DIABETES IS PRIMARY

TIMELY NEWS AND NOTES FOR PRIMARY CARE PROVIDERS

from the American Diabetes Association

FROM THE JOURNALS

By Max Bingham, PhD

Increased Risks of Infections in Diabetes

According to Carey et al. (*Diabetes Care*, doi.org/cjxp), individuals with diabetes, and especially those with type 1 diabetes, likely carry a substantially increased risk for infections in comparison to the general public. The authors say that the risk of infection attributable to diabetes likely represents a considerable burden for both patients and health care systems. They call for research to explore education and management strategies to reduce poor outcomes and point out that diabetes-related infection rates are only likely to go up as diabetes rates increase and the population ages.

Notable for its large size, the study tracked infection rates and infection-related hospitalizations and mortality in just over 100,000 individuals with diabetes and just over 200,000 matched control individuals without diabetes in England between 2008 and 2015. The researchers then compared rates between individuals with and without diabetes and also between individuals with type 1 versus type 2 diabetes versus control individuals. Notably, they also adjusted the findings for a range of confounding factors such as smoking, BMI, and age—something that previous studies have not consistently accounted for.

Compared to those without diabetes, patients with diabetes had higher rates of infections and hospitalization due to infection. Rate disparities were consistently greater in those with type 1 diabetes than in those with type 2 diabetes compared to control subjects. Bone and joint infections, sepsis, and cellulitis showed the largest disparities between individuals with type 2 diabetes and control subjects, whereas, for those with type 1 diabetes, bone and joint infections, sepsis, and endocarditis showed the greatest disparities versus control subjects. Adjusting for factors such as smoking, age, sex, BMI, and deprivation reportedly did not substantially change the outcomes.

"People with diabetes, particularly type 1 diabetes, are at increased risk of serious infection, representing an important population burden," the authors concluded. "Strategies that reduce the risk of developing severe infections and poor treatment outcomes are under-researched and should be explored."

Dipeptidyl Peptidase-4 Inhibitors for Diabetic Foot Ulcers

Occasionally, drugs can have unexpected effects. When those effects are beneficial, we think that's worth a note. According to Long et al. (*Diabetes*, doi.org/cjxq), dipeptidyl peptidase-4 (DPP-4) inhibitors may be able to improve wound healing in diabetes, including diabetic foot ulcers. In a series of in vitro and in vivo experiments that included a trial in humans, they focus mainly on the DPP-4 inhibitor saxagliptin and its potential ability to improve wound healing. Although they mainly investigate the mechanisms involved, they report that, in a clinical trial, saxagliptin resulted in significantly higher rates of wound healing and reduced time to complete wound closure in comparison to placebo. As a result, they suggest that, with further studies, DPP-4 inhibitors might be considered an option for treating diabetic ulcers.

"Most patients with diabetes experience multiple disease complications," author Hongting Zheng told us. "Current research has revealed that some hypoglycemic agents possess both positive and negative effects on these complications, which inspired us to explore the additional effects of hypoglycemic drugs. Our result demonstrated the additional benefits of DPP-4 inhibitors on diabetic wound healing and provided some evidence for the development of individualized treatment strategies for patients with diabetes and diabetic ulcers."

Gestational Diabetes: Very High Risk for Type 2 Diabetes and Heart Disease

Gestational diabetes mellitus (GDM) is likely to be a significant risk factor for type 2 diabetes, hypertension, and ischemic heart disease, according to Daly et al. (*PLOS Medicine*, doi.org/gctwrz). In a U.K.-based retrospective cohort study, they found that women

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with GDM were nearly 22 times more likely to develop subsequent type 2 diabetes than women who did not experience GDM during pregnancy. Additionally, the risk of developing hypertension or ischemic heart disease was about to two to three times higher after GDM than after a normal pregnancy.

