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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References

1. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS: Comparison of diabetes diagnostic categories in the U.S. population according to the 1997 American Diabetes Association and 1980–1985 World Health organization diagnostic criteria. *Diabetes Care* 20:1859–1862, 1997
2. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
3. Jarrett RJ, Shipley MJ: Type 2 (non insulin dependent) diabetes mellitus and cardiovascular disease: putative association via common antecedents: further evidence from the Whitehall Study. *Diabetologia* 31:737–740, 1988
4. Rios JM, Gomez R, Roman V, Villa A, Perez EB, Gomez-Perez F, Rull JA: High rate of progression of impaired glucose tolerance (IGT) to diabetes (DM) in a genetically susceptible population (Abstract). *Diabetes* 44 (Suppl. 1):184A, 1995

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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References

1. Hofmann MA, Kohl B, Zumbach MS, Borcea V, Bierhaus A, Henkels M, Amiral J, Fiehn W, Ziegler R, Wahl P, Nawroth PP: Hyperhomocyst(e)inemia and endothelial dysfunction in IDDM. *Diabetes Care* 20: 1880–1886, 1997 (The version of this paper cited here was withdrawn. A revised version was printed in *Diabetes Care* 21:841–848, 1998.)
2. Colwell JA: Elevated plasma homocysteine and diabetic vascular disease. *Diabetes Care* 20:1805–1806, 1997
3. Robillon JF, Canivet B, Candito M, Sadoul JL, Jullien D, Morand P, Chambon P, Freychet P: Type 1 diabetes mellitus and homocyst(e)ine. *Diabete Metab* 20:494–496, 1994
4. Munshi M, Stone A, Fink L, Fonseca V: Hyperhomocysteinemia following a methionine load in non-insulin dependent diabetes and macrovascular disease. *Metabolism* 45:133–135, 1996
5. Fonseca VA, Mudaliar S, Schmidt B, Fink LM, Kern PA, Henry RR: Plasma homocysteine concentrations are regulated by acute hyperinsulinemia in diabetic but not type II diabetic subjects. *Metabolism*. In press
6. Bostom AG, Brosnan JT, Hall B, Nadeau MR, Selhub J: Net uptake of plasma homocysteine by the rat kidney in vivo. *Atherosclerosis* 116:59–62, 1995
7. Fonseca VA, Stone A, Munshi M, Baliga BS, Aljada A, Thusu K, Fink L, Dandona P: Oxidative stress in diabetes mellitus: does homocysteine have a role? *South Med J* 90:903–906, 1997
8. Guba S, Fonseca V, Fink L: Hyperhomocysteinemia: the emerging and important risk factor for cardiovascular disease. *Am J Clin Pathol* 106:709–722, 1996