OBSERVATIONS

Pseudohypoparathyroidism, Obesity, and Type 2 Diabetes

A hypothesis

Pseudohypoparathyroidism (PHP) type Ia is a disorder of the stimulatory guanine nucleotide-binding protein α-subunit ($G_{s\alpha}$)-mediated signal transduction, with characteristics of Albright's osteodystrophy (AHO), hypocalcemia due to resistance to parathyroid hormone (PTH), hypothyroidism, etc. Pseudopseudohypoparathyroidism (pseudo-PHP) is generally considered to be related to PHP Ia. PHP Ia and pseudo-PHP are not included among "other genetic syndromes sometimes associated with diabetes" in the 1997 report of the American Diabetes Association expert committee (1). However, Wu et al. (2) have recently shown two siblings with pseudo-PHP and type 2 diabetes. They raised a possibility that abnormal $G_{s\alpha}$ activity might directly contribute to insulin resistance, although only $G_{i\alpha 2}$ has been known to relate to insulin action so far (3). They also proposed that the coexistence might be caused by a link between $G_{s\alpha}$ gene mutations (on chromosome 20q) and genetic loci for type 2 diabetes.

We have studied a Japanese family presenting both PHP Ia and type 2 diabetes. The proband was a 25-year-old female. She was 144 cm in height (BMI 34.0 kg/m^2) and showed typical AHO. Her serum calcium level was as low as 1.62 mmol/l, accompanied by a markedly elevated intact PTH concentration (310 pg/ml; normal 15–50 pg/ml). The absence of a response by urinary phosphate and cyclic AMP excretion to human PTH bolus confirmed resistance to PTH. Mild hypothyroidism with a raised thyroid-stimulating hormone level, diminished response of plasma cyclic AMP to intravenous glucagon administration, and history of oligomenorrhea also suggested multiple hormone resistance in the proband. $G_{s\alpha}$ activity and the protein content in the erythrocyte membrane of the proband were ~27 and ~13% that of the control subjects, respectively (4). Notably, her fasting glucose level was 7.4 mmol/l, HbA_{1c} was 6.5% (normal 4.3–5.8%), and 2-h glucose was 13.4 mmol/l in the 75-g oral glucose challenge. Plasma insulin concentrations were 102 pmol/l in the fasting and 552 pmol/l in the 2-h, respectively, suggesting presence of insulin resistance. An insulinogenic index, a marker of early-phase insulin secretion (5), was as low as 0.30 (normal 0.70–1.30). Abdominal computed tomography revealed dominant accumulation of visceral fat rather than subcutaneous fat. Her younger sister had been already diagnosed as having PHP Ia, but her fasting glucose level was reported to be normal. Her mother, who had been treated as a type 2 diabetic patient with diet therapy, showed AHO, normal serum calcium, and mildly increased intact PTH level (85 pg/ml).

Resistance to PTH, thyroid-stimulating hormone, and gonadotropin is an outstanding feature of PHP Ia. However, actions of catecholamines are also mediated via the G-protein–adenylate cyclase pathway. Recent studies show the importance of impaired lipolysis induced by catecholamines in the pathogenesis of obesity (6). Defective stimulation of adipocyte adenylate cyclase and blunted lipolysis by catecholamines were also demonstrated in subjects with PHP Ia (7). Furthermore, oligodeoxynucleotides antisense to $G_{s\alpha}$, i.e., reduced $G_{s\alpha}$ function, accelerated differentiation of fibroblasts to adipocytes (8), and recent data reveal that accelerated differentiation to adipocytes may cause obesity in humans (9). Thus, we hypothesize that decreased catecholamine-induced lipolysis and/or accelerated differentiation to adipocytes due to impaired $G_{s\alpha}$ activity leads to obesity and insulin resistance in PHP Ia subjects. The subjects might finally develop type 2 diabetes when accompanied by diminished early-phase insulin secretion (10). We speculate that the coexistence of PHP Ia (or pseudo-PHP) and type 2 diabetes is not simply an incidental phenomenon, although it remains to be elucidated whether there is a link between the $G_{s\alpha}$ locus and susceptible genes to type 2 diabetes.

AKIO KAWAKAMI, MD
SHOICHIRO NAGASAKA, MD
KUMIKO ROKKAKU, MD
TOMOATSU NAKAMURA, MD
IKUYO KUSAKA, MD
YUKIKO YAJIMA, PHD
SAN-E ISHIKAWA, MD
TOSHIKAZU SAITO, MD

From the Division of Endocrinology and Metabolism (A.K., S.N., K.R., T.N., I.K., S.I., T.S.), Department of Medicine, Jichi Medical School, Tochigi; and the Tokyo Metropolitan Institute of Medical Science (Y.Y.), Tokyo, Japan.

Address correspondence to Shoichiro Nagasaka, MD, Division of Endocrinology and Metabolism, Department of Medicine, Jichi Medical School, Yakushiji 3311-1, Minamikawachi, Tochigi 329-0498, Japan.

References

1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
2. Wu C-J, Sheu WH-H: Type 2 diabetes in adults with pseudopseudohypoparathyroidism: case report (Letter). *DiabetesCare* 21:1575–1576, 1998
3. Moxham CM, Malbon CC: Insulin action impaired by deficiency of the G-protein subunit $G_{i\alpha 2}$. *Nature* 379:840–844, 1996
4. Saito T, Akita Y, Fujita H, Furukawa Y, Tsuchiya Y, Yasuda T, Yamamoto M, Kitagawa T, Nakagawa Y, Takehiro A, Fujita T, Kodama S, Kuzuya T: Stimulatory guanine nucleotide binding protein activity in the erythrocyte membrane of patients with pseudohypoparathyroidism type I and related disorders. *Acta Endocrinol*111: 507–515, 1986
5. Kosaka K, Hagura R, Kuzuya T: Insulin responses in equivocal and definite diabetes, with special reference to subjects who had mild glucose intolerance but later developed definite diabetes. *Diabetes* 26:944–952, 1977
6. Bougnères P, Stunff CL, Pecquer C, Pinglier E, Adnot P, Ricquier D: In vivo resistance of lipolysis to epinephrine: a new feature of childhood onset obesity. *J Clin Invest*99:2568–2573, 1997
7. Kaartinen JM, Käär M-L, Ohisalo JJ: Defective stimulation of adipocyte adenylate cyclase, blunted lipolysis, and obesity in pseudohypoparathyroidism 1a. *Pediatr Res* 35:594–597, 1994
8. Wang H, Watkins DC, Malbon CC: Antisense oligodeoxynucleotides to G_S protein α-subunit sequence accelerate differentiation of fibroblasts to adipocytes. *Nature* 358:334–337, 1992
9. Ristow M, Muller-Wieland D, Pfeiffer A, Krone W, Kahn CR: Obesity associated with a mutation in a genetic regulator of adipocyte differentiation. *N Engl J Med* 339:953–959, 1998
10. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Charles MA, Bennett PH: A two-step model for development of non-insulin-dependent diabetes. *Am J Med*90:229–235, 1991

Hepatocyte Nuclear Factor-1α G319S

A private mutation in Oji-Cree associated with type 2 diabetes

The prevalence of type 2 diabetes in adult Canadian Oji-Cree approaches 40%, which is among the highest found in any subpopulation in the world (1). Management of the complications of type 2 diabetes will challenge the existing paradigms for health care delivery to the ~16,000 Oji-Cree who inhabit a land mass roughly the size of France in the far northwest of Ontario. The especially high prevalence of type 2 diabetes in the Oji-Cree suggests that these people may harbor some genetic predisposition to the disease that has been unmasked by recent lifestyle changes (2). One candidate gene for type 2 diabetes encodes the transcriptional protein hepatic nuclear factor (HNF)-1α, part of the homeobox gene family (3). Mutations in HNF-1α are found in some patients with maturity-onset diabetes of the young, who have defective insulin secretion, and in rare subjects with early-onset type 2 diabetes (4,5).

While sequencing the HNF-1α gene in 117 adult Oji-Cree with apparently typical type 2 diabetes and 334 adult Oji-Cree without type 2 diabetes, we identified a new mutation resulting in the substitution of serine for glycine at codon 319. The G319S mutation resides within the proline 11–rich domain of the transactivation site of HNF-1α and affects a glycine residue that has been conserved throughout evolution (3). There was no other mutation found in any coding region, intron-exon boundary, or 5′ or 3′ flanking region. The overall HNF-1α S319 allele frequency in the Oji-Cree was 0.119 (107/902), which was significantly different ($P < 10^{-13}$) from its complete absence from 990 alleles of subjects from six other ethnic groups, including Canadian Inuit and Ojibway, suggesting that the mutation was private to Oji-Cree.

We next examined allele and genotype frequencies in subjects with and without type 2 diabetes. Genotype frequencies did not deviate from Hardy-Weinberg expectations in each group. We observed that the S319 allele frequency of 0.209 (49/234) in the diabetic Oji-Cree was significantly higher than the S319 allele frequency of 0.087 (58/668) in the nondiabetic Oji-Cree ($P < 10^{-6}$). Compared with G319/G319 homozygotes, the S319/S319 homozygotes had a relative risk for type 2 diabetes of 4.00 (95% CI 2.65–6.03) and the S319/G319 heterozygotes had a relative risk for type 2 diabetes of 1.97 (1.44–2.70). These proportions, ratios, and levels of significance were similar for analyses involving either all study subjects or a subgroup of subjects who were unrelated to each other (6).

Thus, almost 40% of Oji-Cree with type 2 diabetes were either homozygous or heterozygous for the HNF-1α G319S mutation. Assuming that the observed allele and genotype frequencies are representative of the aboriginal people of Northwestern Ontario, there may be as many as 200 S319/S319 homozygotes and 3,000 S319/G319 heterozygotes residing there. These subjects would represent a high-risk group for developing type 2 diabetes. Since the expression of diabetes in susceptible Oji-Cree appears to have been exacerbated by the recent community-wide decreases in physical activity and increases in dietary intake of total calories and saturated fat (1,2), it is possible that having a population-specific marker would target those Oji-Cree subjects who might benefit the most from a strategy that reverses these lifestyle changes.

Acknowledgments — This work was supported by grants from the National Institutes of Health (DK44597-01), the Ontario Ministry of Health (#04307), the Medical Research Council of Canada (MT13430), the Canadian Diabetes Association, and the Blackburn Group. R.A.H. is a Career Investigator of the Heart and Stroke Foundation of Ontario. S.B.H. is a Career Investigator of the Ontario Ministry of Health. A.J.G.H. is supported by Health Canada through a National Health Research and Development Program Research Training Award.