Perhaps the most troubling finding was that follow-up screening of women with GDM for type 2 diabetes and cardiovascular risk factors was "poor," according to the authors. Despite national guidelines recommending screening for type 2 diabetes after GDM, just under 60% of the cohort received any kind of follow-up for diabetes risk in the first year after pregnancy. The rate then dropped to ~40% and 24% in years 2 and 3, respectively.

Equally poor assessment rates for cardiovascular risk were also apparent. For example, although ~80% of the cohort had evidence of blood pressure readings in the first year after pregnancy, that rate dropped by half in years 2 and 3. For serum cholesterol and triglycerides, rates averaged ~28% and 23%, respectively, over the 3 postpartum years.

"Women diagnosed with GDM were at a very high risk of developing type 2 diabetes and had a significantly increased incidence of hypertension and ischemic heart disease," the authors concluded. "Identifying this group of women in general practice and targeting cardiovascular risk factors could improve long-term outcomes."

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TREATMENTS + THERAPIES

Subcutaneous Exenatide Delivery Device Proven in Phase 3 Trial

A matchstick-sized subcutaneous pump has proven successful at delivering exenatide, a glucagon-like peptide-1 receptor agonist, over 39 weeks. The drug delivered via the device resulted in reduced A1C and weight in patients with type 2 diabetes and was found to be safe, according to Rosenstock et al. (*Diabetes Care*, doi.org/cjx5). The findings come from the phase 3 FREEDOM-1 randomized, controlled trial that compared exenatide delivered via the device (termed ITCA 650) to use of the device alone (placebo).

The authors report that the drug/device combination resulted in mean A1C changes at 39 weeks ranging from –1.1 to –1.2%, depending on drug dose, whereas the placebo device resulted in a change of –0.1% over the same period. Weight changes versus placebo ranged from –2.3 to –3.0 kg depending on drug dose.

"Continuous subcutaneous delivery of exenatide with ITCA 650 may help poorly controlled patients with type 2 diabetes achieve better glycemic control," author Michelle Baron told us. "The drug/device combination may also help address the challenge of medication adherence, a significant unmet need in the treatment of chronic diseases like diabetes, since no action on the part of the patient is needed to administer treatment."

An additional open-label study of the drug/device combination from the same group (*Diabetes Care*, doi.org/cjx6) included patients with type 2 diabetes who were ineligible for the FREEDOM-1 trial because of very poor glycemic control (A1C >10%). According to the authors, the findings suggest that it might be possible to achieve a mean A1C reduction of 2.8% and a weight reduction of 1.2 kg over 39 weeks using the drug/device combination in such patients.

So far, ITCA 650 developer Intarcia Therapeutics, Inc., of Boston, Mass., has given no indication of when this investigational device might be market-ready. There are, however, indications that the company has applied for U.S. Food and Drug Administration (FDA) approval for the device (bit.ly/2lkF1YN and bit.ly/2ElWmKN).

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MARKETPLACE

Diabetes Foot Ulcers: A Novel Dressing and Two New Therapeutic Devices

UrgoStart Contact, a novel wound dressing containing sucrose octasulfate from Laboratoire Urgo Medical (Chenôve, France), might be able to reduce neuroischemic diabetic foot ulcers. According to Edmonds et al. (*Lancet Diabetes & Endocrinology*, doi.org/cjxx), wound closure occurred just under 50% of the time with the dressing compared to a 30% wound closure rate for control subjects on standard care.

However, according to an accompanying editorial comment (doi.org/cjx3) and a series of comments in a Medscape summary (wb.md/2EkD0FC), although the trial's design and findings of improved wound healing are positives, there might be limits in terms of generalizability to other types of diabetic foot ulcers.

In other foot news, the U.S. Food and Drug Administration (FDA) has approved two devices for the treatment of diabetic foot ulcers. The first, called the dermaPace from Sanuwave Health, Inc. (Suwanee, Ga.), is an extracorporeal shockwave system that mechanically stimulates wounds to promote healing. According to an FDA press release (bit.ly/2A5Z2by), approval of the device was based on the results of two multicenter randomized, controlled trials showing that, by 24 weeks, use of the device resulted in a 44% wound closure rate. In comparison, usual care (with sham shockwave therapy) resulted in a 30% closure rate.

