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Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

RAMP-DM Diabetes Care Program Is Cost-effective

Last month we learned that the Risk Assessment and Management Programme–Diabetes Mellitus (RAMP-DM), which is used in Hong Kong, is effective in terms of delaying disease progression, preventing complications, and reducing the need for hospital care (see https://doi.org/10.2337/dc17-0426). This month we learn that it is also likely to be cost-effective, at least according to an analysis by Jiao et al. (**p. 250**). They report a prospective cohort study of just over 17,000 patients with diabetes who were either enrolled in the program or who received usual primary care for diabetes. As well as assessing the effectiveness of the program, the authors also examined the costs of the program in terms of setup and ongoing and central administrative costs and compared them to the costs of usual care. According to the authors, the program was effective in terms of health outcomes, specifically showing that there were significantly fewer diabetes-related complications and lower mortality in the RAMP-DM group than in the usual care group (matching the previous successes with the program). In relation to costs, however, the authors state that the RAMP-DM program cost on average $157 per patient over 5 years but that this resulted in a saving of just under $7,300 in overall health care costs over the same period. Reportedly the average cost of treating a patient with usual care was just under $20,000 over 5 years, but just over $12,000 with the RAMP-DM program included. As a result, they say that with the overall effectiveness and apparent cost-effectiveness now established, RAMP-DM should now be considered for routine care of all patients with diabetes. As the authors state, managing diabetes globally costs about $727 billion a year and takes up 12% of the total global health care expenditure. Commenting more widely on the research, author Colman Siu Cheung Fung said: "RAMP-DM complemented to usual primary care was a cost-saving program in managing people with diabetes over 5 years. This evidence leads us to recommend the integration of RAMP-DM as part of routine primary care for all patients with diabetes. To estimate the long-term cost-effectiveness of RAMP-DM, we will model the observed effectiveness and cost data over a lifetime."

Jiao et al. Five-year cost-effectiveness of the multidisciplinary Risk Assessment and Management Programme–Diabetes Mellitus (RAMP-DM). Diabetes Care 2018;41:250–257

Type 2 Diabetes Genetic Variant May Drive Certain Type 1 Diabetes Characteristics

Transcription factor 7 like 2 (*TCF7L2*) gene variants, usually associated with type 2 diabetes risk, are likely to contribute to variations in the phenotype of patients with type 1 diabetes, according to Redondo et al. (**p. 311**). Focusing on patients with newly diagnosed type 1 diabetes (n = 810) identified by the TrialNet consortium, the authors investigated the relationship of two *TCF7L2* single nucleotide polymorphisms (rs4506565 and rs7901695) with the number of islet autoantibodies at diagnosis as well as C-peptide and glucose measures taken from an oral glucose tolerance test. They report that the *TCF7L2* variants were associated with having a single autoantibody at diagnosis, but only among patients who were 12 years of age or older. Additionally, carriers of the variants had higher C-peptide and lower glucose measures during an oral glucose tolerance test in comparison to noncarriers. The findings are consistent with a milder form of type 1 diabetes, with more limited autoimmunity and less severe impairment of insulin secretion. As a result, the authors suggest that diabetes in these patients may reflect the consequences of milder autoimmunity combined with type 2 diabetes–associated mechanisms. Author Maria J. Redondo told *Diabetes Care*: "This study provides a genetic basis for the heterogeneity of type 1 diabetes, in particular for cases with phenotypic characteristics that are intermediate between type 1 and type 2 diabetes. These findings may have implications for disease prevention and treatment, since metabolic alterations associated with these *TCF7L2* variants may, in theory, be ameliorated with therapies usually reserved for patients with type 2 diabetes."

