



DIABETES IS PRIMARY

TIMELY NEWS AND NOTES FOR PRIMARY CARE PROVIDERS

from the American Diabetes Association

By Max Bingham, PhD

FROM THE JOURNALS.....

Diabetes and Surgery Risks

A diagnosis of diabetes and increased A1C levels raise the risk of adverse outcomes after surgery, according to Yong et al. (*Diabetes Care*, doi.org/cn3v). Consequently, they suggest that patients with diabetes or elevated A1C should be treated as high-risk patients, and it is probably time to consider intervention studies on pre- and postoperative glycemic management in patients with diabetes.

The prospective study involved 7,565 surgery patients and examined the relationship between diabetes diagnosis/increased A1C and 6-month mortality. Approximately one-third of the patients had diabetes at baseline and another one-third had prediabetes, with the remainder normoglycemic. Compared to those with normoglycemia, the group with diabetes had an increased risk of mortality 6 months after surgery and elevated risks for a range of secondary outcomes, including major complications and intensive care unit admission. When A1C was assessed as a continuous variable, every additional percentage point increased the risk of adverse outcomes. Meanwhile, prediabetes conferred no increased mortality risk after surgery compared to normoglycemia.

“Diagnosis of diabetes identifies those at higher risk of morbidity and mortality after surgery in general, and not just following cardiac surgery,” author Elif Ekinci said. “Now that we have a much deeper understanding of the adverse surgical outcomes in people with diabetes, we can begin to think about the interventions that we need to plan in order to prevent these outcomes.”

Intensive Lifestyle Intervention and Disability in Type 2 Diabetes

A long-term lifestyle intervention program for overweight or obese adults with type 2 diabetes may be able to reduce long-term disability, according to Gregg et al.

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(*Diabetes Care*, doi.org/cn3w). In their trial, 5,145 adults were randomized to participate in a 10-year intensive lifestyle intervention program or a much less intensive approach involving diabetes support and education. A variety of assessments were performed annually to gauge physical function, activity, and disability. The intensive approach resulted in a lower incidence of physical disability and more disability-free years than the less intensive approach.

“These findings indicate that an intensive lifestyle intervention that focuses on caloric restriction and increased physical activity can reduce long-term physical disability and has an impact on disability-free life expectancy despite not affecting total life expectancy,” write the authors. “Given the continued high prevalence of diabetes in the U.S. and the increasing life spans of adults with diabetes, these findings have important implications for the compression of morbidity and improvement of quality of life among overweight and obese adults with type 2 diabetes.”

Few Adults Follow Nutrition and Lifestyle Recommendations to Avoid Diabetes

According to a report by Siegal et al. (*Diabetes Care*, doi.org/cn3x), few adults in the United States engage in lifestyle behaviors that are known to reduce type 2 diabetes risk. The authors examined dietary and leisure-time physical activity data from the 2007–2012 National Health and Nutrition Examination Surveys (NHANES) for nearly 3,700 individuals who were >20 years of age and did not have diabetes. They found that just 3.1% of these individuals met the majority of type 2 diabetes risk reduction targets. With regard to food intake, between 13 and 54% met targets for food groups such as fruit, vegetables, grains, meats, and fats. Meanwhile, 38% met the physical activity target of 150 minutes/week, and nearly 60% met weight goals.

According to the authors, the results suggest there is “a vast opportunity to reduce type 2 diabetes risk among people with prediabetes as well as the general population in the country through improvement of these modifiable dietary and physical activity behaviors.”



TREATMENTS + THERAPIES

Drugs Roundup

Glucagon-like peptide 1 (GLP-1) receptor agonists were found in a meta-analysis by Tran et al. (*Diabetes, Obesity and Metabolism*, doi.org/gcwxx4) to be superior to dipeptidyl peptidase 4 (DPP-4) inhibitors for weight and A1C reduction, but at the cost of increased gastrointestinal symptoms and potential adherence issues (but not increased hypoglycemia). The authors suggest that replacing DPP-4 inhibitors with GLP-1 receptor agonists might be worth considering for patients not achieving glycemic control with a DPP-4 inhibitor.

Meanwhile, DPP-4 inhibitor use has been tied to a small increased risk for inflammatory bowel disease (IBD). A population-based cohort study by Abrahami et al. (*BMJ*, doi.org/cn4d) that included >140,000 patients with type 2 diabetes in the United Kingdom found that risk for IBD was elevated in patients using a DPP-4 inhibitor compared to those using other antidiabetic medicines. Although the authors stress that the absolute risk appears low and that their findings should be confirmed, they write that health care providers should be aware of the potential association.

