OBSERVATIONS

Effect of Phlebotomy on Plasma Glucose and Insulin Concentrations

Two recent reports in *Diabetes Care* (1,2) showed that iron stores, as assessed by serum ferritin concentration (3), are associated with plasma glucose and insulin concentrations, i.e., the greater the serum ferritin concentration, the greater the plasma glucose and insulin concentrations. Greater plasma glucose and insulin concentrations indicate a more severe degree of insulin resistance (4). Complementary findings were described by Moirand et al. (5), who detected a high prevalence of insulin-resistant states such as obesity, glucose intolerance, and type 2 diabetes in individuals with normal to high iron stores but without the genetic traits of hemochromatosis. In this context, it is possible that insulin-resistant individuals might have a tendency to synthesize more ferritin and/or to accumulate more iron. However, this hypothesis is not supported by studies in polytransfused thalassemic children, who eventually become severely insulin resistant (6), or by findings in Sprague-Dawley rats, in which progressive iron depletion enhances, in a dose-dependent fashion, insulin-mediated glucose uptake (7,8). Thus, the alternative hypothesis is that iron excess or even sufficiency might worsen glucose tolerance, whereas iron deficiency or lowering should induce the opposite phenomenon.

To test such a hypothesis, phlebotomy was used to lower iron stores in 10 healthy blood donors (mean age ± SEM, 42 ± 4 years), and the consequent effects on glucose-stimulated insulin levels are herein reported. Four weeks after phlebotomy, serum ferritin concentration halved (75 ± 18 to 38 ± 10 μg/l; $P < 0.001$); compared with baseline, the 2-h plasma insulin and glucose concentrations after a 75-g oral glucose load were reduced by 37 ± 9% (665 ± 158 to 418 ± 93 pmol/l; $P < 0.02$) and 19 ± 3% (7.4 ± 1.2 to 6.0 ± 0.8 mmol/l; $P < 0.05$), respectively.

Thus, 1 month after a 500-ml phlebotomy, improved glucose tolerance was observed. Such effect correlated with the reduction of serum ferritin concentration ($r = 0.53$; $P < 0.03$) but not with that of hematocrit (Hct). Because all the participating individuals had baseline ferritin concentrations within normal limits, the current finding seems to support the notion that a reduction of body iron stores enhances insulin sensitivity, even in "iron-sufficient" individuals.

Mechanisms other than iron depletion are worthy of consideration. For instance, after phlebotomy, blood volume is restored to normal within 24–48 h by hemodilution, whereas Hct returns to baseline values at a slower rate (9). One can postulate that the reduction in Hct and blood viscosity could increase muscle perfusion and, therefore, glucose uptake (10). This effect might result in improved glucose tolerance. There are inconsistencies, however, that argue against this hypothesis. First, 4 weeks after phlebotomy, Hct was only 1% lower than at baseline (43.9 ± 0.9 vs. 44.5 ± 1.0%; NS); this variation appears too small to explain a persistent change in glucose tolerance of ~40%. In addition, the reduction of Hct was insignificantly correlated to such change. Therefore, it seems unlikely that the variation in Hct, per se, determined the change in glucose tolerance.

In summary, after a 500-ml phlebotomy, enhanced oral glucose tolerance is demonstrated in 10 healthy individuals. Such results help clarify the nature of the recently reported association between insulinemia, insulin resistance, and serum ferritin concentration (1,2).

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References

1. Tuomainen T-P, Nyyssönen K, Salonen R, Tervahauta A, Korpela H, Lakka T, Kaplan GA, Salonen JT: Body iron stores are associated with serum insulin and blood glucose concentrations: population study in 1,013 eastern Finnish men. *Diabetes Care* 20:426–428, 1997
2. Fernández-Real J-M, Ricart-Engel W, Arroyo E, Balançá R, Casamitjana-Abella R, Cabrero D, Fernández-Castañer M, Soler J: Serum ferritin as a component of the insulin resistance syndrome. *Diabetes Care* 21:62–68, 1998
3. Cook JD, Lipschitz DA, Miles LEM, Finch CA: Serum ferritin as a measure of iron stores in normal subjects. *Am J Clin Nutr* 27:681–687, 1974
4. Hollenbeck CB, Chen N, Chen Y-DI, Reaven GM: Relationship between the plasma insulin response to oral glucose and insulin-stimulated glucose utilization in normal subjects. *Diabetes* 33:460–463, 1984
5. Moirand R, Mortaji AM, Loreal O, Paillard F, Brissot P, Deugnier Y: A new syndrome of liver iron overload with normal transferrin saturation. *Lancet* 349:95–97, 1997
6. Merkel PA, Simonson D, Amiel S, Plewe G, Sherwin RS, Pearson HA, Tamborlane WV: Insulin resistance and hyperinsulinemia in patients with thalassemia major treated by hypertransfusion. *N Engl J Med* 318:809–814, 1988
7. Henderson S, Dallman PR, Brooks GE: Glucose turnover and oxidation are increased in the iron-deficient rat. *Am J Physiol* 250:E414–E421, 1986
8. Borel MJ, Beard JL, Farrell PA: Hepatic glucose production and insulin sensitivity and responsiveness in iron-deficient anemic rats. *Am J Physiol* 264:E380–E390, 1993
9. Ebert RV, Stead EA, Gibson JG: Response of normal subjects to acute blood loss. *Arch Intern Med* 68:578–590, 1941
10. Baron AD, Laakso M, Brechtel G, Hoitt C, Watt C, Edelman SV: Reduced postprandial skeletal muscle blood flow contributes to glucose intolerance in human obesity. *J Clin Endocrinol Metab* 70:1525–1533, 1990

Reduction of Macroalbuminuria With Pentoxifylline in Diabetic Nephropathy

Report of three cases

Reduction of macroalbuminuria in diabetic nephropathy, once established, is problematic. Both tight glycemic control and ACE inhibitors (ACEIs) have been shown to be useful in reducing both microalbuminuria (1,2) and the progression of microalbuminuria to overt albuminuria (3,4). Dietary protein restriction may also be useful in reducing progression of albuminuria (5). However, little treatment is available to promote the reduction of macroalbuminuria once that is established. Pentoxifylline has been reported to be beneficial in reducing macroalbuminuria from diabetic nephropathy (6). The cases presented here give further support to the use of this medication, in conjunction with

tight glycemic control, in the treatment of patients with macroalbuminuria from diabetic nephropathy.

In the first case, a 58-year-old woman with type 1 diabetes that was diagnosed when she was 17 years old was found to have 1,260 mg/day of protein in the urine. Her history was pertinent for diabetic retinopathy, neuropathy, and for recurrent congestive heart failure. Medications included digoxin, furosemide, Cozaar, and aspirin, as well as NPH and regular insulin twice daily. The HbA_{1c} was 7.7% (4.1–6.1). The treatment regimen was changed to the insulin pump, and therapy with pentoxifylline (400 mg t.i.d.) was begun. Because of gastrointestinal side effects from the pentoxifylline, the dosage was reduced to 400 mg twice per day, which was tolerated. Three months later, the 24-h urine protein was 284 mg/day, and 6 months after that, 237 mg/day. The HbA_{1c} fluctuated between 7.2 and 7.5% during that time. All other medications were continued as before.

In the second case, a 74-year-old man with type 1 diabetes that was diagnosed when he was 42 years old had been noted at age 70 years to have 312 mg/day of protein in the urine. Therapy with 10 mg/day lisinopril was begun. After 18 months, a 24-h urine sample revealed 3,643 mg/day of protein. Therapy with pentoxifylline (400 mg t.i.d.) was begun. Also at that time, the insulin regimen was changed from three injections per day to use of the insulin pump. After 6 months, a 24-h urine sample revealed 1,836 mg of protein. When tested 6 months later, the urinary protein was 1,056 mg/day, and after an additional 6 months, it was 490 mg/day. Lisinopril therapy was continued during this time. HbA_{1c} levels fluctuated between 7.2 and 8.3% (4.1–6.1) during this time, compared with values between 9.0 and 9.3% before introduction of the insulin pump.

In the third case, an 84-year old female who had type 2 diabetes with diabetic retinopathy and peripheral neuropathy was found to have 3,967 mg/day of urinary protein. Her history was pertinent for hypertension and congestive heart failure, for which she was treated with captopril (25 mg t.i.d.) and furosemide (40 mg b.i.d.). Her diabetes was managed with Humulin N and Humulin R in the morning, Humulin R at supper, and Humulin N at bedtime. Pentoxifylline was begun for the proteinuria at a dosage of 400 mg t.i.d. After 4 months, the 24-h urinary protein had been reduced to 733 mg/day, and 1 year later, the urinary protein was 787 mg/day. During this time, HbA_{1c} ranged between 5.8 and 6.5% (4.1–6.1).

These cases illustrate that pentoxifylline, in conjunction with intensive therapy for diabetes, may be particularly useful in reducing significant proteinuria. All three patients maintained stable serum creatinine levels in the range of 1.0–1.5 mg/dl. Tight glycemic control was maintained in all patients, and in the second case, there was a significant improvement in HbA_{1c} after insulin pump therapy was introduced. Two patients were taking concomitant ACEIs, and the third was on an angiotensin-receptor blocker (ARB). ARBs have been shown in an animal model to attenuate diabetic nephropathy (7). Further studies to elucidate the mechanism of improved macroalbuminuria by pentoxifylline in conjunction with tight glycemic control in the treatment of diabetic nephropathy should be considered. This treatment appears to be beneficial in forestalling the typically relentless downhill course of diabetic nephropathy.