We thank the chief and council of the community of Sandy Lake, the Sandy Lake nurses, and the staff of the Sioux Lookout program.

ROBERT A. HEGELE, MD
HENIAN CAO, MD
STEWART B. HARRIS, MD
ANTHONY J.G. HANLEY, MSC
BERNARD ZINMAN, MD

From the Robarts Research Institute (R.A.H., H.C.) and the Centre for Studies in Family Medicine (S.B.H.), University of Western Ontario, London, Ontario; and the Samuel Lunenfeld Research Institute and Department of Medicine (A.J.G.H., B.Z.), Mount Sinai Hospital, University of Toronto, Ontario, Canada.

Address correspondence to Robert A. Hegele, Blackburn Cardiovascular Genetics Laboratory, Robarts Research Institute, 406-100 Perth Dr., London, Ontario, Canada N6A 5K8. E-mail: robert.hegele@rri.on.ca.

References

1. Harris SB, Gittelsohn J, Hanley AJG, Barnie A, Wolever TMS, Gao J, Logan A, Zinman B: The prevalence of NIDDM and associated risk factors in native Canadians. *Diabetes Care* 20:185–197, 1997
2. Gittelsohn J, Wolever TM, Harris SB, Harris-Giraldo R, Hanley AJ, Zinman B: Specific patterns of food consumption and preparation are associated with diabetes and obesity in a native Canadian community. *J Nutr* 128:541–547, 1998
3. Cereghini S: Liver-enriched transcription factors and hepatocyte differentiation. *FASEB J* 10:267–282, 1996
4. Hattersley AT: Maturity-onset diabetes of the young: clinical heterogeneity explained by genetic heterogeneity. *Diabet Med* 15:15–24, 1998
5. Velho G, Froguel P: Genetic, metabolic and clinical characteristics of maturity onset diabetes of the young. *Eur J Endocrinol* 138:233–239, 1998
6. Hegele RA, Cao H, Harris SB, Hanley AJG, Zinman B: The hepatic nuclear factor-1α G319S variant is associated with early onset type 2 diabetes in Canadian Oji-Cree. *J Clin Endocrinol Metab* In press

Insulin Autoimmune Syndrome After Therapy With Imipenem

Our patient is a 68-year-old Caucasian man born in Germany. He was referred for evaluation of recurrent episodes of hypoglycemia. His medical history consisted of nephrolithiasis with recurrent attempts to perform lithotomy. In the weeks before our acquaintance, he underwent several hospitalizations in the department of urology because of urosepsis. During this period, he was treated with broad-spectrum antibiotics, the most recent of which was imipenem, an carbapenem antibiotic.

During his most recent hospitalization, he began to complain of recurrent attacks of weakness, diaphoresis, and palpitations. Fingertip glucose measurements during

the attacks unfailingly revealed hypoglycemic values, and he was transferred to the department of medicine for further evaluation. On admission, a 72-h fast was instituted, during which hypoglycemic attacks, albeit without loss of consciousness, appeared. Glucose values during these attacks were in the range of 36–87 mg/dl; conversely, glucose values between attacks were in the range of 73–250 mg/dl.

The immunoreactive insulin level was extremely high, with values exceeding 200 μIU/ml (normal range 7–25 μIU/ml) and concurrent C-peptide levels of 7.6–16 nmol/l (normal range 0.8–4 nmol/l). Cortisol levels during and between attacks were within normal range. Because tests for sulfonylurea were repeatedly negative, a presumptive diagnosis of insulinoma was made. Attempts at tumor localization were undertaken: an abdominal computed tomography scan was normal, as was an endoscopic ultrasonogram of the pancreas. Whereas celiac angiography failed to reveal local enhancement, venous sampling exhibited elevated levels of both insulin and C-peptide (1,100–1,300 μIU/ml and 9–11 nmol/ml, respectively). Selective injection of calcium into pancreatic arterioles with simultaneous sampling from the right hepatic vein failed to reveal an increase in insulin levels. Finally, insulin autoantibodies were elevated to a titer of 1,158 nU/ml (normal value <112 nU/ml). DNA analysis revealed a DRB4 haplotype.

The patient continued to experience an average of one symptomatic hypoglycemic attack per day while exhibiting normoglycemic and hyperglycemic values between attacks. After cessation of treatment with imipenem, the frequency and severity of hypoglycemic episodes lessened, and they disappeared altogether after several weeks. No immunosuppressive therapy was required.

The insulin autoimmune syndrome has become an increasingly recognized cause of hypoglycemia. In most cases, an underlying clinical or biochemical autoimmune disorder is found, and an association with HLA types Cw4 and DR4 is well recognized in the Japanese cases (1). Many cases have evolved after exposure to sulfhydryl-containing drugs (2–5) as well as drugs such as hydralazine (6). It is assumed that the sulfhydryl group interacts with the disulfide bonds of insulin and renders it immunogenic, either by haptene formation or by cleavage of the disulfide bonds of the insulin molecule (7). Dissociation of insulin from the insulin-antibody complex thereupon produces hypoglycemia during periods of fasting.

Until now, the insulin autoimmune syndrome has been described mainly in Japan, where it is the third leading cause of hypoglycemia (8), as well as sporadically elsewhere (6). The importance of making a timely diagnosis is twofold. First, it allows any medication that could be implicated in the pathogenesis of the syndrome to be recognized and discontinued. The present case involved recognition of the carbapenem antibiotic imipenem, which was not previously described in association with the formation of insulin autoantibodies, although it contains a sulfhy03493Mdryl group. Second, a timely diagnosis avoids an unnecessary major surgical intervention in a vain search for insulinoma. The differentiation is simple when one keeps in mind that fasting insulin levels in cases of insulinoma are usually <100 μU/ml (9), as opposed to values >1,000 μU/ml in the insulin autoimmune syndrome. In the few cases in which pancreatectomies were performed unduly, β-cell hyperplasia was indeed revealed (7).

For the patient described herein, a timely diagnosis with discontinuation of the offending drug, imipenem, resulted in full clinical recovery within a few weeks.

MERAV LIDAR, MD
RITA RACHMANI, MD
ELISABETH HALF, MD
MORDCHAI RAVID, MD

From the Department of Medicine, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv; and Meir Hospital, Kfar Sava, Israel.

Address correspondence to M. Ravid, MD, Dept. of Medicine, Meir Hospital, Kfar Sava 44281, Israel. E-mail: ravidm@netvision.net.il.

References

1. Benson EA, Ho P, Wang C, Wu PC, Fredlund PN, Yeung RTT: Insulin autoimmunity as a cause of hypoglycemia. *Arch Intern Med* 144:2351–2354, 1984
2. Blackshear PJ, Rotner HE, Kriauciunas AM, Kahn CR: Reactive hypoglycemia and insulin autoantibodies in drug-induced lupus erythematosus. *Ann Intern Med* 99:182–184, 1983
3. Folling I, Norman N: Hyperglycemia, hypoglycemic attacks, and production of anti-insulin antibodies without previously known immunization: immunological and functional studies in a patient. *Diabetes* 21:814–826, 1972
4. Hakamata M, Itoh M, Sudo Y, Miyata N: Insulin autoimmune syndrome after the third therapy with methimazole. *Intern Med* 34:410–412, 1995
5. Uchigata Y, Kuwata S, Tokunaga K, Eguchi Y, Takayama-Hasumi S, Miyamoto M, Omori Y, Juji T, Hirata Y: Strong association of insulin autoimmune syndrome with HLA-DR4. *Lancet* 339:393–394, 1992
6. Burch M, Clement S, Sokol MS, Landry F: Reactive hypoglycemic coma due to insulin autoimmune syndrome: case report and literature review. *Am J Med* 92:681–685, 1992
7. Benson EA, Ho P, Wang C, Wu PC, Fredlund PN, Yeung RTT: Insulin autoimmunity as a cause of hypoglycemia. *Arch Intern Med* 144:2351–2354, 1984
8. Takayama S, Hirata Y: Incidence of insulin autoimmune hypoglycemia in Japan during the three-year period from 1979 to 1981 (Abstract). *Diabetes* 32:150A, 1983
9. Service FJ, Dale AJ, Elveback LR, Jiang NS: Insulinoma: clinical and diagnostic features in 60 consecutive cases. *Mayo Clin Proc* 51:417–429, 1976

C282Y and H63D Mutations of the Hemochromatosis Candidate Gene in Type 2 Diabetes

Screenings with conventional biochemical tests have suggested an increased prevalence of hemochromatosis in patients with type 2 diabetes (1,2). Phelps et al. (1) and Conte et al. (2) have found that diabetes conferred a risk for hereditary hemochromatosis (HH) that was 2.4-fold (1) and 1.34% (2) higher, respectively, among Italian and Australian diabetic patients. In the last years, the characterization of HFE, a strong candidate gene for HH, has allowed researchers to study more directly the prevalence of its mutations in type 2 diabetes. The C282Y mutation leads to a single amino acid change (substitution of tyrosine for cysteine) that results from a missense mutation at nucleotide 845 of the *HFE* gene, and homozygosity for the mutation is generally associated with expressed HH. A second mutation, which leads to substitution of aspartate for histidine (H63D), bears an interesting relationship to HH in

Table 1—*HFE genotypes in type 2 diabetic patients and in control subjects*

C282Y	H63D	Patients (*n* = 170)	Control subjects (*n* = 108)
CC	HH	96 (56.5)	70 (64.8)
CY	HH	7 (4.1)	6 (5.6)
CC	HD	55 (32.3)	28 (25.9)
CC	DD	10 (5.9)	2 (1.8)
CY	HD	2 (1.2)	2 (1.8)
C282Y		2.65 ± 1.71	3.70 ± 2.5
H63D		22.64 ± 4.40	15.7 ± 4.9

Data are *n* (%) or allele frequencies (% ± 95% CI).

the sense that compound heterozygotes (C282Y/H63D) succumb to the disease, although with reduced penetrance (3). These mutations are screened using enzymatic digestion of polymerase chain reaction (PCR) products encompassing the mutation sites. The C282Y creates a new *Rsa*I restriction site, and the H63D mutation destroys an *Mbo*I site in the 294-bp PCR product. Frayling et al. (4) have recently reported that the frequency of the C282Y mutation in the *HFE* gene was similar in patients with type 2 diabetes and control subjects. Two other studies have confirmed a similar prevalence of C282Y and H63D mutations in patients with type 2 diabetes and control subjects of Caucasian origin from Germany (5) and France (6).

