual costs of SH including ambulance attendance (\$391 per item), treatment by emergency physicians (\$115 per item), hospitalization (\$220 per day), and outpatient treatment (\$22 per item) amounted to \$44,338/100,000 inhabitants in type 2 diabetic patients and \$8,129/100,000 inhabitants in type 1 diabetic patients.

SH is a common, cost-intensive complication of diabetes. Due to the high prevalence of type 2 diabetes there was a greater total number of events in type 2 than in type 1 diabetic patients. We believe that the medical and socioeconomic significance of SH in this specific group has been underestimated.

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Psychological Impact of Changing the Scale of Reported HbA_{1c} Results Affects Metabolic Control

HbA_{1c} has been an invaluable tool for the monitoring of long-term complications in type 1 and type 2 diabetes. However, in spite of the wide international use of HbA_{1c}, there has been a substantial lack of harmonization among methods (1). Both the Diabetes Control and Complications Trial (DCCT) (2) and the U.K. Prospective Diabetes Study (UKPDS) (3) used the same method for analysis of HbA_{1c} and, with the help of the National Glycohemoglobin Standardization Program (NGSP), many HbA_{1c} methods have been standardized to the results reported in these landmark trials (4). Pure reference material and reference methods for HbA_{1c} have been under development for many years by the International Fed-

eration of Clinical Chemistry (IFCC) (5) and are now in the final stages (6).

From a clinical point of view, it is essential that HbA_{1c} test results can be traced to the DCCT/UKPDS results where the relationships to risk for vascular complications have been established. Several experts have recommended that HbA_{1c} should be reported in "DCCT-equivalent" percentage units (7,8) in order to avoid the confusion of adding another scale of numbers.

We evaluated the effect on a diabetic patient population of raising the reference scale up to the DCCT level in 1992 and then down to the Swedish national standard in 1997.

All patients at our center who had acquired diabetes at least 3 years before the change in 1992 and who had follow-up HbA_{1c} readings for at least 2 years after the change were included in this study. We retrospectively collected chart data from 49 children and adolescents born between 1971 and 1989 who had their diabetes onset between September 1984 and October 1994. All participating patients have used intensive insulin therapy with four to six multiple daily injections since 1987. HbA_{1c} results within 2 years of diabetes onset were not included to remove any influence of the remission phase. Before 1992, our samples were sent to the local laboratory that used a Mono S HPLC method (Pharmacia, Sweden) with a normal range of 3.0–4.6%

(9). In 1992 we began using the DCA 2000 (Bayer Corporation) for HbA_{1c} measurements (normal range 4.1–5.7%) (10), which is calibrated to be traceable to the DCCT reference. The relationship between the Mono S and DCA 2000 numbers was as follows at that time: (Mono S = DCA × 0.869 – 0.34). In 1997 the calibration of our DCA 2000 was adjusted to be aligned with the Swedish national standard (normal range with DCA 2000 3.1–4.6%); the relationship to the original DCA 2000 results was follows: (Mono S = DCA × 0.973 – 0.908).

A seasonal effect with higher HbA_{1c} toward the end of the year can be seen (Fig. 1), as described earlier (11). After switching methods in 1992, patients received results that were 1.4% higher (mean of 24 paired samples) due to the change in calibration. However, after ~9–12 months, the mean HbA_{1c} level had decreased ~0.5% from the expected level, i.e., patients' glycemic control had actually improved. In 1997 when the national Swedish standard was introduced (12), the calibration of our DCA 2000 analyzer was adjusted to a level ~1.1% lower. Although HbA_{1c} results first decreased beyond the level expected based on the calibration change, several months later, patients' HbA_{1c} results increased, i.e., patients' glycemic control had actually deteriorated.

