OCTOBER 2023

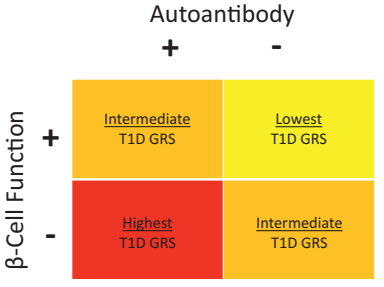
Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

Type 1 Diabetes Genetic Risk Score Improves Differentiation of Individuals With Ketosis-Prone Diabetes

Genetic risk scores (GRS) for type 1 diabetes can further delineate the four subgroups of ketosis-prone diabetes (KPD), according to Osafehinti et al. (**p. 1778**). Individuals with KPD initially present with diabetic ketoacidosis, but members of the different KPD groups then appear to progress diversely toward either type 1 diabetes–like or type 2 diabetes–like natural histories and related treatment recommendations. Using a cohort of 426 patients with KPD and defined Aβ criteria, the authors analyzed type 1 diabetes GRS across the four subgroups and separately according to race/ethnicity and β-cell function/glycemia. They found that individuals positive for islet autoantibodies but negative for β-cell function had higher GRS than individuals who were either positive or negative for both characteristics. Individuals negative for autoantibodies and positive for β-cell function had the lowest GRS. Being positive for autoantibodies and negative for β-cell function notionally places that group closest to automimmune type 1 diabetes, although GRS for these individuals remained lower than those of a separate reference cohort of type 1 diabetes patients. Conversely, those negative for autoantibodies and positive for β-cell function (i.e., notionally closer to type 2 diabetes) had a higher GRS. Finally, the authors note that GRS were consistently lower in African American groups than Hispanic and White groups across all the KPD subgroups. "The T1D GRS further validates and refines the Aβ classification system for KPD and provides insights into the pathophysiology of each of the groups," said author Ashok Balasubramanyam. "The GRS could be an important tool to define endotypes of other atypical forms of diabetes."



Type 1 diabetes genetic risk score (T1D GRS) helps differentiate between types of ketosis-prone diabetes.

Osafehinti et al. Type 1 diabetes genetic risk score differentiates subgroups of ketosis-prone diabetes. Diabetes Care 2023;46:1778–1782

New Guidelines on Laboratory Measures for Diagnosis and Management of Diabetes

The Americans Diabetes Association and the American Association for Clinical Chemistry have published new guidelines on laboratory measures for the diagnosis and management of diabetes. Published simultaneously in *Diabetes Care* (**e151;** Executive Summary **p. 1740**) and *Clinical Chemistry*, the guidelines are primarily aimed at laboratory professionals and clinicians involved in diabetes care. The guidelines represent an update on previously published versions and now cover emerging technologies that are being applied in clinical applications or remain in development and thus are not yet recommended for clinical application. They cover nearly all areas involving measurement in clinical care of diabetes, and they particularly consider traditional blood glucose measurements and the more modern continuous glucose monitoring. They also take an in-depth look at glycated hemoglobin, specifically the widely used HbA_{1c} testing. As with all measurement approaches, the issues of accuracy, precision, and bias are considered in relation to blood glucose measurement. A notable point the guidelines raise concerns blood collection and the risk of glycolysis prior to analysis. They specifically recommend the use of citrate buffer (which is not currently available in the U.S.) to minimize glycolysis and note the wide implications this will likely have on increasing rates of diabetes detection. Other areas of consideration include ketones and urine albumin, which are widely used clinically. Noninvasive glucose monitoring, genetic testing, and measurements of autoantibodies, insulin, and C-peptide also have their place, but overall they have limited clinical applicability at present and are mainly useful currently in research applications. "An evidence-based approach was used to develop recommendations for laboratory analysis in screening, diagnosis, and monitoring of diabetes," said author David B. Sacks. "We hope that the information facilitates the optimum use of laboratory tests in the management of individuals with diabetes."