We determined the prevalence of the C282Y and H63D mutations in 170 unrelated Caucasian Mediterranean patients with type 2 diabetes (average age 59.4 years) and 108 age-matched control subjects with the technique mentioned above. In agreement with previous studies (4–6), we found that the C282Y allele frequency was similar in patients with type 2 diabetes and control subjects (Table 1). However, the H63D allele frequency was significantly higher in patients with type 2 diabetes (P = 0.04, relative risk 1.17 [1.01–1.36]). Patients with HFE mutations showed similar age (58.8 vs. 61.3 years) to carriers of the nonmutant allele. Interestingly, plasma ferritin levels were significantly higher in patients expressing HFE mutations (227.2 ± 21.5 vs. 159.4 ± 11.1, P = 0.006), and 45% of the H63D carriers showed ferritin levels above the upper limit of normal values (300 µg/l in men, 200 µg/l in women).

Our results confirm that the C282Y mutation is not associated with type 2 diabetes. In these patients, however, we have found an increased prevalence of the H63D mutation. Ethnic differences in HFE polymorphism are well known (7,8). In a large population study, Merryweather-Clarke et al. (7) found wide variations in the frequency of H63D. In southern Europe, hemochromatosis is more heterogeneous than that reported in northern Europe (9). Recently, H63D mutations have been linked to nonclassical forms of iron overload in Portugal (10) and to porphyria cutanea tarda in Italy (11). We propose that type 2 diabetes should be added to this list of potential nonclassical forms of iron overload in our population.

The HFE protein binds to a transferrin receptor and reduces its affinity for iron-loaded transferrin. This effect is lost in the mutated H63D protein (12). Thus, a significant proportion of type 2 diabetic patients would be exposed to the deleterious effects of iron overload. In this sense, it is noteworthy that serum ferritin levels were 15–30% greater in type 2 diabetic patients expressing HFE mutations (6).

Further studies are needed to ascertain the impact of the H63D mutation on iron overload and chronic complications in patients with type 2 diabetes.

JOSE-MANUEL FERNANDEZ-REAL, MD, PHD
JOAN VENDRELL, MD, PHD
MONTSERRAT BAIGET, MD, PHD
ENRIC GIMFERRER, MD
WIFREDO RICART, MD

From the Unit of Endocrinology (J.-M.F.-R., W.R.), Diabetes and Nutrition, University Hospital of Girona, Girona; the Unit of Endocrinology (J.V.), University Hospital of Tarragona, Tarragona; and the Departments of Genetics (M.B.) and Hematology (E.G.), Hospital de Sant Paul Barcelona, Barcelona, Spain.

Address correspondence to J.M.Fernandez-Real, MD, PhD, Unitat de Diabetes, Endocrinologia i Nutrició, Hospital Universitario de Girona "Dr Josep Trueta," Ctra. Franca s/n, 17007 Girona, Spain. E-mail: hosptrueta@comg.es.

References

1. Phelps G, Chapman I, Hall P, Braund W, Mackinnon M: Prevalence of genetic haemochromatosis among diabetic patients. *Lancet* ii:233–234, 1989
2. Conte D, Manachino D, Colli A, Guala A, Aimo G, Andreoletti M, Corsetti M, Fraquelli M: Prevalence of genetic hemochromatosis in a cohort of Italian patients with diabetes mellitus. *Ann Intern Med* 128:370–373, 1998
3. Beutler E: The significance of the 187 G (H63D) mutation in hemochromatosis. *Am J Hum Genet* 61:762–776, 1997
4. Frayling T, Ellard S, Grove J, Walker M, Hattersley AT: C282Y mutation in *HFE* (haemochromatosis) gene and type 2 diabetes. *Lancet* 351:1933–1934, 1998
5. Braun J, Donner H, Plock K, Rau H, Usadel KH, Badenhoop K: Hereditary haemochromatosis mutations (HFE) in patients with type II diabetes mellitus. *Diabetologia* 41:983–984, 1998
6. Dubois-Laforgue D, Caillat-Zucman S, Djilali-Saiah I, Larger E, Mercadier A, Boitard C, Bach JF, Timsit J: Mutations in HFE, the hemochromatosis candidate gene, in patients with NIDDM (Letter). *Diabetes Care* 21:1371–1372, 1998
7. Merryweather-Clarke AT, Pointon AJ, Sherman JD, Robson KJH: Global prevalence of putative haemochromatosis mutations. *J Med Genet* 34:275–278, 1997
8. Beckman LE, Saha N, Spitsyn V, Van Landeghem G, Beckman L: Ethnic differences in the HFE codon 282 (Cys/Tyr) polymorphism. *Hum Hered* 47:263–267, 1997
9. Carella M, D'Ambrosio L, Totaro A, Grifa A, Valentino MA, Piperno A, Girelli D, Roetto A, Franco B, Gasparini P, Camaschella C: Mutation analysis of the HLA-H gene in Italian hemochromatosis patients. *Am J Hum Genet* 60:828–832, 1997
10. Porto G, Alves H, Rodrigues P, Cabeda JM, Portal C, Ruivo A, Justica B, Wolff R, De Sousa M: Major histocompatibility complex class I associations in iron overload: evidence for a new link between the HFE H63D mutation, HLA-A29, and non-classical forms of hemochromatosis. *Immunogenetics* 47:404–410, 1998
11. Sampietro M, Piperno A, Lupica L, Arosio C, Vergani A, Corbetta N, Malosio I, Mattioli M, Francanzani AL, Cappellini MD, Fiorelli G, Fargion S: High prevalence of the His63Asp HFE mutation in Italian patients with porphyria cutanea tarda. *Hepatology* 27:181–184, 1998
12. Feder JN, Penny DM, Irrinki A, Lee VK, Lebron JA, Watson N, Tsuchihashi Z, Sigal E, Bjorkman PJ, Schatzman RC: The hemochromatosis gene product complexes with the transferrin receptor and lowers its affinity for ligand binding. *Proc Natl Acad Sci U S A* 95:1472–1477, 1998

Concordance Between the 1997 Fasting American Diabetes Association Criteria and the World Health Organization Criteria in Healthy Mexican Subjects

Table 1—*Concordance between the fasting ADA criteria and the WHO categories in healthy Mexican subjects*

	Fasting ADA criteria			
WHO criteria	Diabetes	Impaired fasting glucose	Normal	Prevalence by WHO criteria
Diabetes	5.9	3.5	0.6	10.0
IGT	3.5	0.6	15.3	19.4
Normal	0.0	5.3	65.3	70.6
Prevalence by fasting ADA criteria	9.4	9.4	81.2	100

Data are % of the target population.

The new guidelines recommending etiology-based criteria for the diagnosis of diabetes proposed by an expert committee of the American Diabetes Association (ADA) (1) has the advantage of the greater simplicity and extended use of the fasting plasma glucose (FPG) value versus glucose tolerance test criteria (2). Previous reports have shown, however, a poor agreement between both sets of criteria (3,4). To address this concern, we determined the concordance between fasting ADA criteria (1) versus World Health Organization (WHO) diagnostic criteria (2) in a random sample of healthy subjects aged ≥30 years from the general population of Durango, Mexico (5).

A comparative cross-sectional study was conducted. Before inclusion, baseline clinical examination and laboratory studies were performed. Previous diabetes or other disease and abnormal laboratory values were considered to be exclusion criteria. For glucose analysis, a venous whole blood sample was collected after 8–10 h of fasting, and 2-h 75-g oral postload glucose (2-h PG) was determined in subsequent days. Plasma glucose was measured using the glucose-oxidase method. Results from the glycemia 2-h PG were considered to be the gold standard. To assess the degree of agreement between the fasting ADA criteria and WHO classification schemes, we used the weighted *k*.

There were 570 individuals, 60.0% women and 40.0% men, included. The average age was 44.1 ± 8.0 years, and the BMI was 29.2 ± 4.5 kg/m^2.

Fasting ADA criteria failed to detect 41.2% of WHO diabetic patients (sensitivity 0.588). The *k* statistic for the agreement between 1997 fasting ADA criteria and the WHO categories was 0.47. Of the participants who were classified as normal by the fasting ADA criteria, 15.3% had impaired glucose tolerance (IGT) and 0.6% had diabetes according to WHO criteria. Whereas, of the subjects with diabetes according to fasting ADA criteria, 5.9% were similarly classified by WHO criteria and 3.5% had IGT. Of the participants with impaired fasting glucose according to fasting ADA criteria, 5.3% were normoglycemic, 0.6% had IGT, and 3.5% had diabetes according to WHO criteria (Table 1).

Considering that an early detection of asymptomatic disease is the main goal of diabetes screening (1), a simpler and more accurate diagnostic test will be required for the reduction of false-negative results. Consequently, the sensitivity of a diagnostic test must be very high. In terms of this, diagnoses of type 2 diabetes based on fasting ADA criteria have a lower sensitivity and a poor agreement with WHO criteria (3,4), results that are in accordance with data recently published by Gómez-Pérez et al. (3).

With fasting ADA criteria, 41.2% of the WHO diabetic subjects had a false-negative test, but when they were tested with glycemia 2-h PG on a subsequent day, diagnosis of type 2 diabetes improved, increasing the sensitivity to 0.941 and reducing the false-negative test to 5.9%.

Diabetes screening with FPG confirmed on a subsequent day by glycemia 2-h PG, if the FPG value was ≥110 mg/dl (6.1 mmol/l), would be an alternative for epidemiological purposes, improving the success for providing reliable data on the presence of disease.

GUERRERO-ROMERO FERNANDO, MD
RODRÍGUEZ-MORÁN MARTHA, MD
ALVARADO-RUIZ RICARDO, MD

From the Medical Research Unit (G.-R.F., R.-M.M.) and General Hospital (R.-M.M.) of the Mexican Social Security Institute; and the Research Group on Diabetes and Chronic Illnesses (G.-R.F., R.-M.M., A.-R.R.), Durango, Mexico.

Address correspondence to Guerrero-Romero Fernando, MD, Siqueiros 225 esq c/Castañeda, 34000 Durango, Dgo., Mexico. E-mail: guerrero@omanet.com.mx.

