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Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

Dramatic Increase in Rates and Costs of Diabetic Ketoacidosis Between 2003 and 2014

A nationwide survey in the U.S. of health care utilization and costs associated with diabetic ketoacidosis (DKA) has revealed significant increases in hospitalizations and its associated costs. The study by Desai et al. (**p. 1631**) suggests there are opportunities for reducing costs related to DKA but the crux of the problem remains prevention of the disease in the first place. Using data from the National Inpatient Sample Database, the authors examined the incidence and costs of hospital admissions relating to DKA over the period 2003–2014. Based on ICD-9 codes, they looked for all cases where the principal discharge diagnosis was DKA and then calculated population incidence as well as temporal trends, length of stay, costs, and in-hospital mortality. In the period they examined, there were just over 1.76 million primary admissions for DKA. They found that in 2003 there were 118,808 cases with a diagnosis of DKA, but that figure rose to 188,965 in 2014, which they point out is an increase of 59%. The length of stay decreased significantly over the period with an average stay of 3.64 days in 2003 and 3.24 days in 2014; however, the costs involved increased. In 2003, the average admission cost was $18,987, while in 2014 each admission averaged $26,566 (after adjusting for inflation). Translating that to a "national bill," DKA costs were $2.2 billion in 2003 compared with $5.1 billion in 2014. While evidently representing a dramatic increase in costs, mortality rates due to DKA did fall from 0.5% in 2003 to 0.3% in 2014. Commenting further on the research, author Dimpi Desai said: "This alarming rise in the number of hospital admissions of diabetic ketoacidosis along with the associated health care costs should now make us all focus on developing strategies to prevent this condition."

Desai et al. Health care utilization and burden of diabetic ketoacidosis in the U.S. over the past decade: a nationwide analysis. Diabetes Care 2018;41:1631–1638

SGLT2 Combinations With Other Glucose-Lowering Drugs: A Call for (Observational) Studies

In a perspective article in this issue of *Diabetes Care*, van Baar et al. (**p. 1543**) focus on sodium–glucose cotransporter 2 inhibitors (SGLT2is) for the treatment of type 2 diabetes specifically in the context of dual therapy with metformin and as part of a triple therapy with a series of other glucose-lowering drugs. While highlighting various studies relating to combination therapies—and that in many cases they can be more effective than single drugs alone—the authors suggest that numerous questions relating to effectiveness remain. Initially covering the pathophysiology of hyperglycemia in type 2 diabetes, the authors go on to describe the effects of SGLT2is alone or with metformin on glucose control as well as pleiotropic effects, effects on cardiovascular and renal outcomes, (potential) mechanisms, and adverse effects. Using a similar approach, they describe in detail the combinations of SGLT2is with glucagon-like peptide 1 receptor agonists and separately with dipeptidyl peptidase 4 inhibitors, concluding in both cases that such combinations can in general terms have positive effects on glucose control, including on occasions substantial HbA_{1c} reductions. They also cover more briefly SGLT2 combinations and separately sulfonylureas, thiazolidinediones, and insulin. They highlight that patient-centered approaches, including the use of such combinations, require numerous considerations and knowledge of the various options available for the treatment of type 2 diabetes. Author Michaël J.B. van Baar told *Diabetes Care*: "Pharmacological management in type 2 diabetes has become increasingly complex since prevailing guidelines advocate a personalized approach. Selecting drug combinations that cause maximal individual benefit is challenging and requires a comprehensive knowledge of the effectiveness of agents used in combination. The sheer number of available drug combinations and numerous end points that are relevant within such a holistic approach make a thorough assessment of effectiveness in clinical trials unfeasible. By discussing current gaps in our knowledge, we hope to stimulate well-designed observational studies that we believe are essential to guide health care providers in their aim for personalized care."

van Baar et al. SGLT2 inhibitors in combination therapy: from mechanisms to clinical considerations in type 2 diabetes management. Diabetes Care 2018;41:1543–1556

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Sustained Benefits of Education/Technological Combination for Awareness of Hypoglycemia in Type 1 Diabetes

