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Diabetes Care®

In This Issue of *Diabetes Care*

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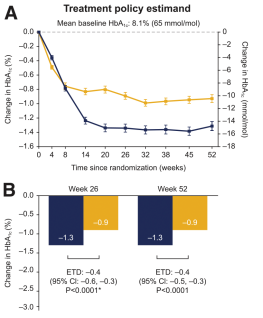
PIONEER 2 Study Results Published: Oral Semaglutide Superior to Empagliflozin in Reducing HbA_{1c}

The full results of PIONEER 2 are published in this issue of *Diabetes Care* (Rodbard et al., **p. 2272**) confirming that oral semaglutide is superior to empagliflozin for reducing HbA_{1c} in patients with type 2 diabetes uncontrolled with metformin. PIONEER 2 was a 52-week, open-label trial with participants enrolled to oral semaglutide 14 mg or empagliflozin 25 mg with a primary outcome of change from baseline to week 26 in HbA_{1c}. The secondary outcome was change in body weight from baseline. The authors report that 400 patients in the oral semaglutide group completed the trial compared with 387 patients in the empagliflozin group. Decreases in HbA_{1c} were superior with oral semaglutide compared with empagliflozin at week 26, with an estimated treatment difference of −0.4% or −0.5% in favor of semaglutide, depending on the estimand used. At week 26, HbA_{1c} was reduced from baseline (~8%) by 1.3% with oral semglutide and by 0.9% with empagliflozin according to the treatment policy estimand. Effects were largely maintained at week 52. They also report that the proportion of participants achieving HbA_{1c} <7% was greater with semaglutide (66–72%) than with empagliflozin (40–47%). In contrast, they report that superior weight loss with oral semaglutide could be demonstrated at week 52 but not at week 26. In terms of safety, they report that there were more gastrointestinal complaints with oral semaglutide but that overall it was well tolerated and that the safety profile was in line with other trials of the drug. Commenting further, author Helena W. Rodbard told us: "This is the first [available] oral glucagon-like peptide 1 receptor agonist. The fact that semaglutide is now available in an oral form [means that] patients that were reluctant or objected to injectable therapy can now benefit from the oral formulation." As part of the wider PIONEER trial series, PIONEER 2 data have since contributed to oral semaglutide receiving U.S. Food and Drug Administration approval for adults with type 2 diabetes to use, along with diet and exercise, to improve blood glucose control.



Observed absolute change in HbA_{1c} over time (A) and estimated changes from baseline in HbA_{1c} at weeks 26 and 52 (B) according to treatment policy estimand. Blue is oral semaglutide 14 mg and orange is empagliflozin 25 mg. ETD, estimated treatment difference.

Rodbard et al. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. Diabetes Care 2019;42:2272–2281

Normal and Low Weight (and Higher Weight) Minorities Have Higher Diabetes Risk Than Whites

While diabetes prevalence among different racial/ethnic groups appears to increase in line with BMI, a study by Zhu et al. (**p. 2211**) suggests that ethnic and racial minorities reach a given diabetes prevalence at a much lower BMI than whites. They also point toward many more individuals in minority groups developing diabetes despite being normal weight or even underweight. They suggest this could mean that factors other than obesity might also be driving the higher rates of diabetes in such minority populations. The conclusions come from an analysis of the health care records of ~4.9 million adults aged 20 years or older enrolled in three U.S. health care insurance systems during 2012–2013. The authors then ascertained prediabetes or diabetes status and also age, BMI, and ethnic/racial background. They found that diabetes and prediabetes prevalence in the entire study cohort was 15.9% and 33.4%, respectively, and that across all ethnic/racial groups, diabetes prevalence increased in line with BMI. The relationship between prediabetes and BMI also suggested increases with weight, but the relationship was less pronounced. Notably, however, they report that all of the minority groups had higher prevalence compared to whites in all weight categories, including those with normal weight or underweight. For example, white origin with normal weight had a diabetes prevalence of 5.0%, while the rate was 18% for those with Hawaiian/Pacific Island origin. In contrast, in the highest weight category, rates varied from 36.6% (black) to 49.1% (Asian). Prevalence of prediabetes, meanwhile, ranged from 17.5% to just under 40% with significant increasing prevalence according to weight only evident in white, black, and American Indian populations. In other groups, prevalence seemed to peak at BMI levels indicating obesity class 1, which suggests that individuals at higher BMI levels could have initiated transition to diabetes. Commenting more widely, author Yeyi Zhu told us: "Future research could focus on body composition, genetics, and other lifestyle factors that may contribute to disparities in chronic disease burden including diabetes."