References

1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: *Diabetes Care* 21 (Suppl. 1):S5–S19, 1998
2. World Health Organization: *WHO Expert Committee on Diabetes Mellitus: Second Report*. Geneva, World Health Org., 1980 (Tech. Rep. Ser., no. 646)
3. Gómez-Pérez FJ, Aguilar-Salinas CA, López-Alveranga JC, Perez-Jauregui J, Guillen-Pineda LE, Rull JA: Lack of agreement between the World Health Organization category of impaired glucose tolerance and the American Diabetes Association category of impaired fasting glucose. *Diabetes Care* 21:1886–1888, 1998
4. Wahl PW, Savage PJ, Psaty BM, Orchard TJ, Robbins JA, Tracy P: Diabetes in older adults: comparison of 1997 American Diabetes Association classification of diabetes mellitus with 1985 WHO classification. *Lancet* 352:1012–1015, 1998
5. Guerrero-Romero JF, Rodríguez-Moran M, Alvarado-Ruiz R: Sensitivity and specificity of fasting plasma glucose as diagnostic test for type 2 diabetes in healthy Mexican individuals. In *XVI Congreso Nacional de Investigación Biomédica* Monterrey, Nuevo León, México, Subdriección de Investigación y Estudios de Posgrado, Facultad de Medicina de la Universidad Autónoma de Nuevo León, 1998, p. 92–93

COMMENTS AND RESPONSES

Metformin As Adjuvant to Insulin Therapy in Type 2 Diabetic Patients

An insulin-resistant obese type 2 diabetic patient can be a tough therapeutical problem and a serious challenge to even the most experienced diabetologist, as we very well know. I'll describe briefly such a case and an unorthodox solution to the problem.

My patient is a heavy gentleman, weighing 132 kg (BMI 40 kg/m^2). He is 68 years old. Type 2 diabetes was diagnosed in 1988. He went through the classical escalation of therapies, ending in a massive multiple injection insulin therapy of up to 270 U per day, but the balance was still poor. Fasting blood glucose was 10–13 mmol/l, and HbA_{1c} was 10–11%. He exhibits a typical example of metabolic syndrome with hypertension, hyperlipidemia, and hyperurichemia. His angina pectoris was getting worse, even after bypass operation, and the near future did not seem promising at all. I was worried and felt helpless. In an attempt to help him, I searched Medline, and in the June 1996 issue of *Diabetes Care*, I found a letter from Dr. Hanuschak (1) in which he detailed a case that seemed to involve a problem of the same scale as mine. He reported an excellent result after combining metformin (up to 2,500 mg per day) with high-dose insulin therapy. I found this interesting. My patient had received metformin earlier as monotherapy and combined with sulfonylurea. Later, metformin was rejected because of nasty dyspeptic symptoms. From this, I have learned to never give up: gastroscopy was made, and an active helicobacterium-positive gastritis was diagnosed and then eradicated successfully. After this operation, the patient got metformin progressively from 500 to 1,000 mg twice daily. The enormous insulin dosage continued.

After 2 weeks, the patient reported that blood glucose was rapidly coming down. He felt well and had no dyspeptic symptoms. I was slightly astonished. Two more weeks went by, and the patient's fasting blood glucose was 4–5 mmol/l; he even got hypoglycemic symptoms. I was really astonished!

The insulin dosage was reduced. After 2 months, HbA_{1c} had come down from 10.1 to 7.3%, and the dosage of insulin from 270 to 210 U per day. After 6 months, HbA_{1c} had stabilized to 7.1–7.4%. The patient was very happy indeed! He still weighed 132 kg, but it was not necessary for him to take lots of nitroglycerin any more; a tablet now and then was good enough. The endothelium of coronary arteries had recovered, I think. I was happy too.

The patient has now undergone 12 months of adjuvant therapy. The situation still seems to be under control. HbA_{1c} is 7.4%.

Because this is only a short case history, I won't dive into the deep waters of the effects of metformin on glucose metabolism. I am a clinician. Anyway, I am sure that this kind of combination therapy is worth remembering and using as an effective tool to break the vicious circle of insulin resistance, which so often blocks our efforts to help our type 2 diabetic patients. I was very pleased to see in a recent issue of *Diabetes Care* (May 1998) an article by Dr. Robinson et al. (2) on this topic. The same principle seems to work with obese and insulin-resistant type 1 diabetic patients as well (3).

With this letter, I would like to thank Dr. Hanuschak and *Diabetes Care* for their help. I have received accolades from my patient, but they belong to you. Here they are—take your fair share please. I wish you all well.

RAIMO VANAMO, MD

From the Central Hospital of South Karelia, Lappeenranta, Finland.

Address correspondence to Raimo Vanamo, MD, The Central Hospital of South Karelia, 53130 Lappeenranta, Finland.

References

1. Hanuschak L: Metformin useful in combination with exogenous insulin (Letter). *Diabetes Care* 19:671–672, 1996
2. Robinson A, Burke J, Robinson S, Johnston DG, Elkeles RS: The effects of metformin on glycemic control and serum lipids in insulin-treated NIDDM patients with suboptimal metabolic control. *Diabetes Care* 21:701–705, 1998
3. Fossati P, Fontaine P, Beuscart R: Interet de l'assiciation metformine-insuline dans le traitement du diabete insulino-dependant. *Diabete Metab* 11:396–398, 1985

Response to Vanamo

Dr. Vanamo (1) clearly describes a patient with type 2 diabetes who fulfils our criteria for insulin treatment failure, exhibiting weight gain and poor metabolic control in association with increasing insulin dosage. His subsequent metabolic response to adjunctive metformin therapy was entirely in keeping with our findings. The reduced requirement for antianginal therapy is interesting. It may reflect improved coronary perfusion related either to the normalized blood glucose levels or to the known benefits of metformin on serum lipids (2,3).

ADAM ROBINSON, MRCP

From the Unit of Metabolic Medicine, Imperial College of Medicine at St. Mary's, Norfolk Place, London, U.K.

Address correspondence to Dr. Adam Robinson, Unit of Metabolic Medicine, Imperial College of Medicine at St. Mary's, Norfolk Place, London W2 1NY, U.K.

A.R. has received research support from Lipha.

References

1. Vanamo R: Metformin as adjuvant to insulin therapy in type 2 diabetic patients (Letter). *Diabetes Care* 22:526, 1999
2. Rains SG, Wilson GA, Richmond W, Elkeles RS: The effect of glibenclamide and metformin on serum lipoproteins in type 2 diabetes. *Diabet Med* 5:653–658, 1988
3. Wu MS, Johnston P, Sheu WH, Hollenbeck CB, Jeng CY, Goldfine ID, Chen YD, Reaven GM: Effect of metformin on carbohydrate and lipoprotein metabolism in NIDDM patients. *Diabetes Care* 13:1–8, 1990

Antioxidant Effects of Gliclazide and Soluble Adhesion Molecules in Type 2 Diabetes

We read with interest the paper by Desfaits et al. (1) and wish to make some comments. We were puzzled by the authors' failure to show any difference at baseline between their diabetic study group and control subjects in levels of intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion mole-

cule-1 (VCAM-1), compared with the level of E-selectin, which showed a significant difference. Furthermore, those levels, as well as those of E-selectin, failed to fall, as one would expect, after 3-month treatment with gliclazide. We think that this might be related to the small number of individuals in their study group ($n = 8$). Both E-selectin and ICAM-1 are sensitive markers of endothelial cell perturbation in type 2 diabetes, as has been documented by our group (2) and by others (3,4). A second confounding factor for such disparity could be related to the fact that 50% of their diabetic group was on ACE inhibitors, and ACE inhibitors have been reported recently to improve endothelial dysfunction in patients with coronary artery disease (5). A third confounding factor is probably related to the fact that all of the patients were on metformin, which is known to have a lipid-lowering effect (6), so the level of lipid peroxidation could be less severe than one would expect, perhaps attenuating its effect on the endothelium.

The authors also suggested that the expression of growth factors like vascular endothelial growth factor, transforming growth factor-β, interleukin-1β, and fibroblast growth factor in vivo is not related to chronic hyperglycemia and that their measurement in diabetic patients is not clinically relevant. In our experience, this might be true for type 2 diabetes; however, again, their number of subject studied is small, and it is difficult to draw firm conclusions from their study, especially since VEGF has been shown by our group to be significantly elevated in patients with type 1 diabetes, and this bears some relationship to the level of chronic hyperglycemia as estimated by HbA_{1c} (9).

Finally, the work by Desfaits et al. is very interesting in that they have shed further scientific light on the role of a sulfonylurase agent, gliclazide, that does not have only an anti-hyperglycemic effect, but may also perform other beneficial metabolic actions, as shown previously by our group (7,8). Validation of the clinical relevance of these findings will require long-term studies examining the cardiovascular protective effects of gliclazide on morbidity and mortality.

TARIK A. ELHADD, MRCP
RAY W. NEWTON, FRCP
PAUL E. JENNINGS, MD
JILL J.F. BELCH, MD

From the Department of Medicine (T.A.E.), School of Postgraduate Medicine, University of Keele, Stoke-on-Trent; University Department of Medicine (R.W.N., J.J.F.B.), Ninewells Hospital and Medical School, Dundee; and the Department of Medicine (P.E.J.), York District General Hospital, York, U.K.

Address correspondence to Dr. T.A. Elhadd, Department of Endocrinology and Diabetes, City General Hospital, Stoke-on-Trent, ST4 6QG, England, U.K.

P.E.J. has received honoraria for speaking engagements from the Institut de Recherches Internationales Servier.

References

1. Desfaits A-C, Serri O, Renier G: Normalization of plasma lipid peroxides, monocyte adhesion, and tumor necrosis factor-α production in NIDDM patients after gliclazide treatment. *Diabetes Care*21:487–493, 1998
2. Elhadd TA, Kirk G, McLaren M, Jung RT, Belch JJF: High levels of cell adhesion molecules, E-selectin and ICAM-1 in diabetic patients with and without asymptomatic peripheral arterial disease (Abstract). *Diabet Med*13 (Suppl. 7):S19, 1996
3. Cominacini L, Fratta-Pacini A, Garbi U, Campaquola M, Davoli A, Rigoni A, Zenti MG, Pasrtrino AM, Casio VL: E-selectin plasma concentration is influenced by glycaemic control in NIDDM. *Diabetologia* 40:584–589, 1997
4. Fasching P, Vietel M, Rohac M, Sterli C, Schneider B, Waldhausl W, Wagner OF: Elevated concentration of circulating adhesion molecules and their association with microvascular complications in insulin dependent diabetes. *J Clin Endocrinol Metab* 81:4313–4317, 1996
5. Mancini GBJ, Henry GC, Macaya C, O'Neil BJ, Pucillo AL, Carere RG, Wargovich TJ, Mudra H, Luscher TF, Klibaner MI, Haber HE, Uprichard ACG, Pepine CJ, Bertram P: Angiotensin-converting enzyme inhibition with quinalapril improves endothelial vasomotor dysfunction in patients with coronary artery disease: the TREND Study. *Circulation*94:259–264, 1996
6. Wu MS, Johnston P, Sheu WH, Hollenbeck CB, Jeng CY, Goldfine ID, Chen YD, Reaven GM: Effect of metformin on carbohydrate and lipoprotein metabolism in NDDM patients. *Diabetes Care*13:1–8, 1990
7. Jennings PE, Scott NA, Saniabadi AR, Belch JJF: Effects of gliclazide on platelet reactivity and free radicals in type II diabetic patients: clinical assessment. *Metabolism* 41 (Suppl. 1):36–39, 1992
8. Scott NA, Jennings PE, Brown J, Belch JJF: Gliclazide: a general free radical scavenger. *Eur J Pharmacol*208:175–177, 1991
9. McLaren M, Elhadd TA, Greene SA, Belch JJF: Elevated plasma vascular endothelial growth factor and thrombomodulin in juvenile diabetic patients. *Clin Appl Thromb Haemost*In press

Response to Elhadd et al.