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References

1. Wiegmann TB, Herron KG, Chonko AM, MacDougall ML, Moore WV: Effect of angiotensin-converting enzyme inhibition on renal function and albuminuria in normotensive type I diabetic patients. *Diabetes* 41:62–67, 1992
2. Bojestig, M, Arnqvist HJ, Karlberg BE, Ludvigsson J: Glycemic control and prognosis in type I diabetic patients with microalbuminuria. *Diabetes Care* 19:313–317, 1996
3. Viberti G, Mogensen CE, Groop LC, Pauls JF: Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria: European Microalbuminuria Captopril Study Group. *JAMA* 271:275–279, 1994
4. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
5. Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH: The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Ann Intern Med* 124:627–632, 1996
6. Guerrero-Romero F, Rodriguez-Moran M, Paniagua-Sierra JR, Garcia-Bulnes G, Salas-Ramirez M, Amato D: Pentoxifylline reduces proteinuria in insulin-dependent and non–insulin-dependent diabetic patients. *Clin Nephrol* 43:116–121, 1995
7. Yotsumoto T, Naitoh T, Shikada K, Tanaka S: Effects of specific antagonists of angiotensin II receptors and captopril on diabetic nephropathy in mice. *Jpn J Pharmacol* 75:59–64, 1997

Correct Homeostasis Model Assessment (HOMA) Evaluation Uses the Computer Program

We read with interest the correspondence between Drs. van Haeften (1) and Matsumoto et al. (2) in a recent issue of *Diabetes Care* about the correct formula for insulin resistance calculated by homeostasis model assessment (HOMA). The HOMA model (3) is a structural computer model of the glucose-insulin feedback system in the homeostatic (overnight-fasted) state. The model consists of a number of nonlinear empirical equations describing the functions of organs and tissues involved in glucose regulation. These are solved numerically to predict glucose, insulin, and C-peptide concentrations in the fasting steady state for any combination of pancreatic β-cell function and insulin sensitivity (or resistance). These predictions allow the deduction of β-cell function (%β) and insulin sensitivity (%S) from pairs of fasting glucose and insulin (or C-peptide) measurements. The nonlinearity of the model precludes an exact algebraic solution, but estimations are possible either graphically or by using simple mathematical approximations, as presented in Matthews et al. (3): *R* (which is the inverse of %S) = (insulin × glucose)/22.5 and %β = 20 × insulin/(glucose − 3.5). The apparent redundancy of the expression in question was due to the removal of terms from an original, more complex, expression. Two developments have taken place since 1985.

First, the physiological basis of the model has been developed, both in terms of insulin secretion (4) and glucose metabolism (5), and further modifications have included a model of proinsulin secretion,

allowing HOMA to be used with either immunoreactive insulin or specific insulin assays, and a model of renal glucose losses, allowing its use in more hyperglycemic states. These modifications provide a more accurate representation of physiology and successfully predict the homeostatic responses to an intravenous glucose infusion. The use of the current HOMA model performs well in comparison with several tests of insulin sensitivity, including the intravenous glucose tolerance test, and with minimal model analysis and the short insulin tolerance test of Bonora (6) and tests of β-cell function (7), including the hyperglycemic clamp (8), the oral glucose tolerance test (9), and the frequently sampled intravenous glucose tolerance test (FSIVGTT) (7).

Second, the model has been incorporated in a simple MS-DOS–based computer program that allows rapid determination of %β and %S from measured values. This program is available free of charge for academic use from one of the authors (J.C.L.). Although the simple equations (3) give a qualitatively useful approximation of the model predictions, we recommend that HOMA calculations use the computer model in preference, in view of its more precise physiological basis and the validation data that are available and in the process of being published.

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References

1. van Haeften TW: Glucose tolerance, insulin sensitivity, and the homeostasis model assessment method (Letter). *Diabetes Care*21:673, 1998
2. Matsumoto K, Yano M, Ueki Y, Miyake S: Response to van Haeften (Letter). *Diabetes Care* 21:673–674, 1998
3. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*28:412–419, 1985
4. Rudenski AS, Hosker JP, Burnett MA, Matthews DR, Turner RC: The β-cell glucose stimulus-response curve in normal humans assessed by insulin and C-peptide secretion rates. *Metabolism* 37:526–534, 1988
5. Rudenski AS, Matthews DR, Levy JC, Turner RC: Understanding "insulin resistance": both glucose resistance and insulin resistance are required to model human diabetes. *Metabolism*40:908–917, 1991
6. Hermans M, Coppack S, Levy J: Comparison of the efficiency of 4 *in vivo* insulin sensitivity tests to discriminate between individuals over the range of glucose tolerance by assessment of their discriminant ratio (Abstract). *Diabetes* 44 (Suppl. 1):200A, 1995
7. Hermans MP, Levy J, Coppack S, Shadid T, Turner RC: Comparison of the ability of 3 *in vivo* tests to discriminate differences in β-cell function over the range of glucose tolerance (Abstract). *Diabetologia* 38 (Suppl. 2):A30, 1995
8. Levy J, Manley S, Sutton P, Camps I: Beta-cell function assessed by the hyperglycaemic clamp: reproducibility compared with HOMA analysis from fasting values, and factors influencing variability (Abstract). *Diabetes* 44 (Suppl. 1):89A, 1995
9. Hammersley M, Levy J, Volpicelli G, Barrow B, Hatterlsey A, Turner R: Glucose tolerance and β-cell function assessed by continuous infusion of glucose and oral glucose tolerance test (Abstract). *Diabetologia*35 (Suppl. 1):99A, 1992

Diabetic Instability and Celiac Disease

A frequent association to keep in mind

Celiac disease (CD) is caused by damage to differentiated villus epithelial cells in response to the ingestion of dietary gluten. The rate of IDDM and CD association is generally estimated to be 1–7% (1). Some clues suggest that these two conditions are linked by a common physiopathology. The first phase of insulin response is altered in islet cell antibody (ICA)-negative children with CD observed in the prediabetic state (2). In addition, some of these children with CD developed IDDM during a follow-up of 10 years (2). Furthermore, CD and IDDM are supported by an identical genetic background (class II HLA DR3 and HLA DQ2 genotypes) (1,3,4). Finally, similar mechanisms of β-cell and enterocyte cell damage mediated by tumor necrosis factor and γ-interferon are observed (4).

The recent routine accessibility of IgA endomysial antibody detection (the most sensitive and specific noninvasive screening test of CD) (1,5) showed that CD and IDDM are more frequently associated than previously reported. The usual symptoms of CD are diarrhea and a chronic malabsorption syndrome. Furthermore, the altered digestive absorption of meals worsened the metabolic control of diabetes, leading to diabetic instability. We report a case of poorly controlled IDDM caused by a severe CD free of any specific symptom.

A 47-year-old IDDM woman was referred for poor diabetic control. Her uncomplicated IDDM was diagnosed at 30 years of age. An intensive insulin therapy maintained diabetes near normoglycemia until 1 year before admission. In the last year, a loss of 1 kg of body weight (BMI 25 kg/m^2) was associated with frequent and unpredictable hypoglycemic or hyperglycemic periods. The daily calorie intake was unchanged, and no eating disorder was noted. Psychiatric pathology and factitious disease were excluded. The search for intercurrent illness was negative. Diarrhea was not present. Clinical examination was normal except for periumbilical subcutaneous lipodystrophies. Their exclusion as insulin injection sites did not improve metabolic parameters. No biological signs of malabsorption were found. Because of the presence of dyspeptic symptoms, we performed an upper digestive track fibroscopy that excluded diabetic gastroparesis. Systematic bowel biopsies showed complete mucosal atrophy typical of severe CD. IgA endomysial antibodies were positive (by indirect immunofluorescence assay). An improvement of metabolic control was observed 6 months after gluten-free diet introduction, and control bowel biopsies showed the disappearance of mucosal atrophy.

Our case was intriguing because of the lack of the usual biological and clinical features of CD. The disappearance of diabetic instability after the introduction of a specific gluten-free diet confirms the responsibility of CD in the bad metabolic control.

Diabetes instability is a severe disease that can endanger a patient's life. Because CD is a curable cause of bad metabolic control more often associated with IDDM than usually admitted, we suggest that all subjects with diabetic instability should be actively screened for CD, even if no spe-

cific digestive or biological symptoms are present. The use of the IgA endomysial antibody test seems to be of great use to facilitate the early diagnosis of CD in an asymptomatic IDDM population.

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References

1. Cronin CC, Shanahan F: Insulin dependent diabetes mellitus and coeliac disease. *Lancet*349:1096–1097, 1997
2. Karagiozoglou-Lampoudi T, Nousia-Arvanitaki S, Augoustidou-Savopoulou P, Salem N, Polymenidis Z, Kanakouditsakalidou F: Insulin secretion decline unrelated to jejunal morphology or exocrine pancreatic function in children with celiac disease. *J Pediatr Endocrinol Metab*9:585–591, 1996
3. Vardtal F, Johansen BH, Friede T, Thorpe CJ, Stevanovic S, Eriksen JE, Sletten K, Thorsby E, Rammensee HG, Sollid LM: The peptide binding motif of the disease associated HLA-DQ molecule. *Eur J Immunol*26:2764–2772, 1996
4. Pena S, Garrote JA, Crusius JB: Advances in the immunogenetics of coeliac disease: clues for understanding the pathogenesis and disease heterogeneity. *Scand J Gastroenterol*225 (Suppl.):56–58, 1998
5. Ferreira M, Davies SL, Butler M, Scott D, Clark M, Kumar P: Endomysial antibody: is it the best screening test for coeliac disease? *Gut*33:1633–1637, 1992

Should Age and Sex Be Taken Into Account in the Determination of HbA_{1c} Reference Range?

