DIABETES IS PRIMARY

TIMELY NEWS AND NOTES FOR PRIMARY CARE PROVIDERS

from the American Diabetes Association

FROM THE JOURNALS

By Max Bingham, PhD

New Guidance on Exercise and Type 2 Diabetes

The idea that exercise should be prescribed to patients with type 2 diabetes has been around for a while, but is it enough simply to tell patients to get more exercise and send them on their way? The answer is no, and a new position paper from the European Association of Preventive Cardiology explains why.

According to Kemps et al. (*European Journal of Preventive Cardiology*, doi.org/c2b5), exercise can improve many of the metabolic and cardiovascular issues facing people with type 2 diabetes. However, simply telling them to get more exercise is not enough. Rather, specific exercise goals should be prescribed to reach targets that are set with each patient. Basically, this means personalizing exercise programs for all patients.

But how? The position paper sets out practical recommendations for clinicians to follow to help patients with exercise, detailing such topics as patient motivation and how to incorporate exercise into daily routines. The authors also cover goal-setting and how to design individualized exercise training programs. They discuss how different types of exercise (e.g., aerobic or resistance training) should be used in relation to specific goals. Perhaps most importantly, they address the failure of some patients to respond to exercise and offer recommendations for addressing that issue.

The paper also provides practical steps to addressing common barriers to exercise, but also notes that, in some circumstances, exercise may carry risks for acute cardiovascular problems.

"Just advising patients to exercise, which is what doctors typically do, is not enough," said lead author Hareld Kemps. "Patients must be assessed for comorbidities, risks related to exercise, and personal preferences. This will be cost-effective in the long run, so we have to wake up policymakers and health care insurers to pay for it. That needs clinicians to take the lead and call for programs to be reimbursed."

In the meantime, Kemps said, "There are also steps patients can take without needing to see a doctor first, such as interrupting sitting time and doing moderate exercise like walking and cycling."

Even Prediabetes Increases Cardiovascular Disease Risk

According to Bancks et al. (*Diabetes Care*, doi.org/c2b7), middle-aged individuals who receive a diagnosis of prediabetes should be strongly encouraged to make lifestyle changes to avoid both full-blown diabetes and cardiovascular disease (CVD) later in life, as they are at a substantially increased absolute risk of progression to both. Additionally, the authors suggest that this increased risk strongly supports the monitoring of glucose levels during middle age.

The conclusions come from an analysis of data from seven observational studies targeting longitudinal cardiovascular outcomes, with cohorts that included men and women of both white European and African-American populations in the United States. Whereas previous studies looking at this issue have had less representative population groups, this one should be generalizable to broader U.S., and perhaps European, populations.

The sample included 19,360 individuals who did not have a previous CVD event but did have blood glucose measurements at baseline. Risk for a CVD event was then determined according to bands of blood glucose values that broadly corresponded to normoglycemia, prediabetes, and diabetes.

The authors found that risks for a CVD event from 55 to 85 years of age ranged from 15 to 39% for women and from 21 to 47% for men and increased along with glucose levels. Having prediabetes or diabetes substantially raised the risk of future CVD events.

"We know that having diabetes increases the risk of developing cardiovascular disease, so, in our study, we wanted to determine what the absolute risk or probability of developing heart disease was for people who were

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Max Bingham, PhD, is a science writer and editor in Rotterdam, Netherlands. He can be reached on Twitter at @maxbingham.

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only at a prediabetic level of blood sugar," lead author, Michael Bancks said. "Our study provides further evidence that, if you can avoid diabetes, you may be able to stave off cardiovascular disease. Prediabetes should serve as a red flag to doctors to closely monitor their patients' blood sugar to try to prevent diabetes through lifestyle interventions like better diet and increased physical activity, and if necessary, with pharmacologic therapies."

TREATMENTS + THERAPIES

Sodium–Glucose Cotransporter 2 Inhibitors: Developments, Risk Assessments, and Approvals

A meta-analysis by Zelniker et al. (*The Lancet*, doi.org/gfhx6s) of major cardiovascular outcomes trials of sodium–glucose cotransporter 2 (SGLT2) inhibitors for type 2 diabetes has concluded that reductions in a series of adverse cardiovascular and renal outcomes can be expected from SGLT2 therapy. Despite evident differences among individual study outcomes, both the authors and an accompanying commentary (doi.org/gfhx6t) suggest that SGLT2 inhibitors should be considered as first-line therapy after metformin for most people with type 2 diabetes.

Meanwhile, the SGLT2 inhibitor empagliflozin can limit nephropathy and loss of kidney function in Asian adults with type 2 diabetes and cardiovascular disease, according to Kadowaki et al. (*Journal of Diabetes Investigation*, doi.org/c2b8). Their conclusions are the result of a subanalysis of data from the EMPA-REG OUTCOME trial.