We thank Drs. Elhadd, Newton, Jennings, and Belch for their interest in our study. In their correspondence (1), they express their concern regarding the absence in our study of differences at baseline between the diabetic and the control groups for the levels of intercellular cell adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and vascular endothelial growth factor (VEGF). They suggest that our failure to detect such differences may be related to the small number of patients and to biguanide and antihypertensive treatments. They also suggest that circulating adhesion molecules, especially E-selectin and ICAM-1, are sensitive markers of endothelial cell perturbation in type 2 diabetes.

Our study was aimed not at the examination of circulating adhesion molecules but rather at monocyte adhesion and cytokine production in type 2 diabetes. Nevertheless, in regard to serum concentrations of circulating adhesion molecules, even studies of large groups of patients with type 2 diabetes have produced discrepant results, probably because of an important overlap between values in diabetic and nondiabetic control subjects. Levels of ICAM-1 were thus found to be identical in diabetic ($n = 60$) and control ($n = 76$) subjects in one study (2) and increased in diabetic ($n = 159$) versus control ($n = 71$) subjects in another study (3). VCAM-1 concentrations were either unchanged (4) or increased by only 14% in diabetic versus nondiabetic patients (3). A plausible explanation for these discrepancies is that type 2 diabetic patients do not constitute a homogeneous population. Serum levels of soluble adhesion molecules are influenced not only by chronic hyperglycemia but also by hypertension and hyperlipidemia. In a recent study, Kawamura et al. (5) have shown that comparison of serum levels of soluble ICAM-1 and E-selectin between type 2 diabetic and nondiabetic subjects revealed significant differences only in diabetic subjects with hypertension or hyperlipidemia. In regard to hypertension, therapy with ACE inhibitors may induce a reduction in VCAM-1 levels (6). Metformin, however, does not affect lipid profile in the long-term use (7) and thus may not account for a reduction of adhesion molecule levels.

Finally, E-selectin, which we have shown to be elevated and correlated to plasma lipid peroxide levels in our diabetic group, is a specific product of the endothelium (8), whereas ICAM-1 and VCAM-1 are produced by other cells, such as epithelium, smooth muscle cells, and macrophages, in addition to endothelial cells. The fact that E-selectin concentrations were not reduced by gliclazide treatment in our study indicates that oxidative stress is not the sole determinant of E-selectin elevation in diabetic subjects.

Similarly, serum levels of VEGF are not increased in unselected series of type 2 diabetic patients (9). However, high levels of VEGF have been reported in half of 110 type 2 diabetic subjects with microangiopathy (10). In this study, the prevalence of high levels of serum VEGF increased in parallel with an increase in the urinary albumin excretion rate and therefore seemed to be linked to the progression of nephropathy.

OMAR SERRI, MD, PHD
GENEVIÈVE RENIER, MD, PHD

From the Metabolic Unit (G.R., O.M.), Centre Hospitalier de l'Universite de Montreal (CHUM) Research Center, Notre-Dame Pavilion; and the Department of Nutrition (G.R., O.M.), University of Montreal, Montreal, Canada.

Address correspondence to Dr. Geneviève Renier, CHUM Research Center, Notre-Dame Campus, J.A. de Seve Pavilion, 3rd floor, door Y3622, 1560 Sherbrooke St. East, Montreal, Quebec, H2L 4M1, Canada. E-mail: renierg@ere.umontreal.ca.

G.R. has received laboratory funding from Servier Canada.

References

1. Elhadd TA, Newton RW, Jennings PE, Belch JJF: Antioxidant effects of gliclazide and soluble adhesion molecules in type 2 diabetes. *Diabetes Care* 22:528–529, 1999
2. Steiner M, Reinhardt KM, Krammer B, Ernst B, Blann AD: Increased levels of soluble adhesion molecules in type 2 (non-insulin dependent) diabetes mellitus are independent of glycaemic control. *Thromb Haemost* 72:979–984, 1994
3. Fasching P, Waldhäusl W, Wagner OF: Elevated circulating adhesion molecules in NIDDM: potential mediators in diabetic macroangiopathy. *Diabetologia* 39:1242–1243, 1996
4. Cominacini L, Fratta Pasini A, Garbin U, Davoli A, De Santis A, Campagnola M, Rigoni A, Zenti MG, Moghetti P, Lo Cascio V: Elevated levels of soluble E-selectin in patients with IDDM and NIDDM: relation to metabolic control. *Diabetologia* 38:1122–1124, 1995
5. Kawamura T, Umemura T, Kanai A, Uno T, Matsumae H, Sano T, Sakamoto N, Sakakibara T, Nakamura J, Hotta N: The incidence and characteristics of silent cerebral infarction in elderly diabetic patients: association with serum-soluble adhesion molecules. *Diabetologia* 41:911–917, 1998
6. Morrissey JJ, Klahr S: Differential effects of ACE and AT1 receptor inhibition on chemoattractant and adhesion molecule synthesis. *Am J Physiol* 274:F580–F586, 1998
7. U.K. Prospective Diabetes Study Group: UKPDS 28: a randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. *Diabetes Care* 21:87–92, 1998
8. Gearing AJH, Newman W: Circulating adhesion molecules in disease. *Immunol Today* 14:506–512, 1993
9. Burgos R, Simo R, Audi L, Mateo C, Mesa J, Garcia-Ramirez M, Carrascosa A: Vitreous levels of vascular endothelial growth factor are not influenced by its serum concentrations in diabetic retinopathy. *Diabetologia* 40:1107–1109, 1997
10. Wasada T, Kawahara R, Katsumori K, Naruse M, Omori Y: Plasma concentration of immunoreactive vascular endothelial growth factor and its relation to smoking. *Metabolism* 47:27–30, 1998

Diabetes Treatment Satisfaction Questionnaire

Change version for use alongside status version provides appropriate solution where ceiling effects occur

In a recent letter, Pouwer et al. (1) commented on the distribution of treatment satisfaction scores measured by the widely used Diabetes Treatment Satisfaction Questionnaire (DTSQ) in a survey reported in *Diabetes Care* by Petterson et al. (2). They pointed out that the scores were highly skewed in the direction of satisfaction, referred to data from elsewhere that had shown similar ceiling effects, and suggested two possible strategies for reducing the skew. The strategies suggested are problematic for reasons that are given below along with a preferred approach for dealing with ceiling effects when they occur.

One of the strategies proposed by Pouwer et al. was that described by Streiner and Norman (3), which involves producing an asymmetric scale on which only two of the points on a seven-point scale describe degrees of dissatisfaction while the remaining five describe varying degrees of satisfaction. Pouwer and colleagues suggested that the DTSQ might be adapted to a seven-point scale, with value labels as follows: 6 (extremely satisfied), 5 (very satisfied), 4 (quite satisfied), 3 (satisfied), 2 (a bit satisfied), 1 (dissatisfied), and 0 (very dissatisfied). Their solution reflects the impact of American English rather than U.K. English on their thinking. In American English, "quite satisfied" denotes more satisfaction than "satisfied," while in U.K. English, "quite satisfied" denotes less satisfaction than "satisfied," and may not be seen to differ from "a bit satisfied." Value labels on each response option would be essential in such an effort to manipulate the distribution of responses, but would also involve a journey through a linguistic minefield for an instrument that is available in more than 20 languages. More importantly perhaps, the solution originally proposed by Streiner and Norman may be entirely appropriate for a particular population known to be highly satisfied with their treatment, but would render the measure less useful in eliciting dissatisfied responses from other populations that are not so satisfied with their treatment. If we wish to encourage patients to express any dissatisfaction they may feel, then we need to include more, not fewer, response options representing dissatisfaction.

Pouwer et al. referred in their letter to another method of counteracting skew that was that reported by Ware and Hays (4). Ware and Hays compared a six-point satisfaction scale ("extremely satisfied" to "very dissatisfied") with a five-point evaluation scale ("excellent" to "poor") in assessing patients' views of consultations. Pouwer et al. misrepresented Ware and Hays's conclusions when they reported that the evaluation scale "showed greater response variability, reliability, and validity." Reliability was reported in the form of internal consistency and shown to be equally high for both methods. Ware and Hays made no sweeping conclusions about validity, but, quite appropriately, referred specifically to the distribution advantages obtained with the evaluation scale, i.e., mean scores closer to the midpoint of the scale and greater response variability. It remains unclear to which aspects of the evaluation scale we should attribute the distribution advantages, since several characteristics varied between the

satisfaction and evaluation scales compared. The satisfaction scale had six points labeled "extremely satisfied," "very satisfied," "somewhat satisfied," "neither satisfied nor dissatisfied," "somewhat dissatisfied," and "very dissatisfied." The evaluation scale had five points labeled "excellent," "very good," "good," "fair," and "poor." Thus, not only did the concepts differ between scales (satisfaction versus excellence), as well as the number of response options (six versus five), but also the availability of a neutral response option (neither one nor the other) and the proportion of response options dealing with negative views (two of six versus one of five). The satisfaction scale offered three positive response options, a neutral response option, and two negative response options out of the six response options provided. However, the evaluation scale offered only one negative response option ("poor"), while all four remaining response options were positive ("fair" to "excellent"). The reduction of skew accompanying the evaluation scale is more likely to be attributable to the greater proportion of positive response options when used with a sample population who tended to be positive about the consultations being evaluated. However, were the scales to be used with a sample population that was more negative, it is likely that a six-point scale that includes more neutral and negative response options would produce more normally distributed results, regardless of whether it measured satisfaction or excellence.