In the last few years, a number of articles have shown the influence of aging on HbA_{1c} values in healthy populations (1–3). Because aging could be associated with weight gain, less exercise, increased drug intake, concomitant illnesses, etc., researchers have taken care to remove the influence of these factors on their studies and have confirmed that a physiological process exclusively linked to aging could be responsible for the increase in HbA_{1c} in older populations. Our aim, in a first study, was to confirm this increase in our population (Mediterranean area). We found that HbA_{1c} results were not related to sex, but they did show a clear increase with aging (4). More recently, we have carried out a broader study in a healthy population, selecting 540 men and 540 women with analytical results in the reference range. Individuals were classified into six age-groups: 20–29, 30–39, 40–49, 50–59, 60–69, and >70 years. Blood was collected in K3-EDTA tubes and stored at 4°C before the analysis. Determination of HbA_{1c} was performed using an HA-8140 high performance liquid chromatography system. The study confirmed (Table 1) the influence of aging in increasing the mean value of HbA_{1c}, but also allowed us to assess some differences related to the sex of the individuals. Effectively, despite the fact that the whole male and female populations did not show different mean HbA_{1c} values (men 4.84 ± 0.41%, women 4.81 ± 0.44%, $P = 0.298$), we found that young women exhibit lower values of HbA_{1c} (Fig. 1), though this difference is reduced with aging, and even higher values are observed in women >70 years of age, compared with men of the same age-group. These results, obtained in a Mediterranean population, agree with those found in a Chinese population and previously published (3).

Table 1—*HbA_{1c} mean differences*

	HbA_{1c} (%)	
	Women	Men
Age-group		
20–29	4.41 ± 0.26*†	4.58 ± 0.31*
30–39	4.56 ± 0.33*†	4.71 ± 0.40
40–49	4.68 ± 0.40*	4.79 ± 0.37*
50–59	4.95 ± 0.36*	4.88 ± 0.33
60–69	5.09 ± 0.31	5.08 ± 0.41
>70	5.17 ± 0.34†	5.01 ± 0.38

Data are means ± SD. $n = 90$ for all groups. *$P <$ 0.05 vs. group 1 decade older; †$P < 0.05$ vs. men.

Nowadays, the effect of aging in the interpretation of HbA_{1c} results could be limited by a number of factors that also affect the accuracy of this measurement. Among others, lack of international standardization is a challenge for the clinical interpretation of HbA_{1c} data because heterogeneity of results due to the use of different analytical techniques has still not been solved. However, if an international standardization for glycohemoglobin is finally reached, the influence of factors such as sex or aging could become clinically important in HbA_{1c} interpretation, and correction factors related to them could be necessary.

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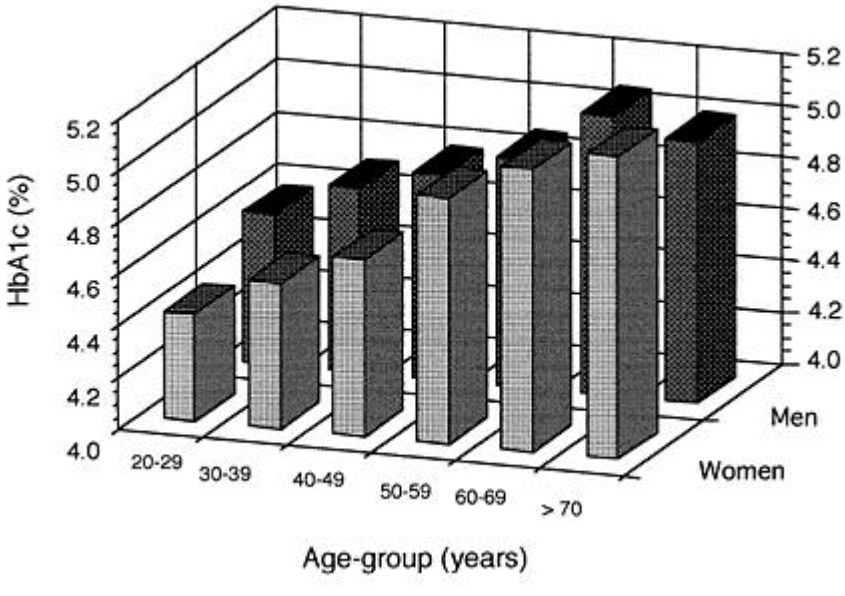

Figure 1—*Increase of HbA_{1c} mean value with aging.*

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References

1. Nakashima K, Nishizaki O, Andoh Y: Acceleration of hemoglobin glycation with aging. *Clin Chim Acta* 214:111–118, 1993
2. Hashimoto Y, Futamura A, Ikushima M: Effect of aging on HbA_{1c} in a working male Japanese population. *Diabetes Care* 18:1337–1340, 1995
3. Yang YC, Lu FH, Wu JS, Chang CJ: Age and sex effects on HbA_{1c}: a study in a healthy Chinese population. *Diabetes Care* 20:988–991, 1997
4. Carrera T, Bonamusa L, Perich C, Juve R, Cosculluela R, Almirall L, Navarro JM: Effect of aging on HbA1c reference values determined by HPLC in an HA-8140 system (Abstract). *Clin Chem* 43 (Suppl. 6):S138, 1997

Vanadyl Sulfate Does Not Enhance Insulin Action in Patients With Type 1 Diabetes

Vanadium, a transition metal found in trace concentrations in humans, has insulin-like effects in vitro (1–3) and in vivo (4,5). In vitro, vanadium stimulates glucose uptake and oxidation, and glycogen synthesis in adipocytes, skeletal muscle, and hepatocytes (6). In diabetic rats, large doses of vanadium improve glucose tolerance without an increase in plasma insulin (5) and cause an increase in hepatic glycogen (5,7,8). Thus, interest in vanadium as a possible treatment for diabetes has been intense.

In humans, we have demonstrated that low doses of vanadyl sulfate (VS) given for 3 weeks increased insulin-mediated glucose uptake, glycogen synthesis, and suppression of endogenous glucose production (EGP) in type 2 diabetic patients (9) but not in obese nondiabetic subjects (10). These improvements in hepatic and peripheral insulin sensitivity were associated with reduced lipid oxidation rates and plasma free fatty acid (FFA) concentrations. On the other hand, a recent study in type 1 diabetic patients given sodium metavanadate demonstrated a decrease in insulin requirements with no change in glucose metabolism (11). However, the relationship between the clinical findings of reduced insulin requirements and vanadium action per se is unclear. For example, the intracellular—and hence active—form of vanadium associated with an insulin-like effect is the vanadyl (V^{4+}) oxidation state of the element, as used in our previous studies, not vanadate (V^{5+}) (12,13). Thus, a plausible mechanism for vanadium action in type 1 diabetes remains unclear.

Because the effects of VS in type 2 diabetes may be to augment insulin action on lipolysis and EGP and both parameters are very sensitive to insulin in vivo, we used a low-dose insulin infusion to determine whether there is enhancement of insulin action, as seen in patients with type 2 diabetes. VS (100 mg/day) was given for 3 weeks and compared with 3 weeks of placebo in five type 1 diabetic subjects (age 31 ± 2 years; BMI 24 ± 1.6 kg/m^2). Plasma vanadium concentrations were 83.0 ± 29.4 µg/l after VS. There were no changes in insulin dose, weight, or appetite during the study period. While HbA_{1c} declined slightly, from 8.1 ± 0.4 to 7.6 ± 0.3%, serum fructosamine levels were unchanged (2.5 ± 0.1 mmol/l after both placebo and VS). Euglycemic-hyperinsulinemic clamps combined with 3-[^{3}H]glucose and constant specific activity were performed after each 3-week period. Glucose disposal was unchanged (26.37 ± 3.16 vs. 23.59 ± 3.89 µmol · kg^{-1} · min^{-1}, placebo vs. VS, respectively, NS). Similarly, glucose infusion rates needed to maintain euglycemia were unchanged (24.53 ± 3.28 vs. 21.59 ± 3.28 µmol · kg^{-1} · min^{-1}, NS). With indirect calorimetry, there were no significant changes in the whole-body oxidation rates of glucose or lipid. Finally, insulin-induced suppression of EGP (by ~70–80%) and plasma FFA (by ~50–60%) were comparable after placebo and VS.

Thus, a dose of VS previously determined to be well tolerated in humans and effective in patients with insulin-resistant type 2 diabetes did not enhance the effects of physiologic hyperinsulinemia on glucose and fat metabolism in type 1 diabetes. These results suggest that vanadium improves insulin action selectively in subjects with insulin resistance. While currently available, vanadium compounds remain as experimental probes to examine the mechanism of altered insulin action (14); more studies will be needed to establish any role for their clinical usage.