Sacks et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care 2023;46:e151–e199

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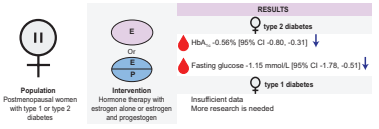
Hormone Therapy Linked to Improved Blood Glucose Regulation in Postmenopausal Women With Type 2 Diabetes

Short-term postmenopause hormone therapy appears to reduce blood glucose levels and HbA_{1c} in women with type 2 diabetes, according to Speksnijder et al. (**p. 1866**). Using a systematic review and meta-analysis, they found that hormone therapy is expected to have a "neutral to beneficial" effect in type 2 diabetes but not in type 1 diabetes, where data availability was much more limited. The findings follow an extensive search for relevant studies, with the authors identifying 12 parallel-group trials and 7 crossover trials that included a total of 1,412 participants. For type 2 diabetes, hormone therapy of any type reduced HbA_{1c} by 0.56% and fasting glucose by 1.15 mmol/L. Approaches to hormone therapy vary, and the authors present stratified analyses according to application routes and combinations. For example, oral therapies reduced HbA_{1c} over a range of ~0.4 to 0.8%, while transdermal therapies made no difference. Combined and unopposed therapy approaches also presented a mixed picture. Fasting glucose reductions were equally mixed, with some approaches clearly having success and others less so. The authors note that nearly 50% of the studies included in the analysis had a high risk of bias, although the bulk of that risk was due to a lack of predefined protocols (due to study age), and bias due to faulty measurements was low. On that basis, they conclude that the reductions in HbA_{1c} and fasting glucose are likely clinically relevant. "The current meta-analysis shows that in postmenopausal women with type 2 diabetes, hormone therapy is expected to have a neutral to beneficial impact on glucose regulation," said author Esther M. Speksnijder. "These findings bear significance for clinicians prescribing hormone therapy as well as for patients with type 2 diabetes for whom postmenopausal hormone therapy is considered, for instance, to treat bothersome vasomotor symptoms."

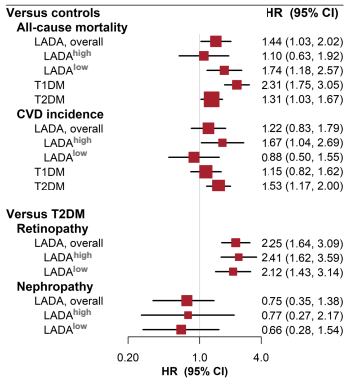


Short-term postmenopausal hormone therapy reduces fasting glucose and HbA_{1c} in women with type 2 diabetes. E, estrogen; P, progestogen.

Speksnijder et al. The effect of postmenopausal hormone therapy on glucose regulation in women with type 1 or type 2 diabetes: a systematic review and meta-analysis. Diabetes Care 2023;46:1866–1875

Study Shows Mixed Picture of Care and Outcomes in Latent Autoimmune Diabetes in Adults

A study on the morbidity and mortality associated with latent autoimmune diabetes in adults (LADA) by Wei et al. (**p. 1857**) reveals a mixed picture of care success in what is a fairly common but relatively unrecognized patient group. According to the analysis, rates of all-cause mortality and cardiovascular disease in LADA were like those found in individuals with type 2 diabetes, while rates of retinopathy were higher. LADA was also characterized by lower metabolic risk, in terms of blood pressure and lipid levels, but individuals with LADA had much lower chances of achieving glycemic control than individuals with type 2 diabetes. In particular, the authors show that individuals with LADA with high levels of one autoantibody (GAD antibody) or with adult-onset type 1 diabetes were much less likely to have glycemic control at diagnosis or at any time during follow-up. In addition, a significant proportion of individuals with LADA were not on any glucose-lowering treatments. The authors go on to discuss some of the differences in characteristics between individuals with LADA and high and low levels of antibodies compared with individuals with (mostly) type 2 diabetes. What emerges is a clear mix of characteristics that resemble elements of type 1 and type 2 diabetes and changed risk profiles specific to LADA. In particular, the authors note the evident treatment gaps with respect to LADA as a major area of concern that needs further investigation. The authors note that stratification by GAD antibody levels is likely important, as it reveals two distinct disease trajectories and, presumably, different considerations when it comes to care and treatment. Commenting further, author Yuxia Wei said, "Our findings highlight the importance of correctly diagnosing LADA in individuals with adult-onset diabetes and the need to carefully monitor glycemic control in this patient group and, if needed, to intensify treatment to reduce the risk of complications."



All-cause mortality and cardiovascular disease (CVD) incidence (hazard ratios [HR]) in latent autoimmune diabetes in adults (LADA) versus population controls. T1DM, type 1 diabetes; T2DM, type 2 diabetes.

Wei et al. All-cause mortality and cardiovascular and microvascular diseases in latent autoimmune diabetes in adults. Diabetes Care 2023;46:1857–1865

https://doi.org/10.2337/dc23-ti10