The DTSQ does not include labels on each point of each scale, but simply labels the extremes. The items that make up the treatment satisfaction score have scales that are intended to be symmetrical, with a neutral midpoint and equal numbers of satisfied and dissatisfied response options on either side of the midpoint. It is indeed often the case, but by no means always the case, that mean and median scores are in the high 20s or low 30s on the total scale score, which can range from 0 to 36 (5). This reflects the fact that many of the patients studied are indeed satisfied with the treatment of their diabetes. If these patients also have highly satisfactory HbA_1 levels and other biomedical outcomes, then high satisfaction scores in a survey such as that conducted by Petterson et al. (2) are a cause for congratulation, not a reason for changing the measures used. However, a problem may arise if we have a new treatment with which we have reason to believe patients will be much more satisfied, but the patients are already registering high levels of satisfaction with their current treatment at baseline. After experiencing the new treatment, the patients may wish to say that they are much more satisfied with the new treatment. However, those patients who had a maximum score on the DTSQ at baseline can do no better than give a maximum score again if they are given the same questionnaire at follow-up. It was for this reason that the DTSQ change version was designed and is being developed in ongoing work. The item stems are identical to those used on the original DTSQ (e.g., "How satisfied are you with your current treatment?"), but the response options change from "very satisfied—very dissatisfied" to "much more satisfied now—much less satisfied now." The instructions of the change version of the DTSQ specify the period of treatment to be compared with the current treatment. In this way, people can say they were very satisfied at baseline, but also that they are much more satisfied with the new treatment at follow-up. If they are unfortunate enough to have to revert to the old treatment, they will be much less satisfied with it than they were at the start of the study (6).

The phenomenon of being satisfied until discovering something better is not confined to diabetes treatments or even to medical treatments more generally. Anyone who has been persuaded to upgrade an old personal computer with which they have been highly satisfied for several years, and then experienced the greater speed and efficiency, the spell checker, and other features of a newer model, will appreciate the need to be able to say that they were fully satisfied before but are even more satisfied now.

The first study to be completed using the DTSQ change version was a comparison of the new fast-acting insulin lispro with regular insulin (7) used by patients trained in the use of functional insulin therapy (characterized by full flexibility of food intake and lifestyle while maintaining control of blood glucose levels with intensive education and insulin use involving correctional as well as preprandial and basal insulin) (8). Despite high satisfaction levels at baseline, the original status version of the DTSQ showed treatment satisfaction scores to improve with lispro. The change version of the DTSQ showed even more significant increases in treatment satisfaction with lispro (7). Further studies are now underway using the DTSQ (change) at follow-up in addition to the DTSQ (status) at baseline and/or follow-up. The change version (currently available in English [suitable for U.K. and U.S.] and German [suitable for Germany and Austria]) and original status version (available in English [for U.K. and U.S.], most European languages, Japanese, and Arabic) can be obtained from me. The DTSQ (change) improves the scope of the DTSQ (status), which in itself has proved responsive to subgroup differences in cross-sectional studies (e.g., 2,9) and sensitive to change in a wide range of clinical trials (e.g., 10–12).

DTSQ (status) scores are often skewed, but can be transformed statistically using standard procedures (13) to permit use of parametric statistics. Skew does not reduce the validity of a measure if the phenomenon being measured is itself skewed. Thus, if patients in a sample tend to be satisfied with their treatment, it is entirely appropriate that the DTSQ scores should be skewed. It is missing the point to suggest that we should be measuring excellence instead of satisfaction in a bid to reduce the skew of the response distribution. The suggestions made by Pouwer et al. (1) for modifying the questionnaire to improve the distribution of responses will themselves cause problems far more serious than that of skew, and are not recommended.

Where ceiling effects at baseline limit capacity to indicate improved satisfaction at follow-up, use of the DTSQ (change) in addition to the DTSQ (status) appears to provide a very satisfactory, and perhaps even excellent, solution.

CLARE BRADLEY, PHD

From the Royal Holloway, University of London, Egham, Surrey, U.K.

Address correspondence to Clare Bradley, PhD, Professor of Health Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX U.K. E-mail: c.bradley@rhbnc.ac.uk.

C.B. has received research support from Lilly Deutschland.

References

1. Pouwer F, Snoek FJ, Heine RJ: Ceiling effect reduces the validity of the Diabetes Treatment Satisfaction Questionnaire (Letter). *Diabetes Care*21:2039, 1998
2. Petterson T, Lee P, Hollis S, Young B, Newton P, Dornan T: Well-being and treatment satisfaction in older people with diabetes. *Diabetes Care*21:930–935, 1998
3. Streiner DL, Norman GR: *Health Measurement Scales: A Practical Guide to Their*

Development and Use. Oxford, U.K., Oxford University Press, 1989
4. Ware JE, Hays RD: Methods for measuring patient satisfaction with specific medical encounters. *Med Care* 26:393–402, 1988
5. Bradley C (Ed.): The Diabetes Treatment Satisfaction Questionnaire (DTSQ). In *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice*. Chur, Switzerland, Harwood Academic, 1994, p. 111–132
6. Bradley C: Psychological issues in clinical trial design. *Irish J Psychol* 18:67–88, 1997
7. Howorka K, Pumprla J, Schlusche C, Wagner D, Bradley C: Insulin lispro changes treatment satisfaction under flexible, functional insulin treatment (Abstract). *Diabetes* 46 (Suppl. 1):13A, 1997
8. Howorka K: *Functional Insulin Treatment*. 2nd ed. Berlin, Germany, Springer, 1996
9. Bradley C, Lewis KS: Measures of psychological well-being and treatment satisfaction developed from the responses of people with tablet-treated diabetes. *Diabet Med* 7:445–451, 1990
10. Jennings AM, Lewis KS, Murdoch S, Talbot JF, Bradley C, Ward JD: Randomized trial comparing continuous subcutaneous insulin infusion with conventional insulin therapy in type II diabetic patients poorly controlled with sulphonylureas. *Diabetes Care* 14:738–744, 1991
11. Taylor R, Foster B, Kyne-Grzebalski D, Vanderpump M: Insulin regimens for the noninsulin dependent: impact on diurnal metabolic state and quality of life. *Diabet Med* 11:551–557, 1994
12. Kinmonth A-L, Woodcock A, Griffin S, Spiegel N, Campbell MJ: Randomised control trial of patient-centred care in general practice: impact on current well-being and future disease risk. *BMJ* 317:1202–1208, 1998
13. Tabachnick BG, Fidell LS: *Using Multivariate Statistics*. 2nd ed. New York, Harper and Row, p. 83–87, 1998

Keep Metformin Guidelines Intact

A recent article in *Diabetes Care* (1) describes baseline rates of lactic acidosis in a group of patients tracked at Kaiser, and the accompanying editorial by Stacpoole (2) encourages a lessening of the restrictions on the use of metformin. We believe, however, that this is the wrong message to send to clinicians. Although the study by Brown et al. (1) was carefully performed, it is difficult to compare event rates using varying survey methods applied across different populations. And although it is impossible to determine metformin's role in the causality of some cases of lactic acidosis, there are reports in which the drug is clearly implicated in causing the disorder (3). When metformin is used following the current warnings, the reports of metformin-induced lactic acidosis fall to zero (4). Most of the reported cases of lactic acidosis in metformin-treated patients occur in instances of renal failure or insufficiency (5). Based on the estimate that 1 million Americans are taking metformin, the reported rate of confirmed lactic acidosis is ~5 cases per 100,000, although the actual rate of occurrence may be higher (6). Therefore, it is very important to avoid use of metformin in patients with abnormal renal function.

Metformin accumulates in the small intestine and is known to increase postprandial lactate levels. This increase can be potentiated by the ingestion of alcohol and by hepatic dysfunction. Metformin lacks the long hydrophobic phenethyl side chain found in phenformin, lowering its affinity for penetrating and binding to mitochondrial membranes, where it can inhibit oxidative phosphorylation. However, since >90% of ingested metformin is excreted through the kidney, with renal insufficiency, its half-life and serum concentrations are increased, raising the risk for precipitating lactic acidosis. Although the exact mechanism of action of any of the biguanides is unknown, it is clear that the difference in rates of lactic acidosis between phenformin and metformin make the latter a far safer drug.

Recent Food and Drug Administration (FDA) guidelines regarding the use of metformin have increased the contraindications for its use, including treatment for congestive heart failure as a risk factor for lactic acidosis in these patients. The FDA also advises caution when using metformin in patients who are elderly, who might have impaired renal function not reflected in their serum creatinine level. Therefore, we recommend continued adherence to the currently recommended guidelines for the use of metformin. In this way, diabetic patients should be able to gain from the benefits of metformin without suffering unnecessary harm.

ANNE L. PETERS, MD
ROBERT HENRY, MD
STEVEN V. EDELMAN, MD
BARRY J. GOLDSTEIN, MD, PHD

From the UCLA School of Medicine (A.L.P.), Los Angeles; the UCSD School of Medicine (R.H., S.V.E.), San Diego, California; and the Thomas Jefferson School of Medicine (B.J.G.), Philadelphia, Pennsylvania.

Address correspondence to Anne L. Peters, MD, 200 UCLA School of Medicine, Ste. 3655, Los Angeles, CA 90095-1693.

References

1. Brown JB, Pedula K, Barzilay J, Herson MK, Latare P: Lactic acidosis rates in type 2 diabetes. *Diabetes Care* 21:1659–1663, 1998
2. Stacpoole PW: Metformin and lactic acidosis: guilt by association? (Editorial) *Diabetes Care* 21:1587–1588, 1998
3. McLelland J: Recovery from metformin overdose. *Diabet Med* 2:410–411, 1985
4. Lucis OJ: The status of metformin in Canada. *CMAJ* 128:24–26, 1983
5. Campbell IW: Metformin and sulphonylurea derivatives: the comparative risks. In *Diabetes and Metformin: A Research and Clinical Update* Krans HMT, Ed. London, Royal Society of Medicine, 1985, p. 43–50
6. Misbin RI, Green L, Stadel BV, Gueriguain JL, Gubbi A, Fleming GA: Lactic acidosis in patients with diabetes treated with metformin. *N Engl J Med* 338:265–266, 1998

Response to Peters et al.

In contrast to the assertion by Peters et al. (1), I did not advocate in my editorial (2) relaxing current restrictions on the use of metformin. Interrogative and declarative statements about a subject, in this case, metformin's package insert, are not equivalent. I did, however, question whether the extant data on metformin-associated lactic acidosis warrant the commonly held assumption that an important cause-effect relationship exists between this drug and the most frequently observed metabolic acidosis in hospitalized subjects. Two points addressed in my editorial appear to warrant further discussion.

