COMMENTS AND RESPONSES

Comment on: Ellervik et al. Elevated Transferrin Saturation and Risk of Diabetes: Three Population-Based Studies. Diabetes Care 2011;34: 2256–2258

I read with fascination the article by Ellervik et al. (1) demonstrating the increased risk of both type 1 and type 2 diabetes associated with elevated transferrin saturation levels. In accord with this, I previously reported significantly increased levels of total hemoglobin concentration in individuals with childhood-onset type 1 diabetes (2). Others have shown significantly higher androgen levels in both males and females with type 1 diabetes compared with nondiabetic controls (3). Androgens have a direct stimulatory effect on erythropoiesis. I agree with Ellervik et al. that very high iron concentrations may cause destruction of pancreatic β-cells in a nonautoimmune manner. However, I propose that other factors may be involved in this complex phenotype, specifically autoimmune factors as well as antihyperglycemic compensatory homeostatic mechanisms.

Transferrin saturation is a measure of the percentage of iron molecules available in the serum that are actually bound to transferrin. The higher the total hemoglobin concentration, the greater the amount of Fe^{3+} generated when hemoglobin breaks down and the greater the amount of Fe^{3+} that will attach to transferrin, which then transports it in the blood stream. Because transferrin transports Fe^{3+} to the bone marrow for synthesis into hemoglobin, it is not clear whether higher hemoglobin levels lead to increased transferrin saturation or whether higher transferrin saturation is leading to increased hemoglobin levels. Perhaps both are happening in a feed-forward mechanism. However, the cross-sectional nature of the study by Ellervick et al. does not clarify this. In addition, Ellervik et al. state that there was an increased risk of type 1 or type 2 diabetes associated with a transferrin saturation level greater than 50%; however, this would more accurately be described as increased odds of having either type of diabetes.

This increased likelihood of having diabetes with a transferrin saturation level greater than 50%, although apparent for both types of diabetes, was stronger for type 1 diabetes. Only for type 1 diabetes was the test of heterogeneity significant. This finding is important because *1*) androgen levels are significantly lower in type 2 than in type 1 diabetes at a similar chronological age and *2*) androgens, particularly testosterone, are associated with increased insulin sensitivity. In NOD mouse models of autoimmune type 1 diabetes, androgen administration has been shown to prevent type 1 diabetes without preventing insulitis (4), whereas castration has been shown to induce type 1 diabetes (4). Finally, upregulation of the heme oxygenase system has been shown to increase insulin sensitivity in murine models (5). Thus, although the increased prevalence of diabetes associated with elevated transferrin saturation might be due to nonautoimmune destruction of pancreatic islets by iron, as suggested by Ellervik et al., given the direct stimulatory role of androgens on erythropoiesis, I posit that the increased transferrin saturation associated with diabetes might reflect a compensation mechanism for insulinopenia taking place in the bone marrow. Therefore, given this, it is possible that the role of phlebotomy in diabetes is far more complicated than the impression given in the article (1).

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