Why does the glycemic control of this population change 9–12 months after a

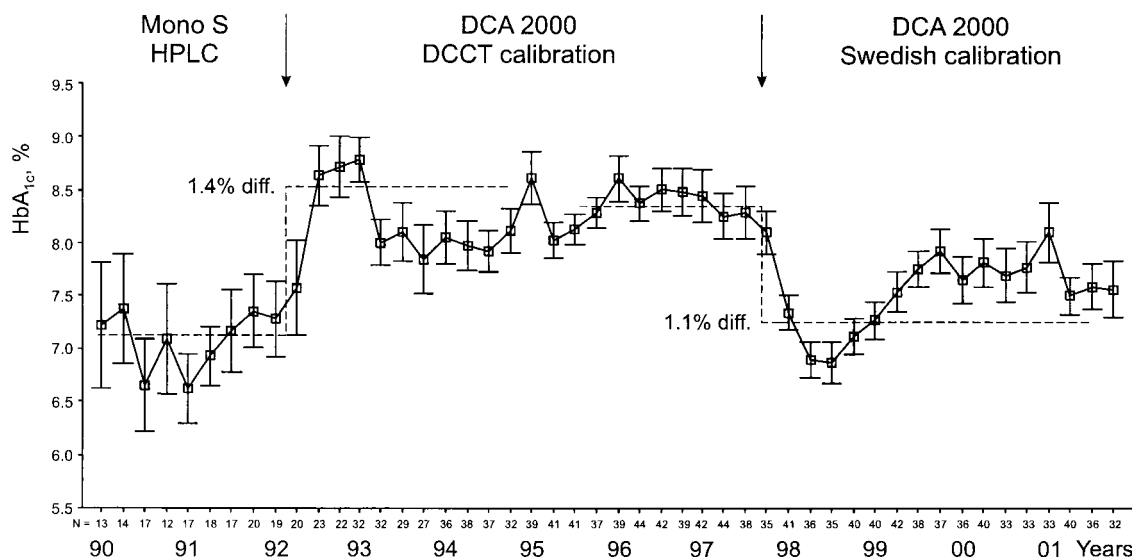


Figure 1—HbA_{1c} in percentage numbers as patients have seen them. The dashed lines indicate the expected change in HbA_{1c} due to the change in reference level (1.4 and 1.1% difference) in 1992 and 1997. Bars indicate ± SE. N refers to number of patients.

change in HbA_{1c} calibration? It seems as if persons and families with diabetes were aiming at a certain level of HbA_{1c} that had been rather stable throughout the years (13). When the numbers changed, we emphasized this to our patients, educating them as to which levels the new values referred. However, in spite of repeated information on this, the HbA_{1c} levels drifted back toward the previous level by ~0.5% on both occasions. This suggests that the psychological impact of the absolute numbers is very high when small changes are made to the patients' reference levels. Two to three years after the change in reference level, the average level in the population stabilized close to the expected original level, indicating psychological acceptance of the new HbA_{1c} scale (patients diagnosed after the HbA_{1c} change will not be affected by older reference levels). Other factors that may have influenced these changes in HbA_{1c} include the introduction of rapid-acting insulin analogs in 1996, long-acting analogs in 2001, and a slight (0.1–0.2% HbA_{1c}) change in calibration of the DCA 2000 analyzed in 1998.

The new international calibrator will be an important step for global harmonization of HbA_{1c}. However, the major question is if we should change the numbers that are presented to our patients with diabetes or just the reference for laboratory calibration (14,15). The new IFCC international calibration was initially thought to be at ~1% below the DCCT level, but after further work, the level is now ~1.5–2% lower than DCCT and 0.5–1% lower than the present Swedish level (16). Our data indicate that if we were to introduce this lower level to patients, there is a considerable risk of a deterioration in metabolic control of the magnitude of 0.5% for at least 2–3 years. Approximately one thousand HbA_{1c} months were needed (on average) for advanced complications to develop in a study on childhood-onset diabetes (17). The above-mentioned change in HbA_{1c} is equivalent to ~15 HbA_{1c} months in one individual, perhaps a small figure in terms of the number of A_{1c} months needed for advanced complications. However, in the DCCT, a 10% reduction in HbA_{1c} (e.g., from 7.0 to 6.3% HbA_{1c}) was associated with a 39% reduction in risk for retinopathy (18). Thus, it is likely that the increase of 0.5% HbA_{1c} observed in our

patient population indicates a clinically significant increased risk for development and/or progression of diabetic complications, causing both a substantial burden for the individual patient and a considerable additional cost for the health care system.

In conclusion, these data show a positive effect on the metabolic control in our patients when the HbA_{1c} reference level was adjusted up to the higher DCCT level. On the contrary, a considerable deterioration of metabolic control was induced when patients were presented with HbA_{1c} results on a lower scale, as would happen if the new IFCC number scale would be used to report HbA_{1c} results to patients.

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Forgot to Fast?

The importance on plasma glucose values

We have recently shown that by using a casual plasma glucose value of >5.5 mmol/l as a cut point for screening, the yield of newly diagnosed diabetic subjects and those with impaired glucose tolerance (IGT) is greatly enhanced in comparison to using 6.5 or 7.5 mmol/l as cut-points for diagnostic assessment using the 1999 World Health Organization (WHO) criteria (1–3). In lowering this screening cut point for casual measurement, factors such as the time of eating before this test on the result may be relevant to its utility and warrant investigation.