First, it is very difficult for lactic acidosis to occur under experimental or clinical conditions in the absence of an acquired or congenital defect in mitochondrial pyruvate oxidation (3). The irreversible decarboxylation of pyruvate to acetyl coenzyme A, which is catalyzed by the pyruvate dehydrogenase (PDH) enzyme complex, represents the rate-determining step in the catabolism of pyruvate, and hence lactate, in animal cells (Fig. 1). A decrease in the activity of PDC or in enzymes of the tricarboxylic acid cycle (TCA) or respiratory chain can lead to the

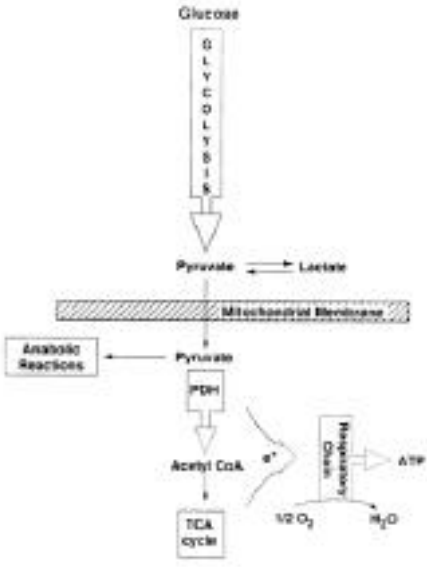

Figure 1—*Pathways of pyruvate metabolism and oxidative phosphorylation. Pyruvate may be reduced to lactate in the cytoplasm or may be transported into the mitochondria for anabolic reactions, such as gluconeogenesis and lipogenesis, or for oxidation to acetyl CoA by the pyruvate dehydrogenase (PDH) complex. Reducing equivalents (NADH, FADH) are generated by reactions catalyzed by PDH and the tricarboxylic acid cycle and donate electrons (e⁻) that enter the respiratory chain. Cytochrome c oxidase catalyzes the reduction of molecular oxygen to water, and ATP synthase generates ATP from ADP.*

abnormal accumulation of lactate and protons, even in the absence of an increased rate of glycolysis. These ions may each independently exert deleterious effects on the host when present in sufficient amounts. In large part, however, lactic acidosis is most accurately viewed as a reflection of a fundamental failure by mitochondria in the efficient conversion of substrate fuel into energy for cellular work (4).

Inhibition of mitochondrial function, viz. gluconeogenesis or other anabolic pathways, is not sufficient to precipitate hyperlactatemia, so metformin's effect on hepatic glucose production per se is not an adequate reason for concern about its potential to cause acid-base mischief. As both Peters et al. (1) and I (2) pointed out, metformin does not appear to disrupt mitochondrial oxidative metabolism significantly, compared with its biguanide predecessor, phenformin.

The second point to reemphasize is the fact that many clinical conditions can lead to mitochondrial energy failure, and thus to hyperlactatemia (3,4). Critically ill individuals who have lactic acidosis commonly have several underlying diseases that may contribute to the development of acidosis. A recent case at our hospital is illustrative. A 77-year-old woman was transferred from another hospital with severe metabolic acidosis, possible sepsis, and acute renal failure. She had an arterial blood pH of 7.0, an arterial blood bicarbonate concentration of 13 mmol/l, a calculated anion gap of 30, and trace amounts of ketones in the urine. A subsequent arterial blood lactate concentration exceeded 13 mmol/l. The responsible house staff identified that this elderly patient was dehydrated, hypotensive, and possibly malnourished, had type 2 diabetes, renal failure, urosepsis, and probable transient bowel ischemia, and was receiving intravenous sodium bicarbonate and dopamine. Without belaboring the reasons (3,4), each of these 10 conditions, including advanced age, may precipitate or exacerbate lactic acidosis. However, because the patient had also received metformin, apparently without interruption for the previous year, and because the concentration of metformin in her blood was >25 μg/ml (therapeutic: 1–2 μg/ml) shortly after transfer, it was concluded that her lactic acidosis was due to metformin intoxication.

What troubles me about this scenario is not the fact that the house staff was ignorant of the weak association between circulating metformin levels and lactic acidosis (5,6). Instead, the problem is that the hypothesis-guided process of clinical diagnosis was abbreviated, once the association between lactic acidosis and metformin was made, and all the other trees in the forest were ignored, or at least minimized, without good reason. In the case of this patient or, for that matter, in most cases of so-called metformin-associated lactic acidosis, a distinct causal relationship between drug and disease is almost impossible to prove. Moreover, while there are experimental data to substantiate biochemical mechanisms for each of the other potential causes of lactic acidosis in the case summarized above, the mechanism(s) by which metformin may induce lactic acidosis is (are) still obscure.

To repeat, I did not and do not "encourage" (1) changing the restriction on the use of metformin in type 2 diabetes. However, I do advocate the application of evidence-based science to evidence-based medicine, particularly when differentiating among the causes and treatments of life-threatening conditions. What is still needed are mechanistically oriented experiments that can better elucidate metformin's true status as perpetrator or bystander in the pathobiology of lactic acidosis in humans.

PETER W. STACPOOLE, PHD, MD

From the Division of Endocrinology and Metabolism, Departments of Medicine and Biochemistry and Molecular Biology, College of Medicine, University of Florida, Gainesville, Florida.

Address correspondence to Peter W. Stacpoole, PhD, MD, Division of Endocrinology and Metabolism, Department of Medicine, Box 100226, JHMHC, Gainesville, FL 32610-0226. E-mail: stacpool@gcrc.ufl.edu.

P.W.S. serves as a member of the speakers faculty for Parke Davis and Pfizer.

References

1. Peters AL, Henry R, Edelman SV, Goldstein BJ. (Letter). *Diabetes Care* 22:532, 1999
2. Stacpoole PW: Metformin and lactic acidosis: guilt by association? (Editorial) *Diabetes Care*21:1587–1588, 1998
3. Stacpoole PW: Lactic acidosis. *Endocrinol Metab Clin North Am*22:221–245, 1993
4. Stacpoole PW: Lactic acidosis and other mitochondrial disorders. *Metabolism* 46:306–321, 1997
5. Lalau JD, Lacroix C, Compagnon P, DeCagny B, Rigand JP, Bleichner G, Chariveau P, Dulbecco P, Guerin C, Haegy JM, Moirat P, Marchand B, Ravand Y, Weyne P, Fournier A: A role of metformin accumulation in metformin-associated lactic acidosis. *Diabetes Care* 18:779–784, 1995
6. Lalau JD, Mourlhon C, Bergeret A, Lacroix C: Consequences of metformin intoxication (Letter). *Diabetes Care*21:2036–2037, 1998

Poor Level of Care Among Diabetic Patients

Is that a unique picture?

Recently Beckles et al. (1) published data from a population-based cross-sectional telephone survey investigating the level of care diabetic patients receive. The authors reported a marked underuse of preventive care practices in the U.S. compared with American Diabetes Association (ADA) guidelines.

Table 1—*Adherence to ADA standards among patients in the Beckles, Csongrád/Hungary and DiabCare Hungary databases*

	Beckles database (1)			Csongrád database		DiabCare database		
Preventive practice	Insulin users	Insulin nonusers	Type 1 diabetes	Insulin users	Insulin nonusers	Type 1 diabetes	Insulin users	Insulin nonusers
n	777	1,237	141	91	643	930	2,449	711
Self-monitors blood glucose	14	17	94	48	1.6*	93	80	16*
HbA_{1c} measurement	33	20	49	67	0.9*	80	73	54*
Visit to health care provider	58	53	91	100	100	100	100	100
Feet inspected	39	44	64	25	23	61	61	52*
Dilated eye examination	70	55	75	40	41	89	89	59*
All five standards	2.6	0.9		2	0	54	44	1*

Data are %. Results are based on the last 12 months. *$P < 0.0001$ between insulin users and nonusers in the Csongrád and DiabCare databases (χ^2 test).

The lack of data on health care delivery of diabetic patients and the gap between goals and reality of treatment led to the formulation of the St. Vincent Declaration in 1989 (2). Under the auspices of the European branches of the World Health Organization and the International Diabetes Federation, 5-year targets (to reduce the frequency of newly developed complications) were set, and various projects on quality improvement of diabetes were initiated (3).

A minimal data set of diabetes care from the previous 12 months to be collected for quality control purposes was developed in both paper form (BIS [Basic Information Sheet]) and as a direct entry format (ProDiab) (4). The indicators collected are very similar to those introduced in the ADA's Diabetes Quality Improvement Project (5).

As a joint project in Europe, we initiated a program for collecting these data on the care of diabetic patients in Hungary in 1993 (6). There were 23 care centers (including general practitioners [GPs]) that participated in this project, collecting altogether more than 5,000 records that were entered into the DiabCare Hungary database (7). One section of our database contains the sheets of all diabetic patients seen by any GP in Csongrád, a city with ~20,000 inhabitants, while the second has data from diabetic patients who are (including type 1 diabetic patients, who are all supposed to be) treated in specialist care centers.

Among the 763 Csongrád patients, 684 (90%) were aged ≥45 years; 408 (53%) were women. All of them had health insurance and had at least one visit to their GP within the last year. Some 86% of the cases were diagnosed after the age of 30 years, and 31% had diabetes for ≥10 years. Overall, 5% were classified as type 1 diabetic patients and 88% as type 2 diabetic patients; 7% could not be categorized. Individuals were classified as type 1 diabetic patients according to Beckles et al. (1) if their age was <30 years at diagnosis and they currently used insulin.

The second database contains 4,362 DiabCare records, and its type 1 patients are representative of Hungarian type 1 cases. Some 70% of them were ≥45 years of age; 57% were women; 71% were diagnosed after the age of 30 years; and 51% had diabetes for >10 years. Of these patients, 21% were classified as type 1 diabetic and 70% as type 2 diabetic; 19% were not classifiable.

The patients in the Csongrád database were divided into insulin users ($n = 91$) and nonusers ($n = 643$). Using the whole DiabCare database, we divided the records into three groups: type 1 patients ($n = 930$), insulin users (including type 1; $n = 2,449$), and insulin nonusers ($n = 711$) (Table 1).

Our data show similar differences between insulin users and nonusers, namely that less care is received by insulin nonusers. While the data IDDM patients are comparable to that reported by Beckles et al. (1) (significantly fewer eye exams and HbA_{1c} measurements in the U.S., $P < 0.0001$), the results found in insulin users and nonusers are very different in our two data sets and are different from those of Beckles and associates. From these controversial results, we can conclude first, that the insulin users in Hungary make significantly more self-monitoring and HbA_{1c} measurements ($P < 0.0001$); second, that insulin users get better care in specialist care centers than in GP offices and compared with the average in the U.S. (all five ADA standards are received by 2.6% in the Beckles database and by 44% in the DiabCare database, $P < 0.0001$); and third, that insulin nonusers perform less self-monitoring and get fewer HbA_{1c} measurements in Hungary than in the U.S. (Beckles vs. Csongrád database, $P < 0.0001$ and 0.0001, respectively).

