

# Therapeutic Importance of Subsets of Type 2 Diabetes?

Both the American Diabetes Association and the World Health Organization classify cases of diabetes into 2 distinct categories, type 1 diabetes and type 2 diabetes. Within both groups, considerable heterogeneity is thought to occur. In phenotypic type 2 diabetes, the measurement of islet cell antibodies (ICAs) and GAD antibodies allows the identification of a subgroup that comprises 10–30% of Caucasian diabetic individuals. This subgroup shows T-cells reactive with islet antigens similar to those of type 1 diabetes (1). Moreover, this subgroup shows more rapid loss of  $\beta$ -cell function and earlier failure with oral agent therapy, as compared with antibody-negative type 2 diabetes (2). The article by Li et al. (3) demonstrates the importance of a family history of types 1 and 2 diabetes in identifying other subsets of type 2 diabetes. Patients with a family history of only type 2 diabetes had a more severe phenotype (i.e., earlier age at onset and more severe  $\beta$ -cell dysfunction) and more features of the metabolic syndrome (i.e., obesity, hypertension, low HDL cholesterol levels, increased cholesterol-to-apolipoprotein[b] ratios, and coronary heart disease), as compared with those patients who had sporadic type 2 diabetes. As one might expect, patients with a family history of both types 1 and 2 diabetes had an increased frequency of type 1 diabetes high-risk genotypes and of GAD antibodies, but, surprisingly, this subset also had a lower frequency of hypertension and cardiovascular disease. The importance of a type 1 and type 2 diabetes family history was further emphasized by the authors' observation that the phenotypic differences were not accounted for by the GAD antibody-positive patients (i.e., those with latent autoimmune diabetes in adults or type 1.5 diabetes).

Why might it be important to identify subsets of type 2 diabetic patients? The Diabetes Control and Complications Trial and the U.K. Prospective Diabetes Study (UKPDS) have conclusively demonstrated the benefits of glycemic control in both types 1 and 2 diabetes, respectively. Consequently, treatment of hyperglycemia is the primary treatment goal for patients with

diabetes. Premature coronary artery disease (CAD) is the major cause of death in patients with diabetes; however, the mechanisms for types 1 and 2 diabetes may in part differ. In type 1 diabetes, premature CAD is associated primarily with nephropathy (4), whereas in type 2 diabetes, premature CAD is strongly associated with the metabolic syndrome (5). This difference in the pathophysiology of premature CAD in type 1 versus type 2 diabetes may also pertain to subsets of type 2 diabetes. The identification of subsets of type 2 diabetes may influence the choice of which drugs are used to treat hyperglycemia and other problems in different subsets of patients with type 2 diabetes. Drugs that are neutral or beneficial to the metabolic syndrome are likely to be more important in the treatment of type 2 diabetic patients who are at a greater risk for the metabolic syndrome (e.g., those patients with a family history of only type 2 diabetes, as identified by Li et al. [3]). In this subset of patients, early treatment of hyperglycemia with agents that improve insulin sensitivity, such as metformin or thiazolidinediones, may reduce the risk of premature CAD more than treatment with insulin or agents that stimulate insulin secretion, even though all of these forms of treatment may achieve similar levels of glycemic control. The improved outcome in the UKPDS of patients randomized to metformin may be an example of this benefit of insulin sensitizers (6). Furthermore, treatment of hypertension, hyperlipidemia, and any other chronic conditions with agents neutral or beneficial to the metabolic syndrome may also be especially important in this subset of patients. The results of the recently reported Heart Outcomes Prevention Evaluation (HOPE) study may be pertinent in this regard (7,8).

Type 2 diabetes is usually a progressive disease. Those individuals at risk initially develop impaired glucose tolerance (IGT) and/or impaired fasting glucose before developing diabetes. Initially, IGT and/or diabetes is responsive to treatment with diet or individual oral agents, but over the course of years, the disease becomes more difficult to treat, requiring the administra-

tion of multiple oral agents and eventually insulin in a large proportion of patients. In the future, treatment aimed at preventing the development of diabetes and at slowing its progression is likely to become as important as treatment of hyperglycemia. In fact, preservation of  $\beta$ -cell function and treatment of hyperglycemia are interrelated. Achieving good glycemic control would be easier and more commonly accomplished if progression of type 2 diabetes could be prevented or slowed. Recognition of subsets of type 2 diabetes is likely to result in identification of different mechanisms responsible for the disease progression of each subset. In turn, therapy to delay or prevent progression of type 2 diabetes may become relatively subset-specific. If the Diabetes Prevention Trial–Type 1 (DPT-1), the European Nicotinamide Diabetes Intervention Trial (ENDIT), or other studies identify treatments that are efficacious in slowing the type 1 diabetes disease process, then these therapies may also be beneficial in slowing the progression of type 2 diabetes in the subset of patients with GAD antibodies and/or with a family history of type 1 diabetes. A pilot study from Japan that demonstrated better preservation of C-peptide with insulin versus sulfonylurea treatment of ICA-positive type 2 diabetic patients suggests that insulin may be beneficial to the disease process in this subset of type 2 diabetic patients (9). Moreover, if the Diabetes Prevention Program demonstrates that therapy to decrease insulin resistance is successful in preventing or delaying progression from IGT to type 2 diabetes, then this form of therapy may be especially useful in a different subset of patients: those individuals with a family history of only type 2 diabetes, in whom insulin resistance is more prominent. The observations that metformin and thiazolidinediones can preserve  $\beta$ -cell function and/or mass in some animal models of type 2 diabetes (10–12) raise the possibility that, in some subsets of human type 2 diabetes, use of these drugs to treat hyperglycemia may achieve the added benefit of slowing the underlying disease process. This concept would apply not only to the choice of antihyperglycemic drugs, but also

to drugs used to treat other coexisting conditions of type 2 diabetic patients. If some drugs used to treat other conditions in type 2 diabetic patients are found to slow or delay diabetes progression in some specific subsets, then these findings will profoundly influence the choice of which drugs should be used to treat these patients. In this regard, the recently reported prevention of type 2 diabetes in the HOPE study (7) suggests that different antihypertensive agents may have different effects on the disease processes responsible for type 2 diabetes and may be preferable, for this reason, in specific subsets of type 2 diabetic patients.

Although type 2 diabetes is a common disease with terrible long-term consequences and is dramatically increasing in prevalence, these are still exciting times for patients with this disease and for their health care providers. Many new drugs to help achieve glycemic control are available, and many more are in various stages of development. The identification of subsets of type 2 diabetes is also potentially exciting, but additional research is needed to determine whether my proposals are valid and whether some treatments will be relatively type 2 diabetes subset-specific in the future. This research will focus on defining differences in the pathophysiology of different type 2 diabetes subsets, on how best to identify relevant subsets clinically, and on clinical trials to determine whether specific drugs to treat hyperglycemia and/or other conditions are more beneficial and

more preferable in 1 subset of type 2 diabetes versus another.

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