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References

1. Dubyak GR, Kleinzeller G: The insulin-mimetic effects of vanadate in isolated rat adipocytes. *J Biol Chem* 255:5306–5312, 1980
2. Shechter Y: Insulin-mimetic effects of vanadate: possible implications for future treatment of diabetes. *Diabetes* 39:1–5, 1990
3. Clausen T, Anderson TL, Sturup-Johansen M, Petkova A: The relationship between the transport of glucose and cations across cell membranes in isolated tissues: the effect of vanadate in ^{45}Ca-efflux and sugar transport in adipose tissue and in skeletal muscle. *Biochim Biophys Acta* 646:261–267, 1981
4. Rossetti L, Laughlin MR: Correction of chronic hyperglycemia with vanadate but not with phlorizin normalizes in vitro glycogen synthase activity in diabetic skeletal muscle. *J Clin Invest* 84:892–899, 1989
5. Brichard SM, Okitolonda W, Henquin JC: Long term improvement of glucose homeostasis by vanadate treatment in diabetic rats. *Endocrinology* 123:2048–2053, 1988
6. Tolman EL, Barris E, Burns M, Pansini A, Partridge R: Effects of vanadium on glucose metabolism in vitro. *Life Sci* 25:1159–1164, 1979
7. Pugazhenthi S, Khandelwla RL: Insulinlike effects of vanadate on hepatic glycogen metabolism in nondiabetic and streptozotocin-induced diabetic rats. *Diabetes* 39: 821–827, 1990
8. Battell ML, Yuen VG, McNeill JH: Treatment of BB rats with vanadyl sulphate. *Pharm Comm* 1:291–301, 1992
9. Cohen N, Halberstam M, Shlimovich P, Chang CJ, Shamoon H, Rossetti L: Oral vanadyl sulfate improves hepatic and peripheral insulin sensitivity in patients with noninsulin dependent diabetes mellitus. *J Clin Invest* 95:2501–2509, 1995
10. Halberstam M, Cohen N, Shlimovich P, Rossetti L, Shamoon H: Oral vanadyl sulfate improves insulin sensitivity in NIDDM but not in obese nondiabetic subjects. *Diabetes* 45:659–666, 1996
11. Goldfine AB, Simonson DC, Folli F, Patti ME, Kahn CR: Metabolic effects of sodium metavanadate in humans with insulin-

dependent and noninsulin-dependent diabetes mellitus: in vivo and in vitro studies. *J Clin Endocrinol Metab* 80:3312–3320, 1995
12. Gegani H, Gichin M, Karlish S, Shechter Y: Electron paramagnetic resonance studies and insulin-like effects of vanadium in rat adipocytes. *Biochemistry* 20:5795–5799, 1981
13. Green A: The insulin-like effect of sodium vanadate on adipocyte glucose transport is mediated at a post-insulin-receptor level. *Biochem J* 238:663–669, 1986
14. Goldfine A, Landaker EJ, Willsky G, Patti ME: Defining the mechanism of action of vanadium *in vivo* in NIDDM (Abstract). *Diabetes* 47 (Suppl. 1):A307, 1998

A Common Glu^{298}→Asp (894G→T) Mutation at Exon 7 of the Endothelial Nitric Oxide Synthase Gene and Vascular Complications in Type 2 Diabetes

Table 1—*Vascular complications and the ecNOS genotypes in type 2 diabetes*

	TT	TG	GG	*P* value
Angina pectoris				
Yes	11 (25.6)	40 (17.2)	40 (13.4)	0.095
No	33	192	258	
Myocardial infarction				
Yes	6 (14.0)	35 (15.1)	54 (18.1)	0.577
No	37	197	244	
Stroke				
Yes	1 (2.6)	7 (3.6)	10 (3.9)	0.913
No	38	187	245	
Peripheral vascular disease				
Yes	5 (12.8)	41 (21.1)	51 (20.0)	0.493
No	34	153	204	
Microalbuminuria				
Yes	7 (20.6)	44 (28.8)	65 (30.5)	0.305
No	27	109	148	
Retinopathy				
Yes	5 (20.8)	23 (16.8)	43 (26.7)	0.119
No	19	114	118	
Neuropathy				
Yes	8 (21.1)	46 (26.0)	49 (21.1)	0.488
No	30	131	183	

Data are *n* or *n* (%). *P* values refer to comparisons of the frequencies of the occurrence of vascular complications among the three ecNOS genotypes by χ^2 analysis.

Nitric oxide (NO) regulates endothelium-dependent vasodilatation and blood pressure, and reduced production has been implicated in hypertension, atherosclerosis, and diabetes (1–3). Endothelial constitutive nitric oxide synthase (ecNOS) mediates the oxidation of L-arginine to produce NO and determines basal vascular wall NO production (4). The gene encoding ecNOS is located on chromosome 7q35-36 and comprises 26 exons (5). To identify genetic markers relevant to NO-related vascular risk, we explored in 574 middle-aged Australian type 2 diabetic patients a possible role for a Glu^{298}→Asp mutation at exon 7 of the ecNOS gene; an association between the mutation and coronary risk was reported in the Cambridge Heart Anti-Oxidant Study (6). Patients recruited were those aged 62.4 ± 0.5 years (mean ± SEM), 329 men and 245 women, with and without documented macro- and microvascular complications. The genotype distribution was 7.5, 40.6, and 51.9% for TT, TG, and GG, respectively. It was in Hardy-Weinberg equilibrium (χ^2 = 0.088, $P > 0.05$) and not different between men and women (χ^2 = 0.713, P = 0.700). The ecNOS TT and TG genotypes were not associated with age, age at onset of documented diabetes, BMI, systolic and diastolic blood pressures (BPs), lipid profile, plasma creatinine and glycosylated hemoglobin (HbA_{1c}) levels, or urinary albumin index (UAI: albumin/creatinine ratio). Furthermore, as shown in Table 1, in χ^2 comparisons, the mutation was not associated with vascular events (χ^2 = 4.698, P = 0.095 for angina pectoris; χ^2 = 1.100, P = 0.577 for myocardial infarction; χ^2 = 0.181, P = 0.913 for stroke; χ^2 = 1.414, P = 0.493 for peripheral vascular disease; χ^2 = 2.372, P = 0.305 for microalbuminuria; χ^2 = 1.434, P = 0.488 for neuropathy; and χ^2 = 4.260, P = 0.119 for retinopathy). In a logistic regression analysis, in which vascular events were entered as dependent variables and age, sex, BMI, current smoking status, systolic and diastolic BPs, total cholesterol, triglycerides, HDL cholesterol, HbA_{1c}, and UAI were entered as independent variables, the ecNOS TT and TG genotypes were still not predictive of the occurrence of vascular events.

In conclusion, we identified a 27.8% allele frequency of the Glu^{298}→Asp mutation at exon 7 of the ecNOS gene in type 2 diabetic patients, but in these patients the mutation was not associated with macro- or microvascular complications or with any of the traditional atherogenic risk factors.

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References
1. Tikkanen I, Fyhrquist F: Nitric oxide in hypertension and renal diseases. *Ann Med* 27:353–357, 1995
2. Gryglewski RJ, Chlopicki S, Swies J, Niezabitowski P: Prostacyclin, nitric oxide, and atherosclerosis. *Ann N Y Acad Sci* 758:194–206, 1995
3. Williams SB, Cusco JA, Roddy MA, Johnstone MT, Creager MA: Impaired nitric oxide mediated vasodilatation in patients with non-insulin dependent diabetes mellitus. *J Am Coll Cardiol* 27:567–574, 1996
4. Cooke JP, Dzau VJ: Nitric oxide synthase: role in the genesis of vascular disease. *Ann*

*Rev Med*48:489–509, 1997
5. Marsden PA, Heng HHQ, Scherer SW, Stewart RJ, Hall AV, Shi XM, Tsui LC, Schappert KT: Structure and chromosomal localization of the human constitutive endothelial nitric oxide synthase gene. *J Biol Chem*268:17478–17488, 1993
6. Hingorani AD, Liang CF, Fatibene J, Parsons A, Hopper RV, Trutwein D, Stephens NG, O'Shaughnessy KM, Brown MJ: A common variant of the endothelial nitric oxide synthase gene is a risk factor for coronary atherosclerosis in the East Anglian Region of the UK (Abstract). *Circulation*96 (Suppl. 8):545, 1997

Influence of a Physical Training Program on Psychological Well-Being in Elderly Type 2 Diabetes Patients

Psychological well-being, physical training, and type 2 diabetes

Physical activity is positively associated with mental health and psychological well-being, but so far only a few studies have investigated the association between physical activity and psychological factors in patients with diabetes (1,2). In a cross-sectional study in this group of patients, of whom the majority had type 2 diabetes, the level of physical activity turned out to be the only significant self-management behavior to predict quality of life (2). We were interested in the effects of a physical training program on psychological well-being in these patients. The present study was part of a prospective randomized trial to evaluate the effects of physical training on glycemic control and lipid profile in elderly obese type 2 diabetes patients (3). We hypothesized first that aerobic physical training results in an improved psychological well-being and second, that an improved psychological well-being is mediated by changes in the maximal aerobic capacity ($V_{O_{2max}}$).

There were 92 patients with type 2 diabetes who applied for the study. Of these, 58 enrolled and were randomized to either a physical training group (TG) (n = 30; aged 64.2 ± 5.4 years [mean ± SD]) or a control group (CG) (n = 28; aged 61.8 ± 5.4 years). There were 51 patients who completed the study. The training program consisted of an intensive supervised 6-week physical training period in which the patients exercised three times a week for 1 h, aiming at 60–80% of their $V_{O_{2max}}$. This period was followed by a 6-week guided home training period. The control group followed a diabetes education program during that time. In the 14-week follow-up phase, patients in the training group were advised to continue their home training, but without supervision. Psychological well-being was assessed by means of the 22-item self-administrated well-being questionnaire of Bradley and Lewis (4), which was completed at baseline, after 6 weeks of training, and at the end of the study. Items referring to physical symptoms possibly related to diabetes were excluded to obtain a pure estimate of the psychological domain of well-being. The scores of the questionnaire were determined by four subscales: depression, anxiety, energy, and positive well-being. A repeated measures analysis of variance with polynomial contrasts was used to determine differences in well-being. To test for $V_{O_{2max}}$ as a mediator variable, regression analyses were performed according to Baron and Kenny (5).