Moving on to the SGLT2 inhibitor canagliflozin, we learn from Fralick et al. (*Annals of Internal Medicine*, doi.org/c2b9) that, for the treatment of type 2 diabetes, the drug is not associated with increased fracture risk in comparison to glucagon-like peptide 1 (GLP-1) receptor agonists. And, according to another analysis of data from the CANVAS Program trial, Zhou et al. (*Stroke*, doi.org/c2cb), the drug might have protective effects against stroke in type 2 diabetes. Meanwhile, the U.S. Food and Drug Administration has approved canagliflozin for the prevention of a range of adverse heart outcomes in type 2 diabetes (bit.ly/2TDiQ0k), making it the first oral diabetes drug to receive this indication.

As with any pharmacological therapy, there is always a balance between risk and benefit, and the same is true for SGLT2 inhibitors. To better understand the risks involved, Ueda et al. (*BMJ*, doi.org/c2cc) used a register-based cohort study to compare real-life risks of SGLT2 inhibitors with those of GLP-1 receptor agonists. They found an increased risk of lower-limb amputation and diabetic ketoacidosis with SGLT2 inhibition, but no increased risk for a range of other serious adverse events that previously raised concerns.

Liraglutide: Real-World Data Support Cardiovascular Risk Reduction

Previous trials have shown that the GLP-1 receptor agonist liraglutide can reduce the risk of major adverse cardiovascular events (MACE) in type 2 diabetes. Now, an analysis of registry data by Svanström et al. (*The Lancet Diabetes & Endocrinology*, doi.org/c2cd) has found the same effects or liraglutide compared to the use of dipeptidyl peptidase 4 inhibitors in routine clinical practice.

"Our study provides support for the cardiovascular effectiveness of liraglutide among a broader unselected group of patients, providing important confirmatory evidence from routine clinical practice," author Björn Pasternak said. "We believe it may be of interest to drug regulators, clinical guidelines, physicians, and patients."

Liraglutide may also reduce risks of MACE and death in older patients with diabetes, according to Gilbert et al. (*Annals of Internal Medicine*, doi.org/c2cf). The findings, from a post-hoc analysis of the LEADER trial, suggest that the drug can reduce the risk in terms of the frequency of MACE by 29–34% in older patients.

MARKETPLACE

FDA Approves Placement of Senseonics' Continuous Glucose Monitoring Device by Certified Providers

The U.S. Food and Drug Administration (FDA) has issued a series of approvals in relation to Senseonics' Eversense continuous glucose monitoring (CGM) system in the months since it initially approved the device in mid-2018. Whereas the majority of these decisions relate to hardware tweaks and testing, one approval gives the nod to a wider group of trained health care providers, including nurse practitioners and physician assistants, to fit and remove the device. Previously, only trained physicians could carry out the procedure.

"We are pleased with this FDA approval, we can now include nurse practitioners and physician assistants in the growing list of diabetes care professionals who can be certified to place the Eversense CGM system," Senseonics President and Chief Executive Office Tim Goodnow said in a statement (bit.ly/2MO5UlQ). "We believe that allowing additional health care providers to perform the in-office placement procedure for Eversense CGM will enable broader access to patients for this long-term diabetes management technology."

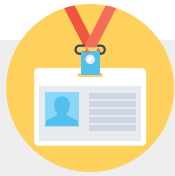
Ready-to-Use Glucagon Rescue Pen Moves Closer to Approval

Xeris Pharmaceuticals has issued a statement (bit.ly/2S731SY) announcing that the FDA has accepted a new drug application for review of the company's ready-to-use glucagon rescue pen designed for use during episodes of severe hypoglycemia in people with diabetes. If approved, the pen would become the first available glucagon rescue product that does not require reconstitution of the glucagon before administration, significantly simplifying the administration of glucagon in emergency situations. The FDA is expected to complete its review by 10 June 2019.

Research Continues Into Skin Autofluorescence to Predict Type 2 Diabetes Risk

A skin test for future diabetes risk? Actually, that possibility has been the topic of study for years, and the latest results, from van Waateringe et al. (*Diabetologia*, doi.org/cxb4), pushes the technique closer to reality, especially since the machine needed for the test is already commercially available.

The study shows that skin autofluorescence, measured noninvasively, predicts future risk of type 2 diabetes, cardiovascular disease, and mortality independently of a series of traditional risk factors. As a result, the authors suggest that the approach could be used as an initial tool to identify individuals at increased risk before performing more rigorous testing such as A1C measurement. They even suggest that the approach could be used in nonmedical or public settings such as pharmacies or supermarkets as a first indicator of risk.



CONFERENCE SPOTLIGHT

Sodium–Glucose Cotransporter 2 Inhibitors Featured at American Heart Association Meeting

The American Heart Association's 2018 Scientific Sessions, which were held in Chicago in November 2018, featured the results of several important diabetes-related trials.

Notable among those presented was the DECLARE-TIMI 58 trial, which looked at the cardiovascular safety of dapagliflozin, a sodium–glucose cotransporter 2 (SGLT2) inhibitor used to treat type 2 diabetes (*New England Journal of Medicine*, doi.org/cw4m). Although dapagliflozin did not result in reduced rates of major adverse cardiovascular events in patients with type 2 diabetes, it did yield significant reductions in hospitalizations due to heart failure—a notable result because it is in line with outcomes for other SGLT2 inhibitors.