It's not all bad news for DPP-4 inhibitors. A study by Hong et al. (*Diabetes Care*, doi.org/cn4f), found that DPP-4 inhibitors were not associated with an increased risk of acute pancreatitis in older adults with diabetes compared to two other second-line diabetes drugs. However, they found that patients with cardiovascular disease (CVD) who use a DPP-4 inhibitor might be at increased risk of acute pancreatitis, although the authors urged caution on this point for a variety of reasons. "Our findings should not alter physicians' treatment decision for patients with diabetes in general, but caution may be warranted in older patients with clinical CVD at higher risk for pancreatitis," they wrote.

In other recent reports, we learn that insulin glargine 300 units/mL combined with a DPP-4 inhibitor is effective in terms of reducing A1C and associated with less hypoglycemia compared to a combination of insulin glargine 100 units/mL and a DPP-4 inhibitor (Yale et al., *PLoS One*, doi.org/cn4g). Meanwhile, canagliflozin, a sodium–glucose

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β-Blockers and All-Cause Mortality in People With Diabetes

β-Blockers may be associated with increased risk of all-cause mortality in people with diabetes, and especially those with coronary heart disease (CHD), according to Tsujimoto et al. (*Mayo Clinic Proceedings*, doi.org/cn34). Their findings come from a prospective cohort study that used 1999–2010 NHANES data and additional prospective follow-up to the end of 2011. The authors identified nearly 3,000 participants with diabetes and found that all-cause mortality over a 5- to 6-year period was significantly higher in those taking a β-blocker than in those who were not, with this effect especially pronounced in those who also had CHD. Meanwhile, for nearly 15,000 participants without diabetes, all-cause mortality was reduced in those taking a β-blocker versus those who were not.

The efficacy of β-blockers for reducing mortality has been shown in numerous trials, some of which took place decades ago. However, their efficacy in specific situations or conditions such as diabetes has not been investigated thoroughly, the authors said. While acknowledging several limitations of their study, they concluded that "[further] studies are needed to assess whether β-blockers are effective in reducing mortality and coronary events in diabetic patients receiving optimal medical treatment."

Pedometers Can Increase Exercise Over the Long Term

Wearing a pedometer, combined with receiving motivational support, can result in increased physical activity in adults, and significantly, these effects remain even after 3 or 4 years, according to a study by Harris et al. (*PLoS Medicine*, doi.org/gdcnhv). As a result, the authors suggest that the approach might help to address physical inactivity challenges that are persistently linked to noncommunicable diseases such as diabetes. Building on previous work showing that pedometers and 12 weeks of support led to increased step counts at 12 months, the authors looked again at physical activity

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Technology Roundup

Closed-loop artificial pancreas systems are safe and effective, according to a systematic review and meta-analysis by Bekiari et al. (*BMJ*, doi.org/cn39), and result in users spending ~10% more time in near-normoglycemia and less time with either hyper- or hypoglycemia than control subjects using other forms of insulin therapy. However, the authors of the review and an accompanying editorial (*BMJ*, doi.org/cn4b) say rigorous evidence is still needed regarding various aspects of these systems.

Meanwhile, children as young as 7 years of age with type 1 diabetes might benefit from a closed-loop system developed by Medtronic, according to a study by Wood et al. (bit.ly/2HH3ceB) that was presented at the Endocrine Society's ENDO 2018 conference in Chicago, Ill. Researchers found that all age-groups tested with the system (children, adolescents, and adults) experienced reductions in A1C and significant increases in time spent in their target blood glucose range over 3 months. The system is currently approved for use in patients with type 1 diabetes who are ≥14 years of age.

The U.S. Food and Drug Administration (FDA) has approved several devices in recent months, including Medtronic's Guardian Connect continuous glucose monitoring (CGM) system, which can reportedly alert users to high and low glucose events up to 60 minutes in advance (bit.ly/2rcRDom). The FDA also approved Dexcom's G6 integrated CGM system (bit.ly/2KstRxB) and gave pre-market notification clearance for DarioHealth's glucose meter (bit.ly/2y1ukEO) for use with Apple's iPhone 7 and later models. Senseonics has received a unanimous vote from an FDA advisory committee in support of the safety and effectiveness of its Eversense implantable CGM device (bit.ly/2JH85EY). Other devices receiving FDA approval include the Glooko insulin dosing system (bit.ly/2l2VSQD) and a long-acting insulin pen from Sanofi (prn.to/2Mlch5I).

Cost-Effectiveness of CGM Device Evaluated

Dexcom's G4 CGM device is likely cost-effective in terms of delivering improved glucose control, reducing nonsevere

hypoglycemic events, and reducing glucose test strip use, according to a study by Wan et al. (*Diabetes Care*, doi.org/cn4c). In a 6-month trial involving 158 patients with type 1 diabetes, they compared clinical and quality-of-life outcomes for CGM use versus daily use of glucose test strips to assess cost-effectiveness. At 6 months, CGM use had cost \$11,032, whereas use of test strips had cost \$7,236, with the cost difference mainly due to the upfront cost of the CGM device. Although costing more, CGM use resulted in improved clinical outcomes, including better glucose control (A1C) and reduced hypoglycemia. Through subsequent statistical modeling, the authors found that CGM use increased quality-adjusted life years (QALYs) and that the cost per QALY gained was just under \$100,000—well below the threshold used by many health insurance plans to determine whether they will cover a new product. When the authors factored in using the system for 10 days instead of the 7 days approved by the FDA, the cost per QALY gained dropped to \$33,000.