At baseline, no differences between TG and CG were found with respect to age, BMI, duration of disease, sex, physical activity status, smoking habits, HbA_{1c}, $V_{O_{2max}}$, the total psychological well-being score, or the four subscales. After 6 weeks of training, a significant improvement was found in TG for total psychological well-being (baseline: 49.2 ± 11.2 [TG], 45.3 ± 14.4 [CG]; after 6 weeks: 54.8 ± 7.6 [TG], 46.9 ± 14.2 [CG]; F = 5.46, P = 0.023), anxiety (baseline: 5.0 ± 4.1 [TG], 5.3 ± 4.0 [CG]; after 6 weeks: 2.8 ± 3.2 [TG], 5.3 ± 4.3 [CG]; F = 7.80, P = 0.007), positive well-being (baseline: 13.9 ± 4.3 [TG], 11.5 ± 5.1 [CG]; after 6 weeks: 14.4 ± 3.1 [TG], 12.2 ± 4.7 [CG]; F = 6.37, P = 0.014), and energy (baseline: 8.0 ± 2.4 [TG], 7.9 ± 3.5 [CG]; after 6 weeks: 9.4 ± 2.1 [TG], 8.0 ± 3.0 [CG]; F = 4.88, P = 0.031). For depression, no significant difference was found. After 6 weeks of training, a significant difference in $V_{O_{2max}}$ levels emerged between TG and CG ($P < 0.01$) and remained significant until the end of the study, although the scores of TG decreased (TG: 21.0 [prestudy], 22.0 [after 6 weeks], and 21.0 ml · kg^{-1} · min^{-1} [after 26 weeks]; CG: 20.8 [prestudy], 19.6 [after 6 weeks], and 18.2 ml · kg^{-1} · min^{-1} [after 26 weeks]). The $V_{O_{2max}}$ difference score was used in the analysis as a mediator variable for total psychological well-being, but no mediation could be observed.

It is important to note that after the supervised period of 6 weeks, well-being scores returned to baseline levels. It is possible that changes in compliance with the training program caused the declining scores of $V_{O_{2max}}$ and well-being at the follow-up measurements. Several factors can influence compliance with training programs, e.g., group participation, spouse support, and periodic testing. It is imaginable that the decreased support and attention for the training group during the unsupervised period caused the declining well-being scores. Another explanation may be that physical training benefits the physiological response to stress (6). The initial improvements in aerobic capacity coupled with the psychological well-being scores and the subsequent return to baseline values of both parameters seems to support this view. However, no statistical proof of direct influence of $V_{O_{2max}}$ on improvement of quality of life could be obtained. Finally, a cognitive explanation for the stress-reducing effects of physical training can be given (7). Training may affect feelings of self-esteem, as a result of the mastering and the increased performance of challenging physical activities, and subsequently improve well-being. When the initially positive excitement and actual performance decline, the positive psychological effects may subside as well. Based on the results of the present study, it seems that feelings of well-being, presumably related to self-efficacy or self-esteem, are only positively affected by a training program when the participant's actual performance of the training activities is continued.

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References
1. Kaplan RM, Hartwell SL, Wilson DK, Wallace JP: Effects of diet and exercise interventions on control and quality of life in non-insulin-dependent diabetes mellitus. *J Gen Int Med*2:220–227, 1987
2. Glasgow RE, Ruggiero L, Eakin EG, Dryfoos J, Chobanian L: Quality of life and associated characteristics in a large national sample of adults with diabetes. *Diabetes Care*20:562–567, 1997
3. Ligtenberg PC, Hoekstra JBL, Zonderland ML, Bol E, Erkelens DW: Effects of physical training on metabolic control in elderly type 2 diabetes mellitus patients. *Clin Sci* 93:127–135, 1997
4. Bradley C, Lewis KS: Measures of psychological well-being and treatment satisfaction developed from the response of people with tablet-treated diabetes. *Diabet Med*7:445–451, 1990
5. Baron RM, Kenny DA: The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psych*51:1173–1182, 1986
6. Blumenthal JA, Emery CF, Walsh MA, Cox DR, Kuhn CM, Williams RB, Williams RS: Exercise training in healthy type A middle-aged men: effects on behavioral and cardiovascular responses. *Psychosom Med* 50:418–433, 1988
7. Long BC: A cognitive perspective on the stress-reducing effects of physical exercise. In *Exercise Psychology: The Influence of Physical Exercise on Psychological Processes* Seraganian P, Ed. New York, Wiley, 1993

Fatal Asymptomatic Hypoglycemia in an Elderly Insulin-Dependent Diabetic Patient Taking an Oral Beta-Blocking Medication

The largest study of the risk of serious insulin- or oral hypoglycemic–related hypoglycemia involving all classes of antihypertensives recently reported that the lowest rate of hypoglycemia over a 4-year study period in 13,559 elderly Medicaid recipients was with beta blockers. The highest rate of serious hypoglycemia was found to be with ACE inhibitors used with antidiabetic agents (1). A 1966–1998 Medline search using the terms beta blockers, insulin, and hypoglycemia produced one case report of topical timolol-associated hypoglycemic attacks in a 65-year-old insulin-dependent diabetic patient (2).

J.P. was a 68-year-old, 5-foot 4-inch, 192-lb, African-American, insulin-dependent diabetic patient who also had high blood pressure, presumed type 1 diabetes, and angina pectoris. Her diet order was 1,600 kcal (American Diabetes Association [ADA]), but her family insisted on bringing in extra food despite numerous warnings about this practice. She had gained 26 lb in the 6 months since her admission to the nursing facility. Her medications were as follows: NPH insulin 42 U subcutaneously every morning at 7:00 A.M., sublingual nitroglycerin 0.4 mg as needed (not used), and propranolol 20 mg q.i.d.. Her fasting blood sugar (FBS) had ranged between 5.7 and 6.8 mmol/l (102–122 mg/dl) weekly for the past month. Her insulin dose had been increased from 20 U on admission to 42 U over the 6-month period in response to monthly FBS readings >8.9 mmol/l (160 mg/dl). When the family went on vacation and the extra food supply was unavailable, on the 3rd day of reduced caloric intake, the patient did not care for the food of the day and was found at 4:00 P.M. semicomatose, with blood pressure (BP) = 158/88, *P* = 76, *R* = 26. Her prior weekly vital signs had ranged from BPs of 110–126/60–72 mmHg, pulses of 56–64 beats/min, and respiration rates of 12–20 breaths/min. She died by 5:00 P.M., with a fingerstick blood sugar of <1.4 mmol/l (25 mg/dl). The patient's nursing aides and roommate denied that she had any of the classic symptoms of hypoglycemia (tachycardia, sweating, excitation, nervousness, or tremors) over the prior week or on the day of her death. The nurses' daily notes for the week before death had no mention of any of these symptoms.

A 1980 study of the safety of beta-blocker usage in insulin-treated diabetic patients found, using the surrogate hypoglycemic measure of unconsciousness, that 50 insulin-treated diabetic patients using beta blockers had the same frequency of episodes (5 vs. 10) as 100 insulin-using diabetic patients matched for age, sex, and duration of diabetes who did not use beta blockers over an 8-month period (3). The latest study previously mentioned found that cardioselective beta blockers had the lowest frequency of serious hypoglycemia (<2.8 mmol/l [50 mg/dl]) in older individuals using insulin or sulfonylureas when compared with the nonselective beta blockers, thiazide diuretics, calcium channel blockers, or ACE inhibitors (1). Intensive treatment of type 1 and type 2 diabetes appears to lower the rates of renal impairment, cardiac and overall morbidity, and mortality (4–6). Insulin usage per se does, however, produce higher rates of hypoglycemia and weight gain when compared with oral hypoglycemic agents in an outpatient setting over 6 years (6) and in the nursing home over a 3-year period (7). Intensive insulin therapy for type 1 diabetes also has been found both to increase blood pressure and to adversely affect lipid profiles proportional to weight gain (8).

This patient appeared to have multiple factors that led to her weight gain: insulin use and excessive outside dietary intake. Her complete diabetes history was not obtainable. The family did state that she had tried the "sugar pill," but that she would not take the pill nor adhere to her diet. Her attending physician on admission to the nursing facility was from a different provider than her community-based physician. The nursing facility physician's therapeutic goal was tight control of blood sugar, which he defined as <6.9 mmol/l (125 mg/dl). Beta-blocker therapy for both high blood pressure and angina pectoris was preferred, because of her history of angina pectoris, for presumed secondary prevention of myocardial infarction, since the patient had complained of several episodes of severe chest pain. No electrocardiographic readings were available on this patient.

The extent to which the nonselective beta blocker propranolol masked the hypoglycemic symptoms that may have been more likely with her tight blood sugar control (i.e., <6.9 mmol/l [125 mg/dl]) is suggested by the negative findings on questioning of health care personnel involved in the care of the patient as well as by the clinical record. The patient and her roommate were both well oriented to time, place, and person and did not have clinical evidence of dementia. The roommate was very concerned with the patient's overall care and was known to have summoned help for her roommate if she suspected any problem. The patient was not known to take naps during the daytime hours. It was this roommate who noticed the patient's unusual drowsiness and sedation and reported this to the charge nurse at 4:00 P.M. on the day of death.

The ADA has recently revised its guidelines to include the category of "impaired glucose tolerance" (FPG 6.1–6.9 mmol/l [110–125 mg/dl]) and has lowered the threshold for clinical diabetes from 7.8 to 6.9 mmol/l (140 to 126 mg/dl) (9). The implications of these new guidelines, as well as recent findings on tight control of diabetes (4–6) and the recommendations that beta-blockers be used in diabetic patients at risk of myocardial infarction for secondary prevention (10), raise the concern that there may be more cases like the one reported.