A smaller featured trial was the EMPA-HEART Cardiolink-6 study that looked at how the SGLT2 inhibitor empagliflozin affects left ventricular structure and function, which might explain how SGLT2 inhibitors improve cardiovascular health. The abstract is available at bit.ly/2D9vQEd.

Initial results of the EMPRISE study were also released, showing that empagliflozin was associated with significant reductions in risk (44% relative risk reduction) for hospitalization for heart failure compared to dipeptidyl peptidase 4 inhibitors. This study was notable in that it was based on real-world data from patients with type 2 diabetes in routine

clinical practice in the United States. The abstract is available at bit.ly/2UHnJpy, and a related press release providing more detail is available from bit.ly/2MR5H17.

Of course, there were many other presentations at the conference. Abstracts can be perused at bit.ly/2DSwOWW.

And Finally . . . Ultrasound for Diabetes Screening

A study presented at the Radiological Society of North America annual meeting (held in November 2018 in Chicago, Ill.) suggests that a specific shoulder muscle that appears unusually bright on ultrasound might predict diabetes. Building on years of clinical experience, the researchers found that, in a blinded review of 186 patient images by two radiologists, they could achieve an 89% positive predictive value and 77% sensitivity where patients were correctly designated as either "suspected" or "definite" for having diabetes. A press release describing the research is available at bit.ly/2StdYxA, where there are also additional resources, including the conference abstract, the presentation slides, and videotaped explanations.

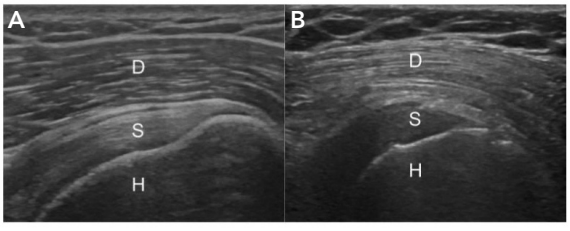


FIGURE 1. Images of the shoulder showing reversal of the rotator cuff to deltoid gradient. Image A displays the normal gradient of the deltoid muscle to the supraspinatus tendon. Image B shows reversal of the normal gradient in a patient with type 2 diabetes. D, deltoid; S, supraspinatus; H, humerus

ADA NEWS

ASSOCIATION FOCUSES ATTENTION ON THERAPEUTIC INERTIA

"Overcoming Therapeutic Inertia: Accelerating Diabetes Care FOR_LIFE" was the title of a full-day summit hosted by the American Diabetes Association (ADA) on 28 November 2018 in Arlington, Va. More than 130 key stakeholders from across the spectrum of health care attended, including clinicians, researchers, payors, and representatives from health systems, industry, diabetes nonprofit organizations, and technology companies. The summit was the first step in a planned multi-year campaign to address and provide solutions to the long-standing problem of therapeutic inertia in diabetes care. The project is supported by Abbott, AstraZeneca, Dexcom, Janssen, Lilly, Medtronic, Merck, Novo Nordisk, and Sanofi.

To maintain the momentum gained from the summit, the ADA plans to publish a "Summary of Proceedings" and distribute it to all attendees and all ADA journal subscribers. This summary will include key points from the summit, plans for the creation of work groups to begin solving key identified problems, and a high-level roadmap of next steps. The latest information and updates on this project will be made available online at professional.diabetes.org/therapeuticinertia.

ADA LAUNCHES PRECISION MEDICINE IN DIABETES INITIATIVE

The ADA recently announced a new initiative—Precision Medicine in Diabetes. With initial collaboration among ADA, the European Association for the Study of

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Diabetes, and the National Institute of Diabetes and Digestive and Kidney Diseases, this is the first organized precision medicine initiative among major diabetes associations.

A steering committee co-chaired by Paul Franks, PhD, of Lund University in Lund, Sweden, and Stephen Rich, PhD, of the University of Virginia in Charlottesville, will lead the initiative, focusing on developing a strategy for the clinical implementation of precision diabetes medicine. The goal of the initiative is to engage diverse stakeholders to realize the promise of precision diabetes medicine to shift diabetes care and, ultimately, promote the prevention of diabetes and its complications and improve treatment for those with diabetes.

Although the initiative is just getting started, the collaborating organizations anticipate that, over the next 5 years, it will lead to the development of consensus on precision diabetes medicine, as well as initiation of complementary activities, including:

- The use of data from "-omics" assays, electronic health records, patient registries, digital imaging technologies and/or wearable devices that address contexts of use relevant to diabetes (i.e., diagnostic stratification and revised classification; prevention, prediction, and management of diabetes; and therapeutic contraindications and responses)
- Clinical implementation of precision diabetes medicine, considering:
  - Cost-effectiveness
  - Legal, social, psychosocial, and ethical factors
  - Regulatory consensus
  - Education
- Public engagement
- Research initiatives focused on precision diabetes medicine

A symposium highlighting precision medicine in diabetes will be held at the ADA's 79th Scientific Sessions in San Francisco, Calif., in June, and interested parties are encouraged to attend and to stay tuned for future opportunities to engage in this initiative. For more information, visit professional.diabetes.org/content-page/precision-medicine.