Our findings highlight that only about half of type 1 diabetic patients get the standards of care from their doctor, while type 2 diabetic patients (and particularly insulin nonusers) get much less attention. There is a wide gap between the standards maintained for patients cared for in diabetes centers and by GPs.

ÁDÁM GY. TABÁK, MD
ZSUZSA KERÉNYI, MD, PHD
JÁNOS PÉNZES, MD
GYULA TAMÁS, MD, PHD

From the National Center for Diabetes Care (Á.Gy.T., Zs.K., Gy.T.); Semmelweis University of Medicine (Á.Gy.T., Gy.T.), 1st Department of Medicine; and Szent Imre Hospital (Zs.K.), 2nd Department of Medicine, Budapest; and from general practice (J.P.), Csongrád-Bokros, Hungary.

Address correspondence to Ádám Gy. Tabák, MD, Diabetes Research Center, Rangos Research Center, Fifth Floor, 3460 Fifth Ave., Pittsburgh, PA 15213. E-mail: tabada1@yahoo.com.

References

1. Beckles GLA, Engelgau MM, Narayan KMV, Herman WH, Aubert RE, Williamson DF: Population-based assessment of the level of care among adults with diabetes in the U.S. *Diabetes Care* 21:1432–1438, 1998
2. Krans HMJ, Porta M, Keen H (Eds.): *Diabetes Care and Research in Europe: The St Vincent Declaration Action Programme* Copenhagen, World Health Org., Regional Office for Europe, 1992
3. Piwernetz K., Benedetti MM, Staehr-Johansen K: Advanced health care initiatives in Europe on quality development, epidemiology and medical documentation. *Diabete et Metabolisme* 19:213–217, 1993
4. Piwernetz K, Home PD, Snorgaard O, Antsiferov M, Staehr-Johansen K, Krans M, for the DiabCare Monitoring Group of

the St Vincent Declaration Steering Committee: Monitoring the targets of the St Vincent Declaration and the implementation of quality management in diabetes care: the DiabCare Initiative. *Diabet Med* 10:371–377, 1993
5. American Diabetes Association: Diabetes Quality Improvement Project: initial measure set (final version). Available at: http://www.diabetes.org/dqip.asp.
6. Tamás Gy, Kerényi Zs, Fövényi J, Turbucz P, Filiczky I, Szövérffy G, Piwernetz K: Quality control of diabetes management using WHO/IDF DiabCare Programme: results of a pilot multicentre study in Hungary. *Diab Nutr Metab* 6:329–332, 1993
7. Kerényi Zs, Tamás Gy, Tabák Ágy, and the DiabCare Hungary Group: DiabCare Hungary: implementation of a tool for continuous quality improvement in diabetes care (Abstract). *Diabetologia* 40:A648, 1997

Screening Low-Risk Women for Gestational Diabetes Mellitus

Let's not muddy the waters further

In their article, Moses et al. (1) report that pregnancy outcomes in lean young Caucasian women were "similar to the outcomes of other women with GDM [gestational diabetes mellitus]." From their observations, they conclude that "the recommendation not to test women from a low-risk group requires further evaluation in different populations before it can be endorsed."

I agree that additional testing of pregnancy outcomes in apparently low-risk groups will add important information to existing ideas about who should be screened for GDM. However, the report by Moses and associates demonstrates a serious design flaw that must be avoided in any such testing: failure to blind caregivers to the glucose tolerance status of patients. It has been demonstrated clearly in randomized (2) and blinded (3) studies that the simple knowledge of the diagnosis of GDM or its treatment with insulin can alter perinatal management in a way that increases perinatal morbidities. This effect was most clearly apparent in the Toronto Tri-Hospital study (3), in which simply making the diagnosis of GDM increased Cesarean delivery rates with no other apparent explanation. Use by Moses and colleagues of admission to a special care nursery, an event that may be influenced highly by knowledge of the mother's medical condition, as the only index of neonatal morbidity in the absence of any defined protocol for such admission or an actual listing of neonatal medical problems is inappropriate and, quite probably, misleading. Given the lower-than-expected rates of large-for-gestational-age infants and the very low Cesarean delivery rates in the low-risk group, it seems likely that infants in that group would have done as well as the general population without maternal insulin treatment or admission to a special care nursery. To the extent that this speculation is true, Moses et al. have provided yet another example of complications arising from the diagnosis of GDM rather than from the biology of the condition. Thus, the 10% of women with GDM in the low-risk group might have been better off left unscreened and undiagnosed. The true biological risk to infants is impossible to ascertain because of the unblinded study design.

The issue of who needs to be screened for GDM has not been settled in all ethnic groups or all geographical areas. However, attempting to settle the issue by analyzing unblinded and retrospective clinical experience is as likely to yield the wrong answer as the right one. Continued conduct and publication of such analyses will only keep the waters of GDM muddy and should be discouraged.

THOMAS A. BUCHANAN, MD

From the University of Southern California, Los Angeles, California.

Address correspondence to Thomas A. Buchanan, MD, Associate Professor of Medicine and Obstetrics and Gynecology, University of Southern California, 1975 Zonal Ave., Los Angeles, CA 90033. E-mail: buchanan@hsc.usc.edu.

References

1. Moses RG, Moses J, Davis WS: Gestational diabetes: do lean young Caucasian women need to be tested? *Diabetes Care* 21: 1803–1806, 1998
2. Buchanan TA, Kjos SL, Montoro MN, Wu PYK, Madrilejo NG, Gonzalez M, Nunez V, Pantoja PM, Xiang A: Use of fetal ultrasound to select metabolic therapy for pregnancies complicated by mild gestational diabetes. *Diabetes Care* 17:275–283, 1994
3. Naylor CD, Sermer M, Chen E, Sykora K: Cesarean delivery in relation to birthweight and gestational glucose tolerance: pathophysiology or practice style? *JAMA* 265:1165–1170, 1996

Response to Buchanan

Professor Buchanan's letter (1) raises two important points. The first relates to the medical imperative "to do no harm" in a diagnosis of gestational diabetes mellitus (GDM). The Toronto Tri-Hospital study that he cites (2) found an increased section rate probably related to the diagnosis of GDM. This finding does present an educational opportunity: an increased section rate does not appear to be a problem in our area, where it is required by 20.4% of the women with GDM and 19.6% of the overall obstetric population. However, we cannot disagree that admission to a special care nursery may have been influenced by a knowledge of the mother's medical condition. It may also relate to the availability of such a facility and local admission policies. The important observation from our paper was that the rate of admission, for whatever reason, was the same for both groups.

The second point relates to the validity of reporting retrospective clinical experience. We agree that a prospective study would be ideal. However, until that comes about, if it comes about, evidence will have to be based on the best available studies. We feel that our paper does provide some useful clinical information. Professor Buchanan writes with passion that studies such as ours will "muddy" the waters of GDM and should be discouraged. What comments will be reserved for the American Diabetes Association, who have introduced a recommendation with no evidence at all?

ROBERT G. MOSES, FRACP
JUSTINE MOSES, BVSC
WARREN S. DAVIS, FRACOG

From the Illawarra Area Health Service.

Address correspondence to Robert G. Moses, FRACP, 4/393 Crown Street, Wollongong NSW 2500, Australia.

References

1. Buchanan TA: Screening low-risk women for gestational diabetes mellitus: let's not muddy the waters further. *Diabetes Care* 22:535, 1999
2. Naylor CD, Sermer M, Chen E, Sykora K: Cesarean delivery in relation to birthweight and gestational glucose tolerance: pathophysiology or practice style? *JAMA* 265:1165–1170, 1996

Erratum

Kelly IE, Han TS, Walsh K, Lean MEJ: Effects of a thiazolidinedione compound on body fat and fat distribution of patients with type 2 diabetes. *Diabetes Care* 22:288–293, 1999

In Table 2 of the above article, an incorrect value was given under "Differences (treated − placebo)." The revised table is printed below with the corrected value (−25.9) shown in bold.

Table 2—*Changes in body composition (end point minus baseline values)*

	Troglitazone	Placebo	Differences (treated − placebo)	*P*
Weight (kg)	0.66 (−0.71 to 2.04)	0.25 (−0.64 to 1.13)	0.42 (−1.15 to 1.98)	0.58
BMI (kg/m^2)	0.25 (−0.25 to 0.75)	0.09 (−0.23 to 0.40)	0.16 (−0.40 to 0.73)	0.55
Waist circumference (cm)	2.11 (0.50 to 3.73)	−0.05 (−3.72 to 3.81)	2.16 (−1.5 to 5.84)	0.23
Waist-to-hip ratio	−0.08 (−0.20 to 0.04)	−0.03 (−0.08 to 0.02)	−0.06 (−0.18 to 0.07)	0.37
Total body fat (% body wt)	1.02 (−1.13 to 3.17)	−0.54 (−1.68 to 0.60)	1.56 (−0.88 to 3.99)	0.20
Total body fat (kg)	1.11 (−0.94 to 3.16)	−0.35 (−1.28 to 0.58)	1.46 (−0.82 to 3.73)	0.20
Extra-abdominal fat (kg)	−0.08 (−0.33 to 0.16)	−0.09 (−0.24 to 0.06)	0.01 (−0.28 to 0.26)	0.94
Intra-abdominal fat (kg)	−0.47 (−0.79 to −0.13)	−0.06 (−0.22 to 0.10)	−0.41 (−0.77 to −0.05)	0.03
Blood glucose (U/l)	−0.88 (−3.56 to 1.80)	0.28 (−1.61 to 2.17)	−1.16 (−4.28 to 1.96)	0.45
HbA_{1c} (%)	−0.84 (−1.41 to −2.83)	0.29 (−0.69 to 1.26)	−1.09 (−2.09 to −0.17)	0.02
γ-Glutamyltransferase (U/l)	−32.3 (−53.2 to −11.4)	21.0 (−27.4 to 69.4)	−53.3 (−100.6 to −6.0)	0.03
Aspartate aminotransferase (U/l)	−0.09 (−2.82 to 2.64)	−3.67 (−10.01 to 2.67)	3.58 (−2.35 to 9.50)	0.22
Alanine aminotransferase (U/l)	−0.27 (−5.52 to 4.98)	2.67 (−2.80 to 8.13)	−2.94 (−10.03 to 4.15)	0.40
Alkaline phosphatase (U/l)	−36.8 (−51.8 to −21.9)	7.2 (−4.0 to 18.4)	−44.0 (−62.2 to **−25.9**)	<0.01

Data are means (95% CI). Values for troglitazone and placebo are from paired *t* test for the differences between baseline and 12 week follow-up data, and values for differences are from independent *t* tests for the differences of changes in measures of adiposity between treatment groups.