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Elevated Glucose Levels Tied to Risks for Microvascular Complications in Prediabetes

Elevated blood glucose levels indicative of prediabetes appear to be associated with increased risks for retinopathy, peripheral neuropathy, and also diabetic nephropathy, according to Emanuelsson et al. (p. 894). As a result, they suggest that screening for micro- and macrovascular complications should be recommended for individuals with raised blood glucose or prediabetes. The conclusions come from an analysis of ~117,000 individuals who had blood glucose levels determined along with genotyping for a series of genes previously associated with elevated blood glucose. The investigators also looked at various micro- and macrovascular end points to determine risks associated with elevated glucose levels. And, crucially, they used Mendelian randomization and validation in further cohorts to determine causality. In total, about 820,000 individuals were considered in the analysis. The authors found that, on an observational level, increasing glucose levels were associated with higher risks for both micro- and macrovascular complications. Based on genetics and causal analyses (Mendelian randomization) they found risk ratios for a 1-mmol/L increase in blood glucose of 2.01 (95% CI 1.18–3.41) for retinopathy, 2.15 (1.38–3.35) for neuropathy, 1.58 (1.04–2.40) for diabetic nephropathy, and 1.49 (1.02–2.17) for myocardial infarction. Risks for estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² (indicating kidney disease) and peripheral arterial disease (PAD) were neither increased nor decreased with raised blood glucose. Validation in the cohorts further confirmed the associations with retinopathy, neuropathy, nephropathy, and myocardial infarction but not PAD and apparently were “refuted” for eGFR. Commenting further, author Marianne Benn told us: “The study shows a causal impact of glycemia on risk of microvascular disease in individuals from the general population. This risk is present at glucose levels within what is currently considered the normal or prediabetic range. The American Diabetes Association recommends screening for prediabetes in overweight and obese adults with risk factors for diabetes. However, this screening does not include examinations for microvascular complications. Future targeted screening may identify individuals who already have microvascular complications and those at very high risk for developing complications, who may benefit the most from risk factor modifications and/or treatment.”

Emanuelsson et al. Impact of glucose levels on micro- and macrovascular disease in the general population: a Mendelian randomization study. *Diabetes Care* 2020;43:894–902

Intensive Glycemic Control Also Reduces Risks of Recurrent CVD Events in Type 1 Diabetes

Further analyses from the Diabetes Control and Complications Trial (DCCT) and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study reveal that glycemic control was the strongest modifiable risk factor for initial and also for subsequent cardiovascular events in type 1 diabetes, according to Bebu et al. (p. 867). To come to these conclusions, the authors looked at CVD events in 1,441 DCCT/EDIC participants who had type 1 diabetes. They found that 239 individuals had 421 composite CVD events over a median follow-up of 29 years. Meanwhile, 120 individuals had 149 major adverse cardiovascular events (MACE). They report that age was the strongest risk factor for acute or silent myocardial infarction, stroke, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft. Glycemia (HbA_{1c}), in turn, was the strongest factor for CVD death, congestive heart failure, and angina and either the second or third factor for all other events, apart from silent myocardial infarction. HbA_{1c} was the strongest modifiable risk factor for first and subsequent composite CVD events. The authors point toward better management of glycemia to lower risk of first and recurrent events (the effect on recurrent events is the new insight). They note that the availability of continuous glucose monitoring and better insulin delivery devices should provide better responses to glucose variability. Commenting further, author Ionut Bebu told us: “With standardized assessments of putative risk factors and CVD outcomes and outstanding follow-up for nearly three decades, the DCCT/EDIC study provides a unique opportunity to evaluate risk factors for first and subsequent CVD events in type 1 diabetes. Our findings show that glycemia is the strongest modifiable risk factor for both first and recurrent CVD events. Therefore, aggressive glycemic management is recommended to lower the risk of initial CVD events in individuals with type 1 diabetes and should be maintained in order to reduce the risk of recurrent CVD events after a first event.”