Zhu et al. Racial/ethnic disparities in the prevalence of diabetes and prediabetes by BMI: Patient Outcomes Research To Advance Learning (PORTAL) multisite cohort of adults in the U.S. Diabetes Care 2019;42:2211–2219

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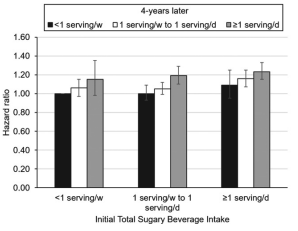
Diabetes Risks Increased With Sugary Beverages, Fruit Juices, and (Maybe) Artificially Sweetened Drinks

Raised consumption of sugary beverages, including naturally sweetened fruit juices, and artificially sweetened drinks is associated with increased risk of type 2 diabetes, according to Drouin-Chartier et al. (**p. 2181**). Conversely, decreasing consumption of sugary beverages and replacing them with zero-calorie (and nonsweetened) beverages such as water, tea, or coffee is associated with decreased diabetes risks. The conclusions come from a pooled analysis of three ongoing U.S. cohort studies involving many thousands of individuals being followed up over many decades. They found that during ~2.8 million person-years of follow-up, there were nearly 12,000 incident cases of diabetes. After adjusting for numerous weight, diet, and lifestyle factors, the authors report that an increased intake of sugary beverages, including 100% fruit juices, of roughly half a serving a day over a 4-year period was associated with a 16% higher risk of diabetes. A similar intake of artificially sweetened beverages was associated with an 18% higher risk of diabetes. Meanwhile, swapping one daily serving of sugary beverage for water, tea, or coffee (but not artificially sweetened beverages) reduced diabetes risks by 2–10%. Explaining the findings, they suggest that consumption of sugary beverages results in lower satiety and may even stimulate appetite, resulting in increased energy intake, adiposity, and, in the longer term, impaired insulin sensitivity. Of course, this would not explain the raised risk associated with artificially sweetened beverages, as they tend to be zero calorie and sugar free. They explain that individuals who consume such beverages might have switched to them as a strategy to control weight because they have raised risks (i.e., reverse causality) and that they might undergo more frequent screening for diabetes (i.e., surveillance bias). Commenting more widely, author Jean-Philippe Drouin-Chartier told us: "The study provides further evidence demonstrating the health benefits associated with decreasing sugary beverage consumption and replacing these drinks with healthier alternatives like water, coffee, or tea."



Pooled hazard ratios (95% CI) for type 2 diabetes according to updated 4-year changes in intake of sugary beverages. Black, <1 serving per week; white, ≥1 serving per week to <1 serving per day; gray, ≥1 serving per day. One serving is 8 ounces.

Drouin-Chartier et al. Changes in consumption of sugary beverages and artificially sweetened beverages and subsequent risk of type 2 diabetes: results from three large prospective U.S. cohorts of women and men. Diabetes Care 2019;42:2181–2189

Real-World Data: Glycemic Control "Worse Than Previously Estimated" in Adults With Type 1 Diabetes

Glycemic control in patients with type 1 diabetes in the U.S. might be worse than previously thought, according to Pettus et al. (**p. 2220**). Rates of complications associated with poor control might also be raised, including those for the incidence of severe hypoglycemia and diabetic ketoacidosis and the prevalence of neuropathy and nephropathy. Notably, the findings are based on real-world data from health records covering individuals who were cared for by both endocrinologists and primary care providers. Reasons for poor overall control are likely to be multifactorial, they explain. However, they highlight that 40% of individuals did not have a specialist encounter in the period of the study, implying that any diabetes management was provided by primary care providers. As a result, they suggest that improved physician training and support might lead to better care for individuals with type 1 diabetes. The findings come from a retrospective observational study that was based on the health records of ~80 million individuals from across the U.S. They identified 31,430 individuals that met inclusion criteria of diagnosed type 1 diabetes with duration >24 months and during a 12-month period were not pregnant and had at least one insulin prescription and one HbA_{1c} measure. They also collected data on both acute and microvascular complications and stratified them according to age and glycemic control. They found that overall just 20% of individuals had an HbA_{1c} <7%. Younger individuals had worse control, with just 12% aged 18–25 years reaching the target compared with 29% of individuals aged >65 years reaching the target. In terms of complications, poorer control (compared to good control) was associated with a twofold increase in incidence of severe hypoglycemia and a 12-fold increase in diabetic ketoacidosis. Prevalence of nephropathy and neurology also increased in line with poorer control across all age-groups.

Pettus et al. Incidences of severe hypoglycemia and diabetic ketoacidosis and prevalence of microvascular complications stratified by age and glycemic control in U.S. adult patients with type 1 diabetes: a real-world study. Diabetes Care 2019;42:2220–2227

https://doi.org/10.2337/dc19-ti12