A total of 4,876 high-risk subjects, identified from 50,859 individuals participating in the Australian Diabetes Screening Study (1), provided fasting plasma glucose (FPG) and 2-h plasma glucose (2hPG) test results to confirm diabetes and IGT status. High risk was defined as having either two or more symptoms and/or two or more diabetes risk factors, casual plasma glucose values of >5.5 mmol/l, and no known diabetes (2). The time between when the subjects last ate and the casual plasma glucose test was calculated in minutes and grouped into hour blocks (0–360 min). Subjects were diagnosed as having diabetes or IGT using the 1999 WHO criteria (3).

A casual plasma glucose of >5.5 mmol/l yielded a positive diagnosis of diabetes in 557 subjects (20%) and of IGT in 776 subjects (28%) >2 h after eating. Within 0–2 h of eating, the diagnostic yield of diabetes was less (316 subjects, –15%) but IGT rate similar (541 subjects, –26%). In subjects with risk factors for diabetes, a casual plasma glucose of >5.5 mmol/l generates a similar proportion of IGT cases irrespective of time since eating.

Eating within 2 h of a casual glucose test in comparison to after 2 h resulted in a significantly higher level (7.09 ± 1.66 vs. 6.6 ± 1.38 mmol/l, respectively). However, if the screening cut point was raised for subjects who had consumed food within 2 h to 6.5 mmol/l, this would have yielded 249 (23%) diabetic subjects and 295 (25%) subjects with IGT. Raising

the casual plasma glucose threshold to 7.5 mmol/l would yield 187 (33%) diabetic subjects and 157 (28%) subjects with IGT. Despite the fact that consuming food within 2 h of a casual glucose test results in significantly increased values, the 5.5 mmol/l cut point identified an additional 67 subjects (27%) with frank diabetes. It is also important to note that the 5.5 mmol/l cut point almost doubled the number of subjects with IGT in comparison to the 6.5 mmol/l cut-point, and the number tripled if 7.5 mmol/l was chosen as a cutoff.

Thus the 5.5 mmol/l cut point seems to be valuable irrespective of the time since eating, as it results in early identification of subjects with IGT, which may aid in the prevention of the micro- and macrovascular complications associated with diabetes.

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The Role of Hemochromatosis C282Y and H63D Gene Mutations in Type 2 Diabetes

Findings from the Rotterdam Study and meta-analysis

Diabetes is a disease commonly found in patients with hemochromatosis (1). The hemochromatosis C282Y and H63D mutations in the HFE gene are associated with increased iron stores (2), which in turn are associated with glucose intolerance and insulin resistance (3). Whether these HFE mutations play an important role in the pathogenesis of type 2 diabetes is still a matter of controversy.

We have studied the frequencies of the C282Y and H63D mutations in 254 subjects with glucose intolerance, 220 patients with type 2 diabetes, and 595 normoglycemic individuals (control subjects), all derived from a population-based cohort study (Rotterdam Study) (4). Glucose levels were measured by the hexokinase method in fasting and post-load serum samples, and participants were classified as diabetic, glucose intolerant, or normoglycemic (4). Genotyping for the C282Y and H63D mutations was carried out as previously described (5).

In our population-based sample, we observed that 26 (10.5%) subjects with glucose intolerance, 24 (11.0%) with type 2 diabetes, and 61 (10.6%) control subjects were carriers of the C282Y mutation. For the H63D mutation, 65 (26.0%) glucose-intolerant subjects, 56 (25.7%) type 2 diabetic patients, and 168 (28.5%) control subjects were carriers. Also, the number of homozygotes for the H63D mutation in glucose-intolerant patients (1.7%) and in type 2 diabetic patients (1.8%) was similar to that seen in control subjects (1.5%). There were too few homozygotes for the C282Y mutation among glucose-intolerant ($n = 2$) and diabetic patients ($n = 1$) to yield reliable results.

