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Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

Low Rates of End-Stage Renal Disease in Sweden

A 38-year prospective nationwide study in Sweden of younger patients with type 1 diabetes suggests that there has been decreasing cumulative incidence and risk of end-stage renal disease (ESRD) in the country. According to Toppe et al. (**p. 27**), the pattern is likely an effect of improved diabetes care. They also suggest that young age at onset of diabetes is likely to prolong the time until severe complications develop. The study included 18,760 unique patients with type 1 diabetes with a duration of at least 14 years and age at onset between zero and 34 years. They combined data from a series of national registries to estimate the rates of ESRD over the study period. The authors found that cumulative incidence was low at 5.6% after up to 38 years of diabetes duration. They also found a decrease in the incidence of ESRD in patients who were diagnosed more recently, which was independent of diabetes duration. On that basis, they suggest that changes in diabetes care approaches may have contributed to the falling incidence rates. For example, a national recommendation was introduced in the 1980s to intensify insulin treatments and home blood glucose monitoring. They also highlight various aspects of the health care system that might have made a difference. These include *1*) all hospital visits and medicines are free of charge up to age 18 years and *2*) regardless of age, insulin, syringes, and glucose monitoring devices are free of charge in the country. They suggest that discrepancies in the design of health care systems around the world might explain the higher rates of ESRD. Commenting more widely, author Cecilia Toppe told *Diabetes Care*: "It is encouraging for clinicians to see that in recent years fewer patients develop ESRD due to diabetes. These findings provide good arguments for intensified treatment of known risk factors such as lipids, hypertension, and smoking habits."

Toppe et al. Decreasing cumulative incidence of end-stage renal disease in young patients with type 1 diabetes in Sweden: a 38-year prospective nationwide study. Diabetes Care 2019;42:27–31

Biomarkers Predict Risk of Carrying Alleles That Lead to MODY

Two potential nongenetic biomarkers can be used to identify individuals with diabetes and potentially risky *HNF1A* alleles and therefore whether they might have maturity-onset diabetes of the young (MODY). According to Juszczak et al. (**p. 17**), identifying such individuals with MODY (as opposed to other types of diabetes) is important clinically as it can have a significant influence on treatment decisions. Sulfonylureas, for example, can provide excellent control for decades in cases of MODY, according to the authors. However, MODY is often not prioritized by physicians as a diagnosis, and individuals with MODY often remain unrecognized and receive suboptimal care. The conclusions come from an investigation of just under 1,000 individuals with diabetes diagnosed before age 45 years, persistent insulin production, and absence of pancreatic autoimmunity (making them candidates for a form of monogenic diabetes). Blood samples were then used to investigate rare *HNF1A* variants via genomic approaches and functional assessments to explore the relationship between the variants and various circulating proteins. The authors managed to identify 29 individuals who had 25 rare *HNF1A* alleles of which three were novel and 12 considered to be damaging and highly likely to cause MODY. Specifically, they managed to identify various fucosylated *N*-glycans and high-sensitivity C-reactive protein (hs-CRP) that could in turn identify individuals with damaging *HNF1A* alleles and differentiate them from those without damaging *HNF1A* alleles. They suggest *N*-glycan and hs-CRP might be useful tools (in conjunction with current clinical approaches) for initially identifying individuals carrying risky alleles to either subsequently perform genetic tests to give a definitive diagnosis or to treat accordingly. According to author Olga Gornik: "Our previous findings of reduced levels of glycans and hs-CRP in individuals with HNF1A-MODY encouraged us to evaluate their diagnostic potential. We believe that, due to their great value in identifying individuals with damaging *HNF1A* alleles, these novel biomarkers will significantly improve the diagnostic protocol and increase diagnosis rates of this monogenic diabetes."