Bebu et al. Risk factors for first and subsequent CVD events in type 1 diabetes: the DCCT/EDIC study. *Diabetes Care* 2020;43:867–874

Dysglycemia and Coronary Artery Disease Guidelines: A “Job Half Done”

Screening for impaired glucose tolerance (IGT) and diabetes among patients with established coronary artery disease is poorly practiced in European countries, according to Ferrannini et al. (p. 726). Moreover, they suggest that the achievement of guideline recommendations with respect to lifestyle risk factors and pharmacological management is “unacceptably poor” in these patients. They also label the implementation of the guidelines and achievement of targets as a “job half done” after successive updates to the guidelines since they were issued in 2007. Their stark conclusions are based on outcomes from EUROASPIRE V, a Europe-wide cross-sectional survey that looked at health outcomes of just under 8,300 patients with coronary artery disease. In this particular analysis, the authors looked at whether patients had a diagnosis of diabetes, and if they did not, they tested for HbA_{1c} and also administered an oral glucose tolerance test (OGTT). They also investigated lifestyle and risk factors and the use of cardioprotective and diabetes medicines. They found that just under 30% of the patients had a diagnosis of diabetes already; in 4,400 patients who did not and in whom it was possible to perform an OGTT, 41% were dysglycemic (i.e., had IGT or diabetes). Of these, 30% of individuals were newly diagnosed with diabetes, and the authors estimate that about 70% of patients with IGT would not have been detected without the test. They underline this means that the presence of dysglycemia basically doubled after administration of the guideline-recommended OGTT. The remaining one-third of patients with coronary artery disease had normal glucose levels. On that basis they question why the guidelines are having such poor outcomes at a patient level. They also call out the apparent poor follow-up in terms of lifestyle interventions and the prescription of medicines and in general terms indicate that poor clinical implementation of the guidelines appears to be a primary issue.

Ferrannini et al. Screening for glucose perturbations and risk factor management in dysglycemic patients with coronary artery disease—a persistent challenge in need of substantial improvement: a report from ESC EORP EUROASPIRE V. *Diabetes Care* 2020;43:726–733

Longer Lifetime Duration of Lactation Reduces Risk of Type 2 Diabetes Following Gestational Diabetes Mellitus

Longer lifetime duration of lactation after pregnancy is associated with reduced risks for type 2 diabetes among women with a history of gestational diabetes mellitus (GDM), according to Ley et al. (p. 793). Based on the results, they suggest that prolonged breastfeeding should be encouraged, particularly among women who have experienced GDM. Their findings come from an analysis of 4,372 women with a history of GDM. Using questionnaires administered over 25 years of follow-up, the authors tracked the occurrence of GDM and incident type 2 diabetes, lactation history, and also medical history and lifestyle. They found that during ~87,000 person-years of follow-up there were 873 incident cases of type 2 diabetes. Longer lifetime duration of lactation was associated with reduced risk of type 2 diabetes, with the overall trend in hazard ratios for total lactation as follows: up to 6 months, 1.05 (95% CI 0.83–1.34); 6 to 12 months, 0.91 (0.72–1.16); 12 to 24 months, 0.85 (0.67–1.06); and >24 months, 0.73 (0.57–0.93), compared with no lactation. The overall trend reached statistical significance. On potential underlying mechanisms, the authors conclude that they are yet to be determined. Equally, they suggest that there are no indications that lactation duration has any effect on diabetes complications if diabetes develops or, more generally, on longer-term morbidity or mortality. They recommend that all these aspects be looked at in further studies to carefully assess causality, mechanisms, and outcomes. Commenting more widely, authors Cuilin Zhang and Sylvia Ley told us: “Although women who developed diabetes during pregnancy usually had a marked increased risk for type 2 diabetes following the index pregnancy, findings from the present study along with our other previous work suggest that adopting a healthy lifestyle may lower the risk. The findings add to growing evidence on health benefits of breastfeeding for women, in addition to the well-known benefits for babies. Since women with gestational diabetes often experience increased difficulty with breastfeeding, this message will be important for these high-risk women.”

Ley et al. Lactation duration and long-term risk for incident type 2 diabetes in women with a history of gestational diabetes mellitus. *Diabetes Care* 2020;43:793–798