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