Because of the low frequency of the C282Y mutation, we reanalyzed all published association studies between the HFE mutations and type 2 diabetes in a meta-analysis. Our meta-analysis included 12 studies for the C282Y mutation

and 8 studies for the H63D mutation. There was no evidence for heterogeneity ($\chi^2 = 18.5$, 11, $P = 0.07$) between studies. Of 2,630 type 2 diabetic patients, 225 (8.6%) were carriers of the C282Y mutations compared with 327 of 3,437 control subjects (9.5%), yielding an odds ratio (OR) (95% CI) of 1.0 (0.8–1.4), suggesting no association between C282Y and the risk of diabetes. When studying the C282Y homozygosity, there was no significant association to diabetes (1.1 [0.6–2.3]). For the H63D mutation, 559 type 2 diabetic patients of 1,889 (29.6%) and 690 control subjects of 2,524 (27.3%) were carriers, yielding an OR of 1.1 (1.0–1.3). The frequency of H63D homozygosity was modestly increased (1.2 [1.1–2.3]) in type 2 diabetic patients, suggesting no major effect of the H63D mutation on type 2 diabetes.

In conclusion, there was no evidence for an increased frequency of the C282Y or H63D mutations in patients with impaired glucose intolerance or type 2 diabetes in our population-based sample or in the meta-analysis. Also, the findings of our meta-analysis suggest that the role of HFE mutations in the pathogenesis of diabetes in the general population is limited.

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The Use of Alkali Therapy in Severe Diabetic Ketoacidosis

The use of bicarbonate in patients with diabetic ketoacidosis (DKA) is controversial (1), especially in patients with severe DKA (pH <7.0). Previous studies have shown that the use of bicarbonate in patients with moderate DKA (pH >7.0) is not associated with better outcomes, when compared with saline-treated control subjects (2–5), and can generate lactate (3). The use of bicarbonate therapy in patients with severe DKA has not been addressed adequately, due to a lack of data on benefit or harm of bicarbonate therapy in severe DKA, but dogmatic use of bicarbonate still continues in such cases. In our initial randomized study, 5 of 11 patients had pH <7.0 (none below 6.9), but the outcome was no different from the group of patients who did not receive bicarbonate (4).

To examine this issue we evaluated records of 41 patients with DKA who were admitted to the medical intensive care unit at the Regional Medical Center, The University of Tennessee, between July 1999 and December 2000. We identified 5 DKA patients (group 1) with pH <7.0 (mean pH 6.85 ± 0.09) and compared their responses to treatment with 36 case subjects (group 2) with pH >7.0 (7.15 ± 0.11). The admission glucose

and biochemical parameters were not significantly different between the two groups. All patients were treated with a low-dose insulin infusion protocol (1). Four of the five patients with severe DKA received a small initial dose of intravenous bicarbonate (50 mmol), whereas none of the patients with pH >7.0 received bicarbonate therapy. One patient with severe DKA died during the hospital stay. She was admitted with pneumonia, sepsis, and multi-organ failure and received bicarbonate therapy for her acidosis. Of the remaining four cases who survived, three received 50 mmol bicarbonate each and one did not. The administration of bicarbonate therapy did not appear to have an impact on the time for resolution of DKA or hospital length of stay in the four patients when compared with the patients who did not get bicarbonate. However, the number of subjects was too few to draw any meaningful conclusion on the utility of bicarbonate. There was no mortality in group 2.

Our review of present cases showed that 12% of patients admitted to the hospital with DKA had pH <7.0. This clearly indicates that the number of patients with severe DKA is large enough to merit a comprehensive study on the efficacy of bicarbonate therapy. Furthermore, the cardiac and, especially, the left ventricular status of such patients is not known (6). This controversial subject could only be settled by evidence-based studies under a prospective randomized protocol, which at this time is not available.

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Alternative-Site Blood Glucose Measurement at the Abdomen

Alternative sites for self-monitoring of blood glucose (SMBG) (e.g., forearm, abdomen, calf, or thigh) are currently being introduced in clinical practice (1). However, blood glucose (BG) concentrations by these methods may differ from those by traditional fingertip pricking (2–4). In an elegant study, Jungheim and Koschinski (3) demonstrated that BG measurements, at the forearm by three commercially available devices, showed a less steep increase after an oral glucose load and a delayed decline after insulin administration. In addition, Ellison et al. (4) showed similar findings, which were less adequately followed at the forearm after a standardized meal.

Given the patients' preference for alternative-site SMBG, an appreciation mainly based on the avoidance of painful fingertip pricking (1), clinical application will certainly ensue and, thereby, will introduce a new problem, i.e., what glucose value is actually measured and how does this relate to reference values?

We compared capillary BG taken at the fingertip (Glucotrend; Roche Diagnostics, Mannheim, Germany) and the abdominal wall (Freestyle; Disentronic, S'ulzbach, Switzerland) in 12 healthy nondiabetic males (age 25 ± 11 years [mean \pm SD], BMI 23.7 ± 3.5 kg/m²).