The second device, called the Integra Omnigraft Dermal Regeneration Matrix (Integra LifeSciences Holdings Corp., Plainsboro, N.J.) was first approved in 1996 for the treatment of life-threatening burns, but has now been given a new indication for the treatment of certain types of foot ulcer, according to an FDA announcement (bit.ly/2DUZrU5). Reportedly a mix of silicone, cow collagen, and shark cartilage, the device is placed over an ulcer to help new skin and tissue develop underneath. New clinical data relating to ulcer healing suggests the device can achieve healing in 51% of patients, compared to a 32% healing rate in patients receiving standard care for foot ulcers.

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Insulin Tolerance Test Predicts Efficacy of Liraglutide in Type 2 Diabetes

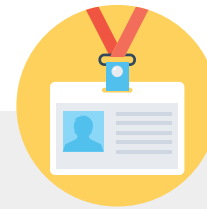
According to a report from Germain et al. (*Diabetes Research and Clinical Practice*, doi.org/cj3x), only 35–40% of patients with type 2 diabetes who receive a glucagon-like peptide-1 (GLP-1) receptor agonist have well-controlled diabetes 1–2 years after initial treatment. As a possible solution, the authors say that the velocity of C-peptide decrease in an insulin tolerance test might predict whether a patient with type 2 diabetes will respond over the long term to liraglutide (a GLP-1 receptor agonist). They suggest that the test can be used to discriminate before initiation of liraglutide between individuals likely to be nonresponders and those likely to experience A1C and weight reduction with the therapy.

In a prospective study, the authors treated 80 patients with type 2 diabetes with liraglutide for up to 2 years, measuring various parameters, including A1C and weight, at baseline and at regular time points thereafter. At baseline, they also administered an insulin tolerance test to measure the velocity of C-peptide decrease.

They found that the percentage of patients who achieved controlled diabetes (A1C <7.0%) after 2 years was 35%. After looking at a range of measures, only the rate of C-peptide decrease during the insulin sensitivity test correlated with A1C reduction during the follow-up period. Specifically, individuals who had a 50% reduction in C-peptide in <120 minutes subsequently had significant benefit in terms of A1C reduction from the liraglutide therapy; those who did not achieve that C-peptide decrease threshold had unmodified A1C levels despite the liraglutide treatment. In terms of the predictive power, the relationship had 82% sensitivity and 80% specificity, the authors reported.

New Sodium–Glucose Cotransporter 2 Inhibitor Gains FDA Approval

The FDA has given its approval to the sodium–glucose cotransporter 2 (SGLT2) inhibitor ertugliflozin for glycemic control in adults with type 2 diabetes (reut.rs/2BJPuE7). Co-developed by Merck and Pfizer, the new SGLT2 inhibitor is now available in the United States in two doses (5- and 15-mg tablets) as a once-daily, single therapy oral agent in combination with diet and exercise. In addition, approval was also given to two combinations of ertugliflozin with either metformin or sitagliptin.



CONFERENCE SPOTLIGHT

Continuous Glucose Monitoring Recommendations Published

A panel of experts that convened in February 2017 at the Advanced Technologies and Treatments Congress to evaluate continuous glucose monitoring (CGM) in diabetes has now published its recommendations (*Diabetes Care*, doi.org/gcm54m). According to authors Danne et al., the purpose of the international expert panel was to provide guidance for clinicians, patients, and researchers on the use, interpretation, and reporting of CGM data in both clinical care and research.

A central theme of their recommendations is that CGM can help to address the shortcomings of A1C testing (which reflects 3-month glycemic control but not acute hypo- and hyperglycemic events) and self-monitoring of blood glucose (which provides glucose data only at discrete time points), but has limitations due to a current lack of standardization of the technology.