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References

1. Shorr RI, Ray WA, Daugherty JR, Grifffin MR: Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas. *JAMA* 278:40–43, 1997
2. Silverstone BZ, Marcus T: Hypoglycemia due to opthalmic timolol in a diabetic. *Harefuah* 118:693–694, 1990
3. Barnett AH, Leslie D, Watkins PJ: Can insulin-treated diabetics be given beta-adrenergic blocking drugs? *Br Med J* 280:976–978, 1980
4. Andersson DK, Svardsudd K: Long-term glycemic control relates to mortality in type II diabetes. *Diabetes Care* 18:1534–1543, 1995
5. Hellman R, Regan J, Rosen H: Effect of intensive treatment of diabetes on the risk of death or renal failure in NIDDM and IDDM. *Diabetes Care* 20:258–264, 1997
6. United Kingdom Prospective Diabetes Study Group: United Kingdom prospective diabetes study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. *Ann Intern Med* 128:165–175, 1998
7. Cooper JW, Gordon JE, Parish RC: Diabetes mellitus prevalence and treatment outcomes in a geriatric nursing home population. *J Geriatr Drug Ther* 5:73–82, 1990
8. Purnell JQ, Hokanson JE, Marcovina SM, Steffes MN, Cleary PA, Brunzell JD: Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure. *JAMA* 280:140–146, 1998
9. 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
10. MacDonald TM, Butler R, Newton RW, Morris AD: Which drugs benefit diabetic patients for secondary prevention of myocardial infarction? DART/MEMO Collaboration. *Diabet Med* 15:282–289, 1998

Glycosylated Hemoglobin Levels and New Diagnostic Criteria

The recent American Diabetes Association (ADA) expert committee report (1) has revised the diagnostic criteria for diabetes by lowering the fasting plasma glucose (FPG) level from 140 mg/dl (7.77 mmol/l) to 126 mg/dl (7.0 mmol/l). The ADA report has also introduced a new statistical risk group called "impaired fasting glucose" (IFG), which is based on an FPG value of 110–125 mg/dl. There are no data on HbA_{1c} levels in relation to the new diagnostic criteria.

The present study is based on an analysis of 2,635 oral glucose tolerance tests (OGTTs) and HbA_{1c} measurements done during a 3-year period from 1 April 1994 to 31 March 1997. All OGTTs were done using a 75-g oral glucose load, with World Health Organization study group recommendations (2). Pregnant women were not included in the analysis. Fasting and half-hourly venous plasma (EDTA) samples up to 2 h were used for glucose estimations, which were done within 15 min of sample collection by the glucose oxidase method, using kits provided by Boehringer Mannheim (Mannheim, Germany) on a Ciba Corning Express Plus Auto Analyzer (Medfield, MA). Quality control was done on a daily basis, and the coefficient of variation for glucose was <3.0%. HbA_{1c} was measured using a dedicated high-performance liquid chromatography system (Variant; BioRad, Hercules, CA). Our center is certified by the unity quality control program of BioRad for precision in HbA_{1c} estimation.

The new categories of glucose intolerance were based on the FPG of the individuals (1). Impaired glucose tolerance (IGT) was diagnosed based on the 2-h plasma glucose (2). Nondiabetic healthy control subjects were selected from an ongoing epidemiology study.

Table 1 presents the HbA_{1c} levels for the different categories of glucose intolerance. HbA_{1c} levels of the IFG and IGT patients were significantly different from those of control subjects and type 2 diabetic patients. The HbA_{1c} levels and the 2-h plasma glucose levels of the subjects with IFG were significantly higher than those of the subjects with IGT ($P < 0.001$).

To our knowledge, there are no data available on the HbA_{1c} levels in different categories of glucose intolerance. We report that the levels of HbA_{1c} are higher in the statistical risk classes of diabetes, namely IGT and IFG, compared with those in healthy control subjects. This suggests that even at this stage of prediabetes, hemoglobin undergoes glycosylation, though it is below the value seen in subjects with type 2 diabetes (3). Our data also suggest that in those patients with IFG, the HbA_{1c} levels and 2-h plasma glucose values are higher than in those with IGT. These data could have significance for future epidemiological studies on diabetes.

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Table 1—*HbA_{1c} levels in patients from different categories of glucose intolerance*

	Control subjects	IFG patients	IGT patients	Type 2 diabetic patients
n	303	419	509	1,053
FPG (mg/dl)*	70 ± 12	117 ± 5	105 ± 14	142 ± 27
HbA_{1c} (%)*	5.3 ± 0.49	6.8 ± 0.9	6.3 ± 0.8	7.8 ± 1.4
2-h plasma glucose (mg/dl)*	94 ± 42	199 ± 58	168 ± 17	277 ± 59

*Groups are significantly different from each other ($P < 0.001$).

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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* 20:1183–1198, 1997
2. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group* Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
3. Peters AL, Davidson MB, Schriger DL, Hasselblad V: A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels. *JAMA* 16:1246–1252, 1996

COMMENTS AND RESPONSES

Response to Allen et al. and Holl et al.

I read with interest the recent article by Allen et al. and the letter by Holl et al. regarding the diagnosis of cystic fibrosis–related diabetes (CFRD) (1,2). CFRD has become increasingly common as cystic fibrosis (CF) patients survive longer. CFRD has distinctive clinical and pathological features compared with type 1 and type 2 diabetes (3), and this condition should be considered as a separate clinical entity. Allen et al. found that random blood glucose (RBG) was the most common method used in the diagnosis of CFRD in the centers studied. It is important to note that RBG has not been found to be sufficiently sensitive or specific in the diagnosis of CFRD. My colleagues and I had previously reported that even in CF patients with normal glucose tolerance, as defined by an oral glucose tolerance test (OGTT), the RBG can exceed 180 mg/dl, provided that a large enough glucose load is taken before blood sampling (4). This finding may be related to a more rapid gut absorption of glucose in patients with CF. Lanng et al. had also reported that whereas OGTT is the "gold standard" diagnostic method in the diagnosis of CFRD, fasting blood glucose and glycosylated hemoglobin are not sufficiently sensitive in the diagnosis of CFRD (5).

Between August 1996 and May 1997, 91 clinically stable adult CF patients (aged ≥16 years) who were not known to be diabetic and who were attending the adult CF clinic at the Royal Brompton Hospital in London (a national CF center) underwent OGTTs according to the standard protocol (6). All patients had RBG measured within 1 month before their OGTTs. The mean age of the studied patients was 27 years (range, 16–60), and the ratio of male to female subjects was 58:33. Of the 91 patients studied, 12 were found to have OGTT-defined diabetes; of these 12 patients, 3 had abnormal fasting blood glucose (>110 mg/dl) and 4 had abnormal RBG (>180 mg/dl). Thus, the sensitivities of the above-mentioned two methods in the diagnosis of CFRD (using OGTT as the "gold standard") were found to be only 25% (95% CI, 1–50) and 33% (7–60), respectively. These data confirm the point made by Holl et al. that OGTTs should be used in preference to other methods in the diagnosis of CFRD. Because there is evidence that the development of CFRD may be associated with a deterioration in patients' clinical status that may be reversed by prompt treatment (7), CF patients should be screened for diabetes regularly using OGTTs.

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References

1. Allen HF, Gay EC, Klingensmith GJ, Hamman RF: Identification and treatment of cystic fibrosis–related diabetes. *Diabetes Care* 21:943–948, 1998
2. Holl RW, Buck C, Cario H, Wolf A, Thon A, Kohne E, Debatin K: Diagnosis of diabetes in cystic fibrosis and thalassemia major (Letter). *Diabetes Care* 21:671–672, 1998
3. Dodge JA, Morrison G: Diabetes mellitus in cystic fibrosis: a review. *J R Soc Med* 85 (Suppl. 19):25–28, 1992
4. Yung B, Kemp M, Hooper J, Hodson M: Random blood glucose alone in the diagnosis of cystic fibrosis–related diabetes (Letter). *Lancet* 349:619, 1997
5. Lanng S, Hansen A, Thorsteinsson B, Nerup J, Koch C: Glucose tolerance in patients with cystic fibrosis: five year prospective study. *BMJ* 311:655–659, 1995
6. World Health Organization: Diabetes Mellitus: Report of a WHO Study Group. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
7. Lanng S, Thorsteinsson B, Nerup J, Koch C: Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. *Acta Pediatr* 83:849–853, 1994

Response to Yung

Should the oral glucose tolerance test be performed as a routine screening test for diabetes in cystic fibrosis patients?

Dr. Yung makes several valid and important points regarding screening for cystic fibrosis–related diabetes (CFRD). The purpose of our study surveying physicians' attitudes and practices for patients with CFRD was not to imply that these attitudes or practices are correct or well informed, but simply to report that this is what the U.S. physicians surveyed are doing. Dr. Yung's observation that random blood glucose (RBG) correlates poorly with glucose tolerance testing in adult British cystic fibrosis (CF) patients is important because there is no literature on the sensitivity or specificity of RBG or urine glucose measurements. Poor correlations between fasting blood glucose or HbA_{1c} and the oral glucose tolerance test (OGTT) have been described by several investigators (1–5), but not by all (6,7). Lanng et al. (3) found in a prospective study that only 16% of CF patients had abnormal elevations of HbA_{1c} on the day of a diabetic glucose response to the OGTT.

If CFRD is defined as diabetic glucose response to OGTT, then by definition the OGTT is 100% sensitive and specific for the diagnosis of CFRD. Defining diabetes in the general population has proved to be a challenge, and recently an Expert Committee on the Diagnosis and Classification has revised blood glucose criteria and de-emphasized the OGTT (8). It is not known whether these criteria are appropriate for the CF population. A factor that is important in determining a meaningful definition of diabetes in any population is whether identification of the disease allows for an intervention that improves outcome. Although some investigators describe a deterioration in clinical status that occurs

before the development of overt diabetes (9) (presumably during a period of decreasing glucose tolerance), others have not found such an association between clinical status and deteriorating glucose tolerance (1,10). One can speculate on the number of ways in which insulinopenia, before causing overt symptoms of hyperglycemia, might be detrimental to CF patients (increased protein catabolism, intermittent glucosuria, altered immune function). Yet, to date, there is no reported evidence that treatment of asymptomatic CF patients with normal fasting glucose levels and a diabetic response to OGTT improves clinical status or delays the onset of overt diabetes.

In February 1998, a Cystic Fibrosis Foundation consensus conference recommended screening with random glucose levels, with follow-up of abnormal random glucose levels (≥126 mg/dl) by fasting glucose level. A confirmed elevated fasting glucose level (≥126 mg/dl) is diagnostic for CFRD. The OGTT is reserved for patients participating in research or for those in high-risk circumstances (unexplained polyuria or polydipsia, failure to gain or maintain weight, delayed puberty, or unexplained chronic decline in pulmonary function).