Redondo et al. *TCF7L2* genetic variants contribute to phenotypic heterogeneity of type 1 diabetes. Diabetes Care 2018;41:311–317

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Efficacy and Safety of Exenatide/Drug Delivery Device Proven in Trial

A small matchstick-sized subcutaneous investigational drug delivery device has proven successful at delivering exenatide, a glucagon-like peptide 1 receptor agonist, over 39 weeks. The investigational combination also significantly reduced HbA_{1c} levels and weight in patients with type 2 diabetes, and was also safe, according to a report by Rosenstock et al. (**p. 333**). The outcomes are the result of the phase 3 FREEDOM-1 trial, a randomized, double-blind, placebo-controlled trial that compared two doses of exenatide delivered via the device, termed ITCA 650, with placebo (the device alone). Reportedly 460 patients with type 2 diabetes took part in the study, and the primary end point was change in HbA_{1c} at 39 weeks. A number of secondary end points were also included. According to the authors, the 40 µg/day and 60 µg/day doses resulted in HbA_{1c} changes from baseline of -1.1 and -1.2%, respectively, while the placebo resulted in a change of -0.1%. Greater reductions in HbA_{1c} were possible in patients who had not received sulfonylureas versus those who had received them. Reductions in body weight ranged from 2.3–3.0 kg depending on the dose. In terms of adverse events, the most common was nausea, which subsided over time. Discontinuation due to gastrointestinal upset occurred in 7.2% of patients that received ITCA 650 and 1.3% who received placebo. Author Michelle Baron commented further on the research: "These data suggest that continuous subcutaneous delivery of exenatide with ITCA 650 may help poorly controlled patients with type 2 diabetes achieve better glycemic control. The ITCA 650 drug/device combination may 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."

Rosenstock et al. Efficacy and safety of ITCA 650, a novel drug-device GLP-1 receptor agonist, in type 2 diabetes uncontrolled with oral antidiabetes drugs: the FREEDOM-1 trial. Diabetes Care 2018;41:333–340

J-Shaped Relationship Between HbA_{1c} and Hypoglycemia Weakened With Continuous Glucose Monitoring

The relationship between HbA_{1c} and hypoglycemia in type 1 diabetes is apparently J-shaped according to Gimenez et al. (**p. 326**), meaning that lower or higher HbA_{1c} values likely result in excess time below threshold values for hypoglycemia. However, that is not all: using continuous glucose monitoring (CGM) weakens or possibly abolishes the relationship, making it possible to achieve lower HbA_{1c} and reduced hypoglycemia risk. The increased risk of hypoglycemia associated with lower HbA_{1c} values has been a key issue in type 1 diabetes because it limits the extent to which treatments can be used to lower the key measure and hence risk of diabetes complications. The study focuses on data obtained from the JDRF CGM randomized trial that reported many years ago on the efficacy and safety of CGM in children and adults with type 1 diabetes. Using data obtained at baseline and then also at follow-up many weeks later, the authors reveal the J-shaped relationship between HbA_{1c} and time spent below a series of different thresholds for hypoglycemia. The lowest risk reportedly occurred between HbA_{1c} values of 8.1 and 8.6%. When compared with control subjects who did not use CGM, 5 days per week of CGM flattened the relationship for a series of hypoglycemia thresholds. Further statistical analysis revealed that at a cutoff of 3.3 mmol/L for hypoglycemia, the relationship with HbA_{1c} was completely abolished. The authors suggest that patients with either low or high HbA_{1c} could benefit from CGM but without CGM, aiming for values between 8.1 and 8.6% is likely associated with lower risk of hypoglycemia. Author Nick Oliver elaborated: "This reanalysis of landmark data shows that the risk of clinically important hypoglyemia extends throughout the HbA_{1c} range, with the higher hypoglycemia risk at higher HbA_{1c} values associated with glucose variability. CGM is effective at reducing hypoglycemia risk throughout the HbA_{1c} range and can empower people with type 1 diabetes to achieve their target HbA_{1c} without a change in hypoglycemia risk."

Gimenez et al. Revisiting the relationships between measures of glycemic control and hypoglycemia in continuous glucose monitoring data sets. Diabetes Care 2018;41:326–332

https://doi.org/10.2337/dc18-ti02