JANUARY 2016

diabetes®

In This Issue of *Diabetes*

By Max Bingham, PhD

Case-Control Study Using Proteomics Reveals Association Between Type 1 Diabetes and Epstein-Barr Virus

The association between viral infections and type 1 diabetes is the focus of a case-control study by Bian et al. (**p. 285**), and it reveals a significantly raised level of association between the Epstein-Barr virus and type 1 diabetes onset in young human subjects. Fifty-two percent of the healthy control subjects had antibody responses to the virus in comparison to eighty-eight percent of the case subjects with type 1 diabetes. Notably, this apparent raised association was found using a proteomics approach capable of analyzing antibody responses to nearly 700 viral targets representing 23 different viral serotypes. No differences between the case and control groups were found in terms of the other viruses and the response rates to them, and this largely matched the infection rates found in epidemiological studies in the area of the study— Florida. For example, influenza A (H1N1), mumps virus, and coxsackievirus B response rates all neared 100%, while for chikungunya (not widely present in Florida at the time of the study), the response neared 0%. While the Epstein-Barr virus has previously been implicated in type 1 diabetes, the question still remains as to whether it is a cause or a consequence. According to the authors, various hypotheses point toward both outcomes, and this will only be resolved with further investigations. As the authors note, their high throughput approach to proteomic profiling of antiviral antibodies may now have utility in broader studies to unravel this apparent relationship more widely in terms of viral infections and the development of type 1 diabetes. Commenting more on the study, author Joshua LaBaer said: "These results demonstrate the importance of unbiased systems approaches because most of these biomarkers would not have been predictable. A critical next step will be to apply this approach to longitudinally collected samples, which will allow us to determine how these markers change over time within the same person."

Bian et al. Immunoproteomic profiling of antiviral antibodies in new-onset type 1 diabetes using protein arrays. Diabetes 2016;65:285–296

Angiogenic microRNAs Are Linked to Diabetic Retinopathy in Type 1 Diabetes

Two microRNAs (miRNAs) termed miR-27b and miR-320a might be associated with the incidence and progression of diabetic retinopathy in type 1 diabetes, according to a report by Zampetaki et al. (**p. 216**). Previously implicated in angiogenesis, the two miRNAs might now represent biomarkers for risk of retinopathy and, with more research, possibly even act as targets for treatment, according to the authors. Using a nested case-control study design, 29 miRNAs were quantified in serum samples of 300 individuals derived from two prospective cohorts of the wider DIRECT (DIabetic Retinopathy Candesartan Trial) program. At baseline, the PROTECT-1 cohort focused on patients with nonproliferative retinopathy, while the PREVENT-1 cohort focused on patients without retinopathy. While the authors found a number of miRNAs that were associated with the incidence and progression of retinopathy, it was miR-27b and miR-320a that were most consistently associated with the incidence and progression of the disease. Indeed, the addition of the two miRNAs to a model of a panel of traditional measurements for diabetes provided increased discriminatory power, further supporting the main observations. To then understand the molecular mechanisms involved, the authors applied a series of proteomics analyses to unravel the potential relationships. Using a variety of endothelial cells, the authors were able to identify thrombospondin-1 (TSP-1), an antiangiogenic protein, as a common target for both miRNAs. Further analysis suggested TSP-1 was a direct target of miR-27b and an indirect target of miR-320a. While pointing out the potential prognostic and diagnostic values of miRNAs, the authors urge some caution about the outcome, suggesting that it is still unclear whether these particular miRNAs are causally involved in retinopathy or represent markers since they are not retina specific and their cellular origins remain to be identified. The authors conclude that: "Taken together, the findings of our study identify miRNA biomarkers for retinopathy in two independent cohorts. These findings await confirmation in larger studies, but our two lead miRNAs may have clinical utility given their established links to angiogenesis."