Our study revealed that screening for glucose abnormalities in CF patients is erratic and is performed using a variety of methods, but that only a handful of CF practices in the U.S. are performing OGTTs. It is hoped that this discussion, in conjunction with the new consensus conference guidelines, will raise the level of consciousness about disorders of carbohydrate metabolism in CF patients and standardize our approach to these problems. Before recommending that all adult CF patients have annual OGTTs, we must have solid evidence that a worthwhile intervention is available to those who have abnormal results.

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References

1. DeSchepper J, Dab I, Derde MP, Loeb H: Oral glucose tolerance testing in cystic fibrosis: correlations with clinical parameters and glycosylated haemoglobin determinations. *Eur J Pediatr* 150:403–406, 1991
2. Hinds A, Sheehan A, Machinda H, Parsons H: Postprandial hyperglycemia and pancreatic function in cystic fibrosis patients. *Diabetes Res* 18:69–78, 1991
3. Lanng S, Hansen A, Thorsteinsson B, Nerup J, Koch C: Glucose tolerance in patients with cystic fibrosis: five year prospective study. *BMJ* 311:655–659, 1995
4. Moran A, Doherty L, Wang X, Thomas W: Abnormal glucose metabolism in cystic fibrosis. *J Pediatr* 133:10–17, 1998
5. De Luca F, Arrigo T, Conti Nibali S, Sferlazzas C, Gigante A, Di Cesare E, Cucinotta D: Insulin secretion, glycosylated haemoglobin and islet cell antibodies in cystic fibrosis children and adolescents with different degrees of glucose tolerance. *Horm Metab Res* 23:495–498, 1991
6. Austin A, Kalhan SC, Orenstein D, Nixon P, Arslanian S: Roles of insulin resistance and beta-cell dysfunction in the pathogenesis of glucose intolerance in cystic fibrosis. *J Clin Endocrinol Metab* 79:80–85, 1994
7. Stutchfield P, O'Halloran S, Teale J, Isherwood D, Smith C, Heaf D: Glycosylated haemoglobin and glucose intolerance in cystic fibrosis. *Arch Dis Child* 62:805–810, 1987
8. 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
9. Lanng S, Thorsteinsson B, Nerup J, Koch C: Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. *Acta Pediatrica* 83:849–853, 1994
10. Cucinotta D, Arrigo T, De Luca F, Di Benedetto A, Lombardo F, Scoglio R, Sferlazzas C, Magazzu G: Metabolic and clinical events preceding diabetes mellitus onset in cystic fibrosis. *Eur J Endocrinol* 134:731–736, 1996

Glycemic Control in Type 1 Diabetes

A cross-sectional study in 1,200 Belgian patients

We read with interest the recent article by Rosilio et al. (1) reporting an HbA_{1c} value of 8.97 ± 1.98% (mean ± SD) in a French population of 2,579 patients with type 1 diabetes aged 1–19 years. Approximately 33% of their cohort had HbA_{1c} <8%, whereas 14.5% had values >11%. Rosilio et al. conclude that these overall results are unsatisfactory, since they will expose a majority of these young patients to developing microangiopathic complications.

We analyzed, in a cross-sectional survey, the clinical characteristics of a cohort of 1,200 insulin-treated Belgian patients attending our University Diabetes Center, consisting mostly (>80%) of subjects with type 1 diabetes (2,3). As in the study of Rosilio et al., the Belgian Health Service offers near total coverage of diabetes care. Patients were followed on an outpatient basis (1–4 visits/year). None had participated in interventional trials aimed at improved glucose control. Their mean age was 43 ± 19 years, with 9% of the subjects being <18 years old. Respectively 51, 22, and 23% of patients were treated with two (2ii), three (3ii), or four (4ii) daily insulin injections; continuous subcutaneous insulin infusion (CSII) was used in 4%.

In this mostly adult population, we observed a level of glycemic control, as assessed by HbA_{1c}, similar to that reported by Rosilio et al. in their pediatric cohort. Thus, HbA_{1c} was 8.63 ± 1.55% (8.54 ± 1.46% in male subjects and 8.72 ± 1.62% in female subjects). It is remarkable that this overall value of HbA_{1c} was identical to that recorded in France in the subgroup of patients followed by Rosilio et al. in university-affiliated hospitals. We found that 36 (2ii), 31 (3ii), 38 (2ii), and 21% (CSII group) had an HbA_{1c} <8%, a proportion comparable to that reported by these authors (33%). As far as home blood glucose monitoring was concerned, the mean strip consumption in our Belgian cohort was 2.2 per subject per day (vs. 2.8 in the French study). We observed no correlation between daily insulin injection number or strip consumption and HbA_{1c} levels.

In conclusion, in a mainly adult Belgian population with type 1 diabetes and free access to diabetes care, overall glycemic control, assessed by HbA_{1c} was comparable to that measured in a mostly pediatric French population.

Global HbA_{1c} levels in both studies were above the threshold suggested by the Diabetes Control and Complications Trial (DCCT) results and those of other studies (4,5), since only a third of patients in the Belgian and French cohorts could attain HbA_{1c} values <8% (i.e., below the realistic threshold beyond which there is a rapid increase in the likelihood of developing microangiopathy). Thus, both surveys

demonstrate that the degree of glycemic control in these two populations remains insufficient throughout the age span, even for those patients routinely followed in university centers. Optimizing treatment modalities, deliveries, and education to achieve levels of glycemic control comparable to those obtained during the DCCT or in similar, intervention-modified, environments, requires more medical and paramedical resources, thus producing a significant long-term demand for human and financial support.

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References

1. Rosilio M, Cotton J-B, Wieliczko M-C, Gendrault B, Carel J-C, Couvaras O, Ser N, Gillet P, Soskin S, Garandeau P, Stuckens C, Le luyer B, Jos J, Bony-Trifunovic H, Bertrand A-M, Leturcq F, Lafuma A, the French Pediatric Diabetes Group, Bougnères P-F: Factors associated with glycemic control: a cross-sectional nationwide study in 2,579 French children with type 1 diabetes. *Diabetes Care* 21:1146–1153, 1998
2. Hermans MP, Maes M, Vandeleene B, Pirard F, Buysschaert M: The Belgian Health Service HBGM scheme: cost-effectiveness in a cross-sectional survey of an insulin-treated population registry (Abstract). In *Proceedings of the 10th International Congress of Endocrinology, San Francisco, CA, 1996*p. 335
3. Buysschaert M, Maes M, Hermans MP: Traitement et contrôle glycémique de 1200 diabétiques inscrits dans la Convention INAMI "diabète" (in French). *Acta Clin Belg*57:211–218, 1997
4. The Diabetes Control and Complications Trial Research Group: The effects of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
5. Krolewski A, Laffel L, Krolewski M, Quinn M, Warram J: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. *N Engl J Med*332:1251–1255, 1995

Response to Paris et al.

Pediatricians and diabetologists

Should it be methodologically correct to compare French and Belgian patients and doctors? We thank Dr. Paris and colleagues (1) for reassuring us collectively, as pediatricians taking care of young patients with diabetes. As a young resident in endocrinology 20 years ago, I was trained in the intangible idea that the results of adult diabetologists' efforts were indisputably more efficacious in terms of glycemic control than those of pediatricians. Was it true in those times? Remember that in many countries, including France, pediatricians were advocating free diet (freedom meaning a lot of sugar) and one insulin shot daily and discouraging the use of capillary blood in favor of the good old urinary measurements.

Those times are gone, fortunately for our patients, and we can now enjoy shameless comparisons of results with our colleagues. As an echo to Dr. Paris's letter, let us regret that besides well-known intervention studies of intensive therapy in highly selected centers and patients, there are too few reports of actual glycemic results in large cohorts (mostly adult) of patients with type 1 diabetes.

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References

1. Paris I, Hermans M, Buysschaert M: Glycemic control in type 1 diabetes: a cross-sectional study in 1,200 Belgian patients (Letter). *Diabetes Care* 21:2200–2201, 1998

LDL Cholesterol and Troglitazone Therapy

The recent study by Tack et al. (1) reported larger average LDL size in individuals on troglitazone therapy and appears to suggest that the increases in LDL cholesterol concentration typically observed with this agent (2,3) are not ultimately harmful to patients with type 2 diabetes because they are offset by potentially beneficial changes in lipoprotein composition and susceptibility to oxidation. This conclusion must be interpreted with caution for several reasons.

First, although several observational studies have shown an association between small, dense LDL and coronary heart disease (CHD) in patients with diabetes (4,5), the effects of changing LDL size have never been directly evaluated in any patient population. In contrast, increases in LDL cholesterol concentrations have been shown to be a strong and consistent risk factor for coronary artery disease in both cross-sectional and longitudinal analyses of individuals with or without diabetes. Furthermore, lowering LDL cholesterol concentration has been proven to decrease the incidence of cardiovascular events in several interventional studies (6,7).

Neither the American Diabetes Association nor the National Cholesterol Education Program has treatment recommendations suggesting that increases in LDL concentration are ameliorated by changes in LDL size. Thus, increases in LDL size should not be construed to negate the known risk of increases in total LDL cholesterol concentrations.

Second, the data from Tack et al. (1) showed decreased susceptibility to oxidation in the LDL after troglitazone therapy. This is consistent with the change in size because small, dense LDL are known to be more susceptible to oxidation in vitro (8). Although there are a large number of in vitro studies pointing to the importance of LDL oxidation in the atherosclerotic process, there are no clinical trials showing that changes in LDL oxidation can alter CHD risk. Manipulations that decrease oxidization ability might be of potential benefit; until clinical trial data are available, however, such manipulations associated with increasing LDL cholesterol concentrations cannot be assumed to be beneficial.