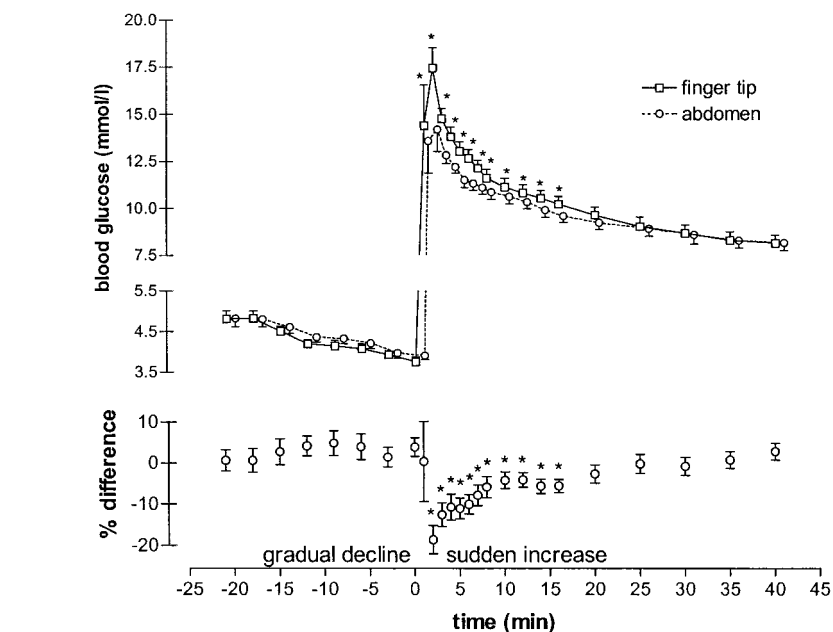


Figure 1—Fingertip and abdominally measured capillary blood glucose concentrations after a gradual decline and sudden increase in blood glucose level. * $P < 0.01$.

The participants arrived at the outpatient clinic after an overnight fast. They were clamped on their fasting BG by a varying glucose infusion and received an intravenous insulin infusion of $30 \text{ mU} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. After 60 min, the glucose infusion was stopped and BG was allowed to drop to near hypoglycemic levels. Then, after BG was increased by intravenously administered glucose (20% by weight, $0.15 \times \text{body weight} \times 12$ [ml]), which was intended to increase BG 12 mmol/l above the actual BG level, the glucose infusion rate was increased. BG was measured every 5 min at the abdomen and fingertip. This was done every minute for 15 min after the sudden increase in BG. The agreement in fingertip and abdominal BG measurements during the gradual decrement and the sudden increment in BG levels was evaluated by repeated measurement ANOVA. Abdominal BG measurement adequately followed the decline in BG measured at the fingertip (see figure). In contrast, abdominal BG concentrations were 10–18% lower than fingertip BG the first 15 min after the rise in BG ($P < 0.01$, see figure).

Our finding that an increase in BG was less well followed by abdominal BG measurements supports the contention of Jungheim and Kochinsky (3) that alternative-site SMBG differs from classic fingertip pricking. It illustrates the existence

of tissue-specific differences in glucose kinetics, and we previously noted that distribution effects may play a role in abdominal BG measurements (6,7). Obviously, compartment-dependent glucose characteristics should be taken into account with alternative-site SMBG. One solution is adjustment of glucose values generated from alternative sampling sites (forearm, abdomen, thigh, or calf) to arterial or nearby fingertip capillary values, known as the golden reference, and this was actually done in the report of Jungheim and Koschinski (3). Another approach could be that BG measurements are interpreted according to the site-specific characteristics. For instance, hypoglycemic episodes were more protracted in abdominal subcutaneous adipose tissue (8), suggesting that clinically relevant tissue glucopenia may be overlooked by conventional BG measurements. This illustrates that alternative sites may be preferable as they may better reflect tissue glucose homeostasis. Therefore, we challenge the view that fingertip capillary BG is the only reference in denoting BG excursions. We are entering a new era of BG monitoring with the first available glucose sensors that will provide us with a wealth of data on previously unavailable BG excursions, but at the same time confront us with compartment-

specific differences in BG concentrations from traditional fingertip pricking.

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COMMENTS AND RESPONSES

The Long-Term Effects of Self-Management Education for Patients With Type 2 Diabetes on Glycemic Control

Response to Norris et al.