The panelists made a series of recommendations regarding different approaches to CGM to guide diabetes management and assess outcomes. They stress the need for minimum performance requirements for CGM systems and the need for a standardized definition of hypoglycemia. They also consider approaches for assessing glycemic variability and the concept of "time spent in range." Finally, they consider the visualization, analysis, and documentation of key CGM metrics, suggesting 14 key measures for assessing glycemic control.

They conclude: "In clinical practice, the advanced metrics of assessing continuous glucose data presented here are appropriate as outcome parameters that complement HbA_{1c} for a wide range of patients with diabetes and should be considered for use to help them improve glycemic control provided that appropriate educational and technical support is available."

CODING, REGULATIONS, + REIMBURSEMENTS

MEDICARE EXTENDS COVERAGE TO TWO DIABETES DEVICES

The Freestyle Libre continuous glucose monitoring device (Abbott, Abbott Park, Ill.), which gained approval in the United States last year, is now available for Medicare patients. Coverage reportedly extends to all Medicare patients with diabetes who use insulin and meet certain eligibility criteria. For non-Medicare patients, the device is available through major retail pharmacies. More information is available via a press release from the company (prn.to/2CEOFAT).

Meanwhile, the Omnipod insulin management system (Insulet Corporation, Billerica, Mass.) may now be covered under the Medicare Part D (prescription) program. This means Part D carriers can now add the system to their formularies. According to Insulet, most plans should have coverage in place by early 2019. More information is available from Insulet (bit.ly/2EnKJD8).

ADA NEWS

MENTAL HEALTH REFERRAL DIRECTORY AVAILABLE

The American Diabetes Association (ADA) recommends that diabetes care providers routinely screen patients for psychosocial issues and make referrals to mental health providers with expertise in supporting the behavioral and psychological needs of people with diabetes. Now, ADA is developing an online directory to help health care providers locate such professionals in their community. The searchable directory will be available at professional.diabetes.org/mhdirectory.

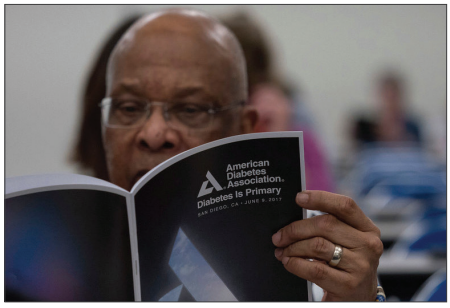
PRIMARY CARE PRECONFERENCE SCHEDULED FOR 2018 SCIENTIFIC SESSIONS

The ADA Diabetes Is Primary continuing education program will take place on Friday, 22 June 2018, in advance of the 78th Scientific Sessions in Orlando, Fla. This interactive educational initiative, aimed at the primary care community, will offer information needed to improve patient outcomes and enhance patient engagement.

The program will include a panel discussion on new ADA guidelines related to cardiovascular risk, an update on the latest ADA *Standards of Medical Care in Diabetes*, and presentations on psychosocial care, prediabetes, diabetic kidney disease, and obesity management. Presentations will be delivered in an interactive format, and attendees will be able to follow along on tablets, weigh in on case studies, and access additional resources online.

Diabetes Is Primary will offer up to 6 continuing education (CE) credits.

"It can be challenging to keep up with the rapid pace of improvements in diabetes care," said Eric L. Johnson, MD, chair of the Association's Primary Care Advisory Group. "We hope clinicians leave Diabetes Is Primary with the confidence to incorporate these latest updates into their daily practice."



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The $100 registration fee includes admission, CE credits, course materials, and lunch. Scientific Sessions attendees can sign up for the Diabetes Is Primary preconference through the online Scientific Sessions registration process. Clinicians not attending the Scientific Sessions can register at professional.diabetes.org/primary.

To learn more about ADA's continuing education opportunities, including Diabetes Is Primary events in your community, please visit **professional.diabetes.org/ce**.