Juszczak et al. Plasma fucosylated glycans and C-reactive protein as biomarkers of HNF1A-MODY in young adult–onset nonautoimmune diabetes. Diabetes Care 2019;42:17–26

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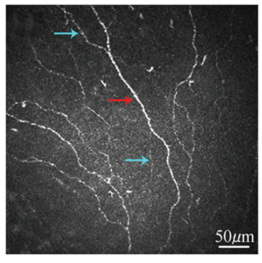
Increases in Diabetes-Related Amputation Rates in the U.S. After Years of Decline

After decades of progress in reducing the numbers of nontraumatic lower-extremity amputations (NLEAs) due to diabetes, it appears from a report by Geiss et al. (**p. 50**) that with the turn of this decade, rates are now on the rise again in the U.S. While they do not go on to specifically identify reasons for the trends, they do point out that the measure can be viewed as an index for wider diabetes care and as such potentially indicates that efforts are needed to improve preventive approaches. The study uses data from the Nationwide Inpatient Sample from the period 2000–2015 to identify hospital discharges involving both diabetes and NLEAs (identified via ICD codes). They further categorize the types of amputation into minor (toe and foot) and major (above foot but below knee and above knee). They found that in terms of rates per 1,000 adults with diabetes, there was a 43% decrease between 2000 (5.4 per 1,000) and 2009 (3.1 per 1,000) but that between 2009 and 2015, rates rebounded by 50% to 4.6 per 1,000 adults. In contrast, in adults without diabetes, already much lower rates fell by 28% between 2000 and 2015. The increases in diabetes-related amputations were driven primarily by increases (62%) in minor amputations, although major amputations also rose (29%). The increases were primarily seen in young and middle-aged adults and were more pronounced in men than in women. The authors stress that the reasons for the increases in rates are unclear, at least from their data. However, they speculate that the increases in amputations may reflect changing clinical practices in terms of favoring earlier minor operations to avoid more serious amputations further down the line (even though there were also increases in major operations).

Geiss et al. Resurgence of diabetes-related nontraumatic lower-extremity amputation in the young and middle-aged adult U.S. population. Diabetes Care 2019;42:50–54

Improvements in Neuropathy After Normalizing HbA_{1c} in Patients With Diabetes

According to Ishibashi et al. (**p. 110**), normalizing HbA_{1c} levels in individuals with type 2 diabetes of short duration to ~5.8% through dietary restrictions and medications improves various microvascular complications, including neuropathy and nephropathy. This was in comparison to standard diabetes care approaches where HbA_{1c} was reduced to 7.0% where there were very few improvements in the same measures. The conclusions come from a study that compared two groups of (each) 38 individuals with type 2 diabetes who were then tracked over 4 years with various measures taken for blood glucose, neuropathy, nephropathy, and clinical and biochemical outcomes, including monthly HbA_{1c} levels. There were also two additional groups evaluated only at baseline: 48 control subjects with normal glucose tolerance and 34 individuals with impaired glucose tolerance. They found that individuals who received intensive treatment for HbA_{1c} normalization managed to achieve mean HbA_{1c} levels of 6.1% over the 4.3 years of follow-up and 5.8% in the last 2 years. These individuals also achieved mean weight reduction of 7.3 kg during the study; 50% returned to impaired glucose tolerance at the end point while 29% achieved normal glucose tolerance. Normalized HbA_{1c} in the individuals with type 2 diabetes also resulted in improved measures of neurophysiological and central nervous function as well as neuropathy outcomes measures. In comparison, individuals with type 2 diabetes who received standard care only saw improvements in relation to vibration perception. Albumin excretion rate also improved but there were no effects on measures of retinopathy. The authors highlight a number of limitations with the study and suggest that longer, larger studies will be needed to confirm the results. Nevertheless, they conclude that normalizing HbA_{1c} levels is more effective than standard care for preventing the development of neuropathy.



Representative confocal microscopic image of corneal subbasal nerve plexus in a patient at baseline with extensive HbA_{1c} control. Red arrow, main nerve fibers; blue arrows, branches.

Ishibashi et al. Improvement in neuropathy outcomes with normalizing HbA_{1c} in patients with type 2 diabetes. Diabetes Care 2019;42:110–118

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