Finally, the study reported by Tack et al. (1) was not conducted in patients with diabetes. Individuals with diabetes are known to have increases in several CHD risk factors and to be at significantly increased risk for cardiovascular disease (CVD). Thus, any therapeutic regimen that results in increased LDL cholesterol concentrations in patients with diabetes must be viewed as increasing the risk of atherosclerosis in affected indi-

viduals, even if LDL size is larger or in vitro susceptibility to oxidation is diminished. Statements to the contrary should be established by clinical trials before their acceptance for the care of patients with diabetes.

Improvement in insulin sensitivity in type 2 diabetes would be expected to improve the dyslipidemia associated with this syndrome. The relative role of this dyslipidemia versus LDL cholesterol concentrations in the etiology of CVD in diabetic individuals remains an unanswered question. Interventions aimed at investigating this issue are needed.

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References

1. Tack CJJ, Smits P, Demacker PNM, Stalenhoef AFH: Troglitazone decreases the proportion of small, dense LDL and increases the resistance of LDL to oxidation in obese subjects. *Diabetes Care* 21:796–799, 1998
2. *Rezulin (Troglitazone) Prescribing Information*. Parke-Davis, 1998
3. Schwartz S, Raskin P, Fonseca V, Graveline JF: Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. *N Engl J Med* 338:861–866, 1998
4. Griffin BA, Freeman DJ, Tait GW, Thomson J, Caslake MJ, Packard CJ, Shepherd J: Role of plasma triglyceride in the regulation of plasma low density lipoprotein (LDL) subfractions: relative contribution of small dense LDL to coronary heart risk. *Atherosclerosis* 106:241–253, 1994
5. Stewart MW, Laker MF, Dyer RG, Game F, Mitchenson J, Winocour PH, Alberti KGMM: Lipoprotein compositional abnormalities and insulin resistance in type 2 diabetic patients with mild hyperlipidaemia. *Arterioscler Thromb* 13:1046–1052, 1993
6. Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G, The Scandinavian Simvastatin Survival Study (4S) Group: Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 20:614–620, 1997
7. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, West of Scotland Coronary Prevention Study Group: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 333:1301–1307, 1995
8. deGraff J, Hak-Lemmers HLM, Hectors MPC, Demaker PCM, Hendriks JCM, Stalenhoef AFH: Enhanced susceptibility to in vitro oxidation of the dense low density lipoprotein subfraction in healthy subjects. *Atheroscler Thromb* 11:298–306, 1991

Response to Howard and Howard

Drs. Howard and Howard (1) express caution about the suggestion that the risk of an increase in LDL cholesterol, as observed during troglitazone treatment, may be offset by beneficial changes in LDL composition and LDL susceptibility to oxidation. Although we largely agree with the points they raise, we would like to add the following comments.

There is indeed firm evidence that the absolute plasma concentration of LDL cholesterol is the major determinant of cardiovascular morbidity and mortality in nondiabetic, as well as diabetic, populations and that lowering LDL cholesterol concentration is of clinical benefit. Regarding the susceptibility of LDL for in vitro oxidation, this evidence is less strong. A number of observations suggest that lipid peroxidation does occur in humans (2). Epitopes of oxidized LDL and autoantibodies against these epitopes can be detected in human plasma. Patients with coronary heart disease show an increased susceptibility of LDL to oxidation (3). Cross-sectional studies have reported an association between higher dietary antioxidant levels and reduced risk of CVD (4). However, only a few studies have reported on the relation between oxidation parameters and coronary heart disease, and there is only one randomized intervention trial suggesting a beneficial effect of vitamin E treatment on nonfatal myocardial infarction but not on total mortality (5). We found, in an animal model for familial hypercholesterolemia (Watanabe rabbit), that improving LDL susceptibility to oxidation by administration of vitamin E, without changing the absolute level of LDL cholesterol, had no effect on the progression of the atherosclerotic process (6). Thus, whether enhancing susceptibility of LDL to oxidation is of any clinical benefit is not (yet) supported by clinical evidence.

Regarding particle size and cardiovascular disease, the situation is complex. Small, dense LDL is part of the atherogenic lipoprotein phenotype, which is characterized by raised plasma triglycerides and low HDL cholesterol in addition to the presence of small, dense LDL particles. This so-called "pattern B" confers increased risk for coronary heart disease (7). Prospective studies have shown that the small, dense LDL particle predicts the risk of ischemic heart disease, an effect that may be partly independent of plasma lipoprotein concentrations (8). Studies showing a beneficial clinical effect of changes in particle size are currently lacking. Treatment with fibrates may shift the LDL particles to a subpopulation of intermediate density and larger size (9); treatment with gemfibrozil has a proven beneficial effect on cardiovascular mortality (10). Changes in LDL composition are difficult to dissect from changes in HDL and triglyceride metabolism. Therefore, it cannot be determined whether changing LDL composition alone (if at all possible) would change cardiovascular risk. The effects of troglitazone on lipids in larger trials show a small increase in HDL cholesterol and/or a decrease in triglyceride concentration (11,12). In our sample of 15 subjects, HDL cholesterol did not change during troglitazone; triglycerides tended to decrease, albeit not significantly.

The fact that our studies were performed in obese subjects is of methodological advantage; a short-term study like this, however, is not able to answer study questions regarding atherosclerosis-related cardiovascular events, no matter whether it is performed in obese or in diabetic subjects.

In summary, we agree that with currently available scientific evidence, the risk of the troglitazone-induced increase in LDL concentration is not necessarily offset by a more favorable LDL composition profile or an enhanced susceptibility of LDL to in vitro oxidation. However, evidence that LDL composition may be clinically relevant is emerging. Awaiting the results of formal clinical trials studying the effect of troglitazone on cardiovascular disease, clinical decisions will have to be based on available indirect evidence.

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References

1. Howard BV, Howard WJ: LDL cholesterol and troglitazone therapy (Letter). *Diabetes Care* 21:2201–2202, 1998
2. Van de Vijver LPL, Kardinaal AFM, Van Duyvenvoorde W, Kruijssen DACM, Grobbee DE, Van Poppel G, Princen HMG: LDL oxidation and extent of coronary atherosclerosis. *Arterioscler Thomb Vasc Biol* 18:193–199, 1998
3. Regnström J, Nilsson J, Tornval P, Landou C, Hamsten A: Susceptibility to low density lipoprotein oxidation and coronary atherosclerosis in man. *Lancet* 339:1183–1186, 1992
4. Rimm EB, Stampfer MJ, Ascherio A, Giovannucci E, Colditz GA, Willett WC: Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med* 328:1450–1456, 1993
5. Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ: Randomised trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet* 347:781–786, 1996
6. Kleinveld HA, Hak-Lemmers HL, Hectors MP, de Fouw NJ, Demacker PN, Stalenhoef AF: Vitamin E and fatty acid intervention does not attenuate the progression of atherosclerosis in Watanabe heritable hyperlipidemic rabbits. *Arterioscler Thromb Vasc Biol* 15:290–297, 1995
7. Austin MA, King M-C, Vranizan KM, Krauss RM: Atherogenic lipoprotein phenotype: a proposed genetic marker for coronary heart disease risk. *Circulation* 82:495–506, 1990
8. Lamarche B, Tchernof A, Moorjani S, Cantin B, Dagenais GR, Lupien PJ, Despres JP: Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. *Circulation* 95:1–4, 1997
9. Bredie SJ, de Bruin TW, Demacker PN, Kastelein JJ, Stalenhoef AF: Comparison of gemfibrozil versus simvastatin in familial combined hyperlipidemia and effects on apolipoprotein-B-containing lipoproteins, low-density lipoprotein subfraction profile, and low-density lipoprotein oxidizability. *Am J Cardiol* 75:348–353, 1995
10. Huttunen JK, Manninen V, Manttari M, Koskinen P, Romo M, Tenkanen L, Heinonen OP, Frick MH: The Helsinki Heart Study: central findings and clinical implications. *Ann Med* 23:155–159, 1991
11. Maggs DG, Buchanan TA, Burant CF, Cline G, Gumbiner B, Hsueh WA, Inzucchi S, Kelley D, Nolan J, Olefsky JM, Polonsky KS, Silver D, Valiquett TR, Shulman GI: Metabolic effects of troglitazone monotherapy in type 2 diabetes mellitus. *Ann Intern Med* 128:176–185, 1998
12. Schwartz S, Raskin P, Fonseca V, Graveline JF, the Troglitazone and Exogenous Insulin Study Group: Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. *N Engl J Med* 338:861–866, 1998

Erratum

Brown JB, Pedula K, Barzilay J, Herson MK, Latare P: Lactic acidosis rates in type 2 diabetes. *Diabetes Care* 21:1659–1663, 1998

Incorrect data were given in Table 1. The table is shown below, with the corrected data in bold.

Table 1—*Frequency of lactic acidosis*

	Mean age (years)	Person-years reviewed	Events reviewed	Identified lactic acidosis events		
				Confirmed	Possible	Borderline
KP-Northwest						
1993	63.5 ± 12.4	10,983	10	0	0	0
1994	63.7 ± 12.3	10,667	9	1	0	1
KP-Georgia						
1993	55.2 ± 8.5	3,803	6	0	2	—
1994	55.6 ± 8.7	4,027	12	0	1	—
KP-Hawaii						
1993	62.6 ± 10.8	4,710	13	1	0	1
1994	64.3 ± 10.9	7,236	25	2	0	1
Total						
1993	61.7 ± 11.4	19,506	29	1	2	1
1994	62.4 ± 11.3	21,930	46	3	1	2
Overall	—	41,436	75	4	3	3
Rate per 100,000 person-years	—	—	—	9.7	7.2	7.2
95% CI	—	—	—	0.2 to 19.1	−1.0 to 15.4	−1.0 to 15.4

Data are means ± SD or *n*.