"If you map out the lifetime of a patient, it's impressive. The CGM adds years of life and years of quality life," author Elbert Huang said. "While it does cost additional money, the costs saved by lower risk of complications offset the upfront costs."

With sensors now coming out with extended life (Dexcom's newer G6 sensor is approved for 10 days, and the Eversense implantable sensor is good for 90 days), costs will likely fall further, which may lead to expanded insurance coverage.

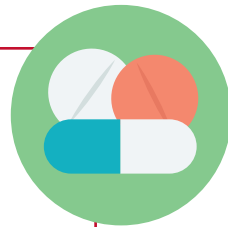
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cotransporter 2 (SGLT2) inhibitor used to reduce blood glucose levels in diabetes, can reportedly reduce the risk of death and heart failure from CVD (Rådholm et al., *Circulation*, doi.org/cn4h). The results of another study comparing canagliflozin to other antidiabetes drugs largely point in the same direction for cardiovascular outcomes (Patrono et al., *BMJ*, doi.org/cn4j). We also learn that a metformin/sitagliptin combination can reportedly improve glucose, insulin, and cholesterol measures in women with prediabetes and recent gestational diabetes (Elkind-Hirsch et al., *Endocrine Practice*, doi.org/cn4m). Novo Nordisk has apparently seen success with its oral semaglutide in the first of 10 phase 3 trials (bit.ly/2HJyDEW) showing that use of the drug improved A1C and resulted in significant weight loss in adults with type 2 diabetes. Similar positive outcomes relating to the SGLT2 inhibitor ertugliflozin were also reported recently (Aronson et al., *Diabetes, Obesity and Metabolism*, doi.org/cn4n).

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levels at either 3 or 4 years. The physical activity gains at 1 year were maintained over the longer term.

"We knew that pedometers could improve physical activity levels in the population in the short-term, but long-term health benefits require sustained increases in physical activity levels," author Tess Harris said in a statement (bit.ly/2Ksevcd). "We have shown that short, simple pedometer-based walking interventions, whether delivered by post or with advice and support from practice nurses, can lead to greater objectively measured physical activity levels 3 to 4 years later."



ADA NEWS

INSULIN AFFORDABILITY: ADA WORKING GROUP REPORTS RECOMMENDATIONS

An American Diabetes Association (ADA) working group charged with investigating insulin affordability in the United States recently reported its conclusions and recommendations (Cefalu et al., *Diabetes Care*, doi.org/cqr6). List prices (those set by manufacturers) of insulin have increased by ~10–20% per year for the past decade at a time when inflation has been ~2% and spending on prescription drugs has only increased by ~3% per year.

Using public information sources and meetings/interviews with key stakeholders, the working group describes a complex insulin supply chain, including opaque pricing mechanisms and a myriad of different health insurance policies, which have contributed to steeply rising insulin prices. In particular, the working group notes that there may be numerous incentives to increase prices within a system that it says cannot be beneficial to the health of patients with diabetes.

Detailing the many complexities in the pricing system, the group points out that, although list prices appeared to triple between 2002 and 2012, the net price (reflecting what the manufacturer receives) is much less. The group singles out a system of rebates as a major issue when accounting for the apparent difference between list and net prices. The article also notes that a lack of transparency has made it difficult to understand where the money flows; rebates often do not make it to the point of sale for patients.

The working group highlights a number of other issues and then offers conclusions and recommendations regarding insulin affordability and access and expresses concern about the complexity and opaqueness of the system that ultimately appears to be driving prices higher and higher.

“The working group was convened to provide high-level direction in the implementation of insulin access and affordability initiatives,” said working group chair William T. Cefalu, MD, ADA’s Chief Scientific, Medical & Mission Officer. “After discussions with over 20 stakeholders in the insulin supply chain, we remain concerned with the complexity of the system. It was the consensus of the working group that the incentives throughout the insulin supply chain that facilitate high list prices need to be addressed.”

UPDATED TYPE 2 DIABETES RISK TEST AVAILABLE

An estimated 84 million Americans have prediabetes, with blood glucose levels higher than normal but not high enough to be considered type 2 diabetes. Unfortunately, 90% of people with prediabetes do not know they have it. The American Diabetes Association’s recently revamped Type 2 Diabetes Risk Test is a 60-second tool that uses simple questions to help people learn their risk for prediabetes. The risk test is now housed on a more user-friendly online platform that provides links to key resources. Find it at diabetes.org/risktest.

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