

morbidity and a greater risk for developing diabetes (3,4). The merit of a simple test as a diagnostic tool cannot be disputed; however, some of its usefulness is lost when it is not followed by the proper use of complementary tests. A selective testing using a 2-h postchallenge plasma glucose in high-risk individuals (as defined by the Expert Committee) would be a better alternative in this subset of the population. In the U.S., according to the data from Harris et al., the vast majority of the 2.1 million cases currently unidentified as diabetic by the ADA criteria could be properly diagnosed using this approach.

In conclusion, we believe that the data reported by Harris et al. give a nice demonstration that the fasting plasma glucose and the 2-h postchallenge plasma glucose are complementary tests for diagnosing diabetes in subjects in whom a fasting plasma glucose <126 mg/dl is found.

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Hyperhomocysteinemia and Microalbuminuria in Diabetes

We read with interest the study by Hofmann et al. (1) on hyperhomocysteinemia [HH(e)] and endothelial dysfunction in patients with IDDM, and the accompanying editorial by Dr. Colwell (2). These data are compatible with previous observations that patients with IDDM without microalbuminuria or vascular disease have normal homocysteine [H(e)] metabolism (3,4). In contrast, patients with NIDDM without microalbuminuria have an increased prevalence of postload HH(e) with normal fasting plasma H(e) concentrations (4). In this context, it may be relevant that insulin plays a role in amino acid metabolism and acute hyperinsulinemia during a hyperinsulinemic-euglycemic clamp lowers plasma H(e) concentrations in normal subjects but not in insulin-resistant patients with NIDDM (5).

Dr. Colwell suggests that the HH(e) in patients with IDDM and microalbuminuria may be due to preexisting endothelial function. However, the pattern of HH(e) with both fasting and postload elevations in H(e) suggests another possible explanation. Plasma H(e) concentrations are determined by the activity of several enzymes, the two most important of which are methylene tetrahydrofolate reductase (MTHFR) and cystathionine-β-synthase. The kidney plays a pivotal role in maintaining normal plasma H(e) (6). The enzyme MTHFR is highly expressed and active in the kidney, and its dysfunction leads to HH(e) in patients with renal impairment. Decreased activity of this enzyme leads to elevated fasting plasma H(e), as in the patients of Hofmann et al. Thus, it is possible that even in the early stage of microalbuminuria, the function of this enzyme in the kidney is impaired, leading to HH(e).

Hofmann et al. suggest that HH(e) causes endothelial dysfunction by induction of oxidative stress. However, it is well recognized that diabetes itself leads to oxidative stress. We have recently established that in the presence of vascular disease, plasma concentrations of thiobarbituric acid-reactive substances (a marker of oxidative stress) are elevated in diabetic patients with vascular disease and that no further elevation occurs in the presence of

coexistent HH(e) (7).

HH(e) is well established as a risk factor for macrovascular disease (8). Further investigation is required into the mechanisms of HH(e) in patients with diabetes and its role in the progression of microvascular and macrovascular disease in these patients.

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