A combination of educational, therapeutic, and technological support appears to improve awareness of and reduce severe hypoglycemia in type 1 diabetes, according to Little et al. (**p. 1600**). Of note, the benefits of the 6-month intervention could be sustained a full 24 months after baseline and 18 months after returning to routine clinical care. As a result, the authors suggest that optimized insulin replacement and glucose monitoring as well as structured education should be provided to all individuals with type 1 diabetes and impaired awareness of hypoglycemia. The findings come from the HypoCOMPaSS trial, which was a 6-month intervention that compared various approaches to insulin delivery and glucose monitoring in combination with a brief educational session designed to help participants recognize and deal with (a lack of) awareness of hypoglycemia. In the current report, the authors focus on the outcomes at 24 months after baseline. They found that improvements in hypoglycemia awareness were sustained at 24 months and that the rate of hypoglycemia episodes reduced from ~9 per year per person prestudy to just under half an episode at 24 months. HbA_{1c} levels also reduced from ~8.2% prestudy to ~7.7% at 24 months. The authors also reported improvement in treatment satisfaction and reduced fear of hypoglycemia and again, the effects were sustained at 24 months. There was no difference in outcomes according to the intervention combinations used, which were either insulin pump or daily multiple insulin injections and either continuous glucose monitoring or self-monitoring of blood glucose. Commenting more widely on the study, author James A.M. Shaw said: "The HypoCOMPaSS study has shown us that impaired awareness of hypoglycemia with high risk of severe events should not be accepted as an irreversible inevitability of long-standing type 1 diabetes. Recovery of hypoglycemia awareness has not been reported in technology-alone studies underlining the importance of fostering optimal safe self-management through life-long education in parallel with technological advances in diabetes care."

Little et al. Sustained reduction in severe hypoglycemia in adults with type 1 diabetes complicated by impaired awareness of hypoglycemia: two-year follow-up in the HypoCOMPaSS randomized clinical trial. Diabetes Care 2018;41:1600–1607

Saturated Fat Harmful to Liver in Nonalcoholic Liver Disease/Obesity: Human Trial Data

Saturated fat maybe more harmful to the liver than unsaturated fat or sugar in the context of nonalcoholic liver disease and obesity, according to Luukkonen et al. (**p. 1732**). As a result, they suggest decreasing intakes of saturated fats should be beneficial in reducing the intrahepatic triglyceride content associated with nonalcoholic fatty liver disease (NAFLD) and hence the associated risk of diabetes. In a study of 38 overweight subjects (BMI ~31 kg/m^2), the authors provided 1,000 extra kcal per day for 3 weeks as either saturated or unsaturated fat or as simple sugars. They then compared a range of measures at baseline and after 3 weeks of overnutrition with a focus on intrahepatic triglycerides, de novo lipogenesis, adipose tissue lipolysis, insulin resistance, and a range of other outcomes. They found that overfeeding of saturated fat increased intrahepatic triglycerides by about 55%. This compared with unsaturated fat that led to a 15% increase. Simple sugars also resulted in a 33% increase in intrahepatic triglycerides but this time via a 98% increase in de novo lipogenesis. Saturated fat meanwhile significantly increased lipolysis while unsaturated fat decreased the measure. Saturated fat also resulted in increased insulin resistance, endotoxemia, and multiple plasma ceramides. As a result, the authors conclude that saturated fat is likely the most harmful dietary constituent with respect to intrahepatic triglycerides accumulation (i.e., NAFLD) and because NAFLD increases the risk of type 2 diabetes, avoidance of foods rich in saturated fats might also help in preventing diabetes. According to author Hannele Yki-Järvinen: "The data echo current dietary recommendations of consuming unsaturated rather than saturated fat. They are novel in showing that ceramides are the bioactive lipid species, which are strikingly increased by overeating saturated fat. Ceramides have previously been shown to be increased by saturated fat in mice and have recently been shown in several human prospective studies to increase the risk of cardiovascular disease, independent of LDL cholesterol."

Luukkonen et al. Saturated fat is more metabolically harmful for the human liver than unsaturated fat or simple sugars. Diabetes Care 2018;41:1732–1739

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