Zampetaki et al. Angiogenic microRNAs linked to incidence and progression of diabetic retinopathy in type 1 diabetes. Diabetes 2016;65:216–227

JANUARY 2016

diabetes®

1,5-AG as a Biomarker for Cardiovascular Disease and Mortality in Diabetes

An alternative biomarker for hyperglycemia, 1,5-anhydroglucitol (1,5-AG) may have "prognostic value" for long-term complications of diabetes including risk of coronary heart disease, stroke, heart failure, and death. That is according to an ~11,000 strong population-based study by Selvin et al. (**p. 201**) who followed the development of cardiovascular disease and mortality events in the population over a period of ~20 years. At baseline in 1990–1992, none of the participants had cardiovascular disease and ~7% of the population had diabetes. 1,5-AG was then determined in stored serum samples taken at baseline. The marker, normally present in the blood at high levels and derived mainly from diet, typically drops when hyperglycemia is present as the high levels of circulating glucose block its reabsorption in the kidneys. Using modeling approaches, the authors then found that participants with diabetes and low (<6 µg/mL) 1,5-AG had strong increased risks for coronary heart disease, stroke, heart failure, and death in comparison to participants with no diabetes and higher (≥6 µg/mL) 1,5-AG. The outcomes held true even after additional adjustments for a range of factors. Significantly, most of the participants in the group without diabetes were above 10 µg/mL 1,5-AG, a level where risk associations started to disappear. According to the authors, 1,5-AG may add useful prognostic information beyond HbA_{1c}, since it does not require fasting for a successful measurement and reflects hyperglycemic episodes over a period of 1–2 weeks prior to the test—a period that HbA_{1c} cannot resolve. They also suggest that the associations they uncovered relating long-term outcomes and 1,5-AG "adds depth" to the debate around postprandial hyperglycemia being an independent risk factor for cardiovascular outcomes. Commenting more widely on the study, author Elizabeth Selvin stated that: "Open questions remain about the clinical utility of 1,5-AG and how it might improve care in persons with diabetes, but our results suggest that it may have important prognostic value and could complement HbA_{1c} in some settings."

Selvin et al. Association of 1,5-anhydroglucitol with cardiovascular disease and mortality. Diabetes 2016;65:201–208

Cardiovascular Control Following Induced Hypoglycemia Is Likely Reduced in Healthy Adults

Cardiovascular control may be impaired following an episode of hypoglycemia, according to a study by Rao et al. (**p. 209**), raising concerns about repeated episodes of hypoglycemia and ultimately the effects in terms of long-term cardiovascular outcomes in diabetes. In a tightly controlled clinical assessment, the authors exposed 17 healthy volunteers to experimental hypoglycemia and investigated the effects of this on baroreflex function, an autonomic mechanism used to regulate blood pressure. Using a pharmacological approach to control blood pressure during baseline and hypoglycemic periods and insulin infusions to induce hypoglycemia (a hypoglycemic clamp approach), it was possible to then monitor a variety of cardiovascular control parameters in detail. Compared with baseline euglycemic conditions, hypoglycemia decreased baroreflex sensitivity, increased the systolic blood pressure threshold at which baroreflex activation occurs, and decreased the R-R interval response (the time between heartbeats) and its maximal range. Taken in parallel with their previously published data that showed baroreflex sensitivity to be impaired for up to 16 h following hypoglycemia, the authors suggest that this impaired cardiovascular control could be contributing to the adverse clinical outcomes of hypoglycemia. What is not clear from the study are the mechanisms involved in the decrease in sensitivity and, at this stage, the relative roles of hyperinsulinemia and hypoglycemia in the effects, which remain to be determined. In terms of follow-up studies, the authors suggest that such changes should now be studied in individuals with diabetes and also determine how these alterations affect clinical outcomes. Commenting more widely on the study, author Roy Freeman said: "Episodic hypoglycemia is an inevitable consequence of rigorous glycemic control. In this study, we show that homeostatic defense mechanisms against cardiovascular stresses are impaired during hypoglycemia. This impairment may underlie cardiovascular morbidity and mortality associated with hypoglycemia in some patients. Future studies are necessary to delineate the mechanisms that induce the changes in autonomic control of the cardiovascular system, the individuals at risk, the clinical outcomes, and the therapeutic interventions to attenuate these changes."

Rao et al. Baroreflex sensitivity impairment during hypoglycemia: implications for cardiovascular control. Diabetes 2016;65:209–215

DOI: 10.2337/db16-ti01