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Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

Autoantibody Profiles Over 20 Years Indicate Type 1 Diabetes Risk

A 20-year follow-up of relatives and offspring of type 1 diabetes patients has again highlighted that the presence of multiple autoantibodies is a significant risk factor for progression to type 1 diabetes. Importantly, the profile of autoantibodies present and its relationship with age and the *HLA-DQ* genotype may be more revealing about the progression rate of the underlying asymptomatic disease process and the development of clinically overt disease, according to Gorus et al. (**p. 1065**). The study focused on relatives and offspring of patients with type 1 diabetes in the Belgian Diabetes Registry and tracked both the development of type 1 diabetes over a ~26-year period and also the profile of various autoantibodies known to signal type 1 diabetes risk over time. The influence of the *HLA-DQ* genotype was also included as certain combinations can also modulate autoantibody-inferred type 1 diabetes risk, according to the authors. They report that out of the ~7,000 relatives included, 462 were persistently positive for one or more autoantibodies against insulin (IAA), GAD (GADA), islet antigen 2 (IA-2A), and/or zinc transporter 8 (ZnT8A). All have previously been linked to the development of the disease. However, the combination of autoantibodies present as well as genotype and age reportedly dictated outcomes over the 20-year follow-up. Commenting more widely on the study, author Ilse Weets told *Diabetes Care*: "Further research should now focus on how the various autoantibody profiles—and their changes over time—relate to critical switches in the underlying pathological process. This could be achieved by closely monitoring functional β-cell mass and glycemic control in risk groups according to autoantibody profile and genetic risk and by histopathological analysis of donor pancreata from autoantibody-positive healthy individuals with various risk profiles. We believe these observations may ultimately contribute to tailoring selection criteria for participation in prevention trials to the type of intervention and the targeted disease stage."

Gorus et al. Twenty-year progression rate to clinical onset according to autoantibody profile, age, and *HLA-DQ* genotype in a registry-based group of children and adults with a first-degree relative with type 1 diabetes. Diabetes Care 2017;40:1065–1072

Red Meat: Barbecuing, Roasting, and Broiling Increase Type 2 Diabetes Risk

Red meat consumption has been widely associated with type 2 diabetes risk but how it is cooked and whether this might also determine risk has largely been a matter of speculation. According to Liu et al. (**p. 1041**), cooking red meat regularly at high temperatures and over an open flame is likely to raise risk in the long term. The conclusions come from the large prospective Nurses' Health Study and involved ~59,000 healthy women aged 30–55 years at baseline being studied between 1986 and 2012. The authors tracked general health and disease information over the period and also regularly administered food frequency questionnaires that included questions on food preparation methods. According to the authors, there were just over 6,000 incident cases of type 2 diabetes in the period of follow-up and total red meat consumption and processed red meat were both associated with an increased risk of type 2 diabetes. They then looked at each individual cooking method and found that broiling, barbecuing, and roasting were each independently associated with increased risk of type 2 diabetes. They go on to suggest many of the ways the methods might be associated with the increased risk of diabetes suggesting that certain components of the Maillard reaction might contribute to risk as well as chemicals resulting from the burning of fat in open flames. According to author Qi Sun: "Despite dietary recommendations to reduce red meat intake, red meats remain one of the primary sources of protein in the American diet. Our research suggests that cooking methods may modulate diabetes risk beyond red meat intake per se. Of course, new studies are needed in this regard, although the role of cooking in the relationship between diet and health can be fairly important and should be recognized by the public and in future dietary guidelines."

Liu et al. Cooking methods for red meats and risk of type 2 diabetes: a prospective study of U.S. women. Diabetes Care 2017;40:1041–1049

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Distinguishing Monogenic Diabetes From Other Diagnoses With a Biomarker-Based Screening Approach

A biomarker screening approach to identify monogenic diabetes is reported this month in *Diabetes Care* by Shields et al. (**p. 1017**). They state that it should now be possible to screen all young-onset diabetes patients to accurately diagnose the exact form of diabetes that they have. While ~90% of diabetes in the young is type 1 diabetes, other forms exist and are often misdiagnosed. The three-step approach they describe essentially attempts to rule out type 1 diabetes by first testing for endogenous insulin secretion. If there was then any evidence of insulin being produced, the researchers then examined two type 1 diabetes–associated islet autoantibodies. If that step was negative, diagnostic molecular genetic screening was then used to diagnose the specific form of diabetes. To confirm the validity of the approach, the authors report a study of ~1,400 young patients with diabetes where the majority had no known genetic cause for their disease. However, 34 patients did have known monogenic diabetes at the outset. After progressing through the various screening steps, they identified an additional 17 patients with some form of monogenic diabetes. The researchers state that the biomarker approach is an efficient way to identify monogenic patients and should help to provide appropriate clinical care. Currently, sequencing for mutations linked to monogenic diabetes in all young patients with diabetes is out of the question due to costs. Author Andrew T. Hattersley said: "It is important to identify the 3% of young patients with monogenic diabetes and to do this we need to be efficient and selective with our genetic sequencing. This study shows that if a patient is on insulin you should not test for monogenic diabetes until you have excluded type 1 diabetes by showing they have significant C-peptide and do not have islet autoantibodies. The next step is to integrate clinical features to improve the targeting of patients for further testing."

Shields et al. Population-based assessment of a biomarker-based screening pathway to aid diagnosis of monogenic diabetes in young-onset patients. Diabetes Care 2017;40:1017–1025

Genetic Risk Variant for Type 2 Diabetes Is Also Active in Adolescents

A genetic variant in the *TCF7L2* gene implicated in increasing the risk of type 2 diabetes in adults also increases risk in obese adolescents and it does so by impairing β-cell function and hepatic insulin sensitivity. This is according to Cropano et al. (**p. 1082**). They suggest that the variant might be used to predict the development of impaired glucose tolerance and type 2 diabetes in youth, who they say are increasingly developing the disease at very young ages with lifelong consequences. The study focuses on the rs7903146 variant of the *TCF7L2* gene, where individuals can be homozygous for the C and T alleles or heterozygous for both. Previously the T allele was linked to increasing risk of type 2 diabetes but only in adults—not in children. To assess the relationship, the authors report that they initially focused on genotyping the variant in a multiethnic cohort of just under 1,000 obese youth followed by an oral glucose tolerance test coupled to the oral minimal model to assess insulin secretion. For ~300 participants, they additionally ran another glucose test 3 years later to assess the development or otherwise of impaired glucose tolerance and/or type 2 diabetes. In a separate assessment, 33 participants additionally underwent a hyperinsulinemic-euglycemic clamp test to get a direct readout on insulin sensitivity according to the variant type that was present. The researchers report that overall the presence of the T allele was associated with higher glucose levels in most of the ethnic groups and that it was also associated with decreased β-cell responsiveness and impaired glucose tolerance. There was also reduced suppression of hepatic glucose production when the T allele was present. At the 3-year follow-up, the T allele was associated with a doubling of the risk for impaired glucose tolerance and ultimately type 2 diabetes. As a result, the variant might go some way toward explaining the development of hyperglycemia. The authors speculate about underlying mechanisms but stress that knowledge in that area is currently limited.

Cropano et al. The rs7903146 variant in the *TCF7L2* gene increases the risk of prediabetes/type 2 diabetes in obese adolescents by impairing β-cell function and hepatic insulin sensitivity. Diabetes Care 2017;40:1082–1089

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