Hepatitis C Virus Infection: Evidence for an Association With Type 2 Diabetes

Response to Skowroński et al.

We agree with Skowroński et al. (1) that the type of diabetes manifested by patients with HCV chronic infection (HCV^+) may not be classical type 2 diabetes, and the phenotypic characterization of our patients shows just that. The labeling of HCV^+ patients as type 2 diabetes is purely conventional and possibly inaccurate: the lines separating type 1 diabetes, from latent autoimmune diabetes in adults and from type 2 diabetes, are fading away as new pathogenetic information is obtained (2).

HCV chronic infection may be responsible for a constellation of extrahepatic immune-mediated manifestations (3). HCV lymphotropism may trigger lymphocyte expansion followed by the production of different autoantibodies (3). For example, we have previously reported (4) on 229 HCV-related mixed cryoglobulinemia (MC-HCV^+) patients without cirrhosis. We found that *1*) the prevalence of type 2 diabetes was significantly higher in MC-HCV^+ patients without cirrhosis than in control subjects (14.4 vs. 6.9%), *2*) MC-HCV^+ patients with type 2 diabetes were leaner than type 2 diabetic control subjects (24.2 vs. 30.4 kg/m^2) and showed significantly lower LDL cholesterol and systolic and diastolic blood pressure, and *3*) MC-HCV^+ patients with type 2 diabetes had non–organ-specific autoantibodies more frequently (34 vs. 18%) than nondiabetic MC-HCV^+ patients. Thus, in HCV chronic infection, the clinical phenotype of diabetes has been found to be similar across three studies (1,4,5) and different from classical type 2 diabetes. An immune-mediated mechanism for MC-HCV^+–associated diabetes has been postulated (4), and a similar pathogenesis might be involved in the diabetes of HCV^+ patients. This hypothesis is strengthened by the finding that autoimmune phenomena in type 2 diabetic patients are more common than previously thought (6). Since the prevalence of classic β-cell autoimmune markers in HCV^+ patients has not been found to be increased (1), other immune phenomena might be involved, and viral damage to the β-cells may occur by a direct mechanism (7).

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Metformin and Heart Failure: Innocent Until Proven Guilty

Response to Inzucchi

The editorial by Inzucchi (1) in the October 2005 issue of *Diabetes Care* on the effects of metformin in type 2 diabetic patients with heart failure deals in a masterly manner with the choice of the most suitable treatment of this condition. Since both diabetic heart failure and mechanism of metformin action are not completely understood, it is difficult, in the author's opinion, to find a convincing explanation of the benefit from the use of this drug. However, as the contracting heart gets most of its energy from nonesterified fatty acids (FFAs), and even does so more in the insulin-resistant state of diabetes, the author correctly states that a drug that enhances the uptake of the more metabolically efficient glucose instead of FFA may improve the function of the failing heart.

What the author is not aware of is that the mechanism of shift from one substrate to another has just been demonstrated for metformin and the other biguanides. In fact, dose-dependent inhibition of long-chain fatty acid oxidation in red muscle restores the glucose oxidation when depressed by concurrent oxidation of palmitic acid; hence, the proposed definition of biguanides as drugs of the Randle's cycle (2,3).

Fischer et al. (4) describe increased content of glucose transporters GLUT1 and GLUT4 produced by metformin in heart cells.

Essop and Opie (5) stress the concept that high blood FFAs, especially in the presence of a hyperadrenergic state, can damage the ischemic myocardium and that agents that inhibit myocardial FFA oxidation should improve the work efficiency of the failing heart.

In conclusion, in my opinion there is good evidence that the beneficial effect of metformin in heart failure in type 2 diabetic patients rests on the same underlying mechanism shared by other well-known effects of the drug, i.e., increased utilization of glucose by red muscle and hindered gluconeogenesis in liver, as consequences of depressed fatty acid oxidation (2,3).

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