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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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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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,