We read with interest the recently published meta-analysis by Norris et al. (1), which focuses on the effects of diabetes self-management education (DSME) on glycemic control in adult patients with type 2 diabetes. They report that this intervention decreases patients' GHb levels by 0.76% at immediate follow-up, by 0.26% at the 1- to 3-month follow-up and by 0.26% at ≥ 4 months of follow-up. They conclude in both this meta-analysis and their previous systemic review (2) that DSME alone moderately but significantly improves GHb levels in the short term but that its long-term effects still need to be determined in a study of randomized controlled intervention.

As part of the Japan Diabetes Complications Study (JDCS), we have been evaluating the long-term effects of DSME for >5 years in 2,205 adult patients with type 2 diabetes. Our study is longer and involves more patients than any of the trials included in the meta-analysis by Norris et al. Ours is a randomized, controlled, multicenter, intervention trial that aims to evaluate the effects of DSME. The trial involves 59 institutes specializing in diabetes care, and the 3-year interim report will be published shortly (3). In brief, we randomly allocated patients with previously diagnosed type 2 diabetes and HbA_{1c} levels of $\geq 6.5\%$ into either an intervention (INT) group or a control (CON) group. The patients in the CON group received regular conventional care before or during the study period. Although changes in medication were not restricted in either group, there were no significant differences in terms of therapeutic contents between the CON and INT groups even after

3 years. The patients in the INT group received DSME, which comprised all of the categories that Norris et al. included in their meta-analysis (1) and consisted mainly of intensive lifestyle management at each outpatient clinic visit and frequent telephone counseling by trained diabetes educators. Our results show that there are small but significant differences in HbA_{1c} levels between the INT and CON groups that are still maintained 3 years after the start of intervention (CON group $7.78 \pm 1.27\%$ vs. INT group $7.62 \pm 1.20\%$, $P = 0.0023$). Although the difference between the two groups is small, it should be noted that a bias arising from variations in the techniques of GHb measurement, as discussed by Norris et al. (1), does not exist in Japan, where a highly standardized assay is used throughout the country. Therefore, the difference in the JDCS study is likely to be a realistic measurement of the effect of DSME intervention.

The improvement in GHb levels of <1% seen in the results of the meta-analysis (1), as well as in our longer-term trial (3), seems to be clinically trivial and disappointing as compared with medical interventions (i.e., drugs or insulin). As Norris et al. discuss in their article (1), however, it is still clinically meaningful because each 1% reduction in HbA_{1c} levels over 10 years has been shown to be associated with a 37% reduction in the risk of microvascular complications in the U.K. Prospective Diabetes Study (UK-PDS) (4). We expect that further meta-analyses regarding differences in long-term costs and the patients' quality of life between DSME and medications that lower GHb levels will be carried out. In the JDCS, however, the long-term effects on lifestyle brought about by DSME and the cost of its implementation are already under analysis.

In summary, on the basis of the large-scale JDCS trial, we can conclude that the moderate but significant improvement effected by DSME on the glycemic control of adult patients with type 2 diabetes is maintained even in the long term.

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Editor's Comment: "It Ain't Necessarily So"

As much as we may wish to believe that diabetes education per se leads to improved long-term glycemic outcomes, the evidence is not particularly strong. The review by Norris et al. (1), to which the letter by Sone et al. (3), above, is addressed, and an earlier one by Clement (2) do not support this contention. Likewise, neither does the accompanying letter by Sone et al. (3). They contend that the 0.16% difference in HbA_{1c} levels after 3 years between an intervention group receiving diabetes self-management education and a control group receiving regular conventional care in the Japanese Complications Study would be “clinically meaningful because each 1% reduction in HbA_{1c} levels over 10 years has been shown to be associated with a 37% reduction in the risk of microvascular complications in the U.K. Prospective Diabetes Study (UKPDS) (4).” Unfortunately for the hypothesis, it is an average reduction of 1% in HbA_{1c} levels per year over 10 years—not a cumulative decrease over 10 years—that leads to this favorable outcome.

For those of you who remember trying to prove mathematical theorems, the concepts of necessary and sufficient are germane, in my view, to the situation concerning diabetes education and glycemic outcomes. Certain conditions are necessary to prove theorems, but they won't do

it by themselves. On the other hand, for some theorems, if a specific condition is met, it is sufficient to prove that theorem all by itself. I think of diabetes education as a necessary condition, but without an appropriate management component, it is not sufficient. On the other hand, without appropriate education, a management piece is usually not all that effective. Therefore, in this analogy, the difficulty of showing the effectiveness of diabetes self-management education is that patients often return to medical environments in which appropriate management is lacking.

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