HEALTHCARE GROUP

CENTRE FOR DIABETES & ENDOCRINOLOGY

CDE Academy - Diabetes Literature Review

73: 2023 QUARTER 1 2023

Academy

Glycemia Reduction in Type 2 Diabetes Microvascular and Cardiovascular Outcomes

@bstract

BACKGROUND

Data are lacking on the comparative effectiveness of commonly used glucose-lowering medications, when added to metformin, with respect to microvascular and cardiovascular disease outcomes in persons with type 2 diabetes.

METHODS

We assessed the comparative effectiveness of four commonly used glucose-lowering medications, added to metformin, in achieving and maintaining a glycated haemoglobin level of less than 7.0% in participants with type 2 diabetes. The randomly assigned therapies were insulin glargine U-100 (hereafter, glargine), glimepiride, liraglutide, and sitagliptin. Prespecified secondary outcomes with respect to microvascular and cardiovascular disease included hypertension and dyslipidaemia, confirmed moderately or severely increased albuminuria or an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 of body-surface area, diabetic peripheral neuropathy assessed with the Michigan Neuropathy Screening Instrument, cardiovascular events (major adverse cardiovascular events [MACE], hospitalisation for heart failure, or an aggregate outcome of any cardiovascular event), and death. Hazard ratios are presented with 95% confidence limits that are not adjusted for multiple comparisons.

RESULTS

During a mean 5.0 years of follow-up in 5047 participants, there were no material differences among the interventions with respect to the development of hypertension or dyslipidaemia, or with respect to microvascular outcomes; the mean overall rate (i.e., events per 100 participant-years) of moderately increased albuminuria levels was 2.6, of severely increased albuminuria levels 1.1, of renal impairment 2.9, and of diabetic peripheral neuropathy 16.7. The treatment groups did not differ with respect to MACE (overall rate, 1.0), hospitalisation for heart failure (0.4), death from cardiovascular causes (0.3), or all deaths (0.6). There were small differences with respect to rates of any cardiovascular disease, with 1.9, 1.9, 1.4, and 2.0 in the glargine, glimepiride, liraglutide, and sitagliptin groups, respectively. When one treatment was compared with the combined results of the other three treatments, the hazard ratios for any cardiovascular disease were 1.1 (95% confidence interval [CI], 0.9 to 1.3) in the glargine group, 1.1 (95% CI, 0.9 to 1.4) in the glimepiride group, 0.7 (95% CI, 0.6 to 0.9) in the liraglutide group, and 1.2 (95% CI, 1.0 to 1.5) in the sitagliptin group.

CONCLUSIONS

In participants with type 2 diabetes, the incidences of microvascular complications and death were not materially different among the four treatment groups. The findings indicated possible differences among the groups in the incidence of any cardiovascular disease.

(Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; GRADE ClinicalTrials.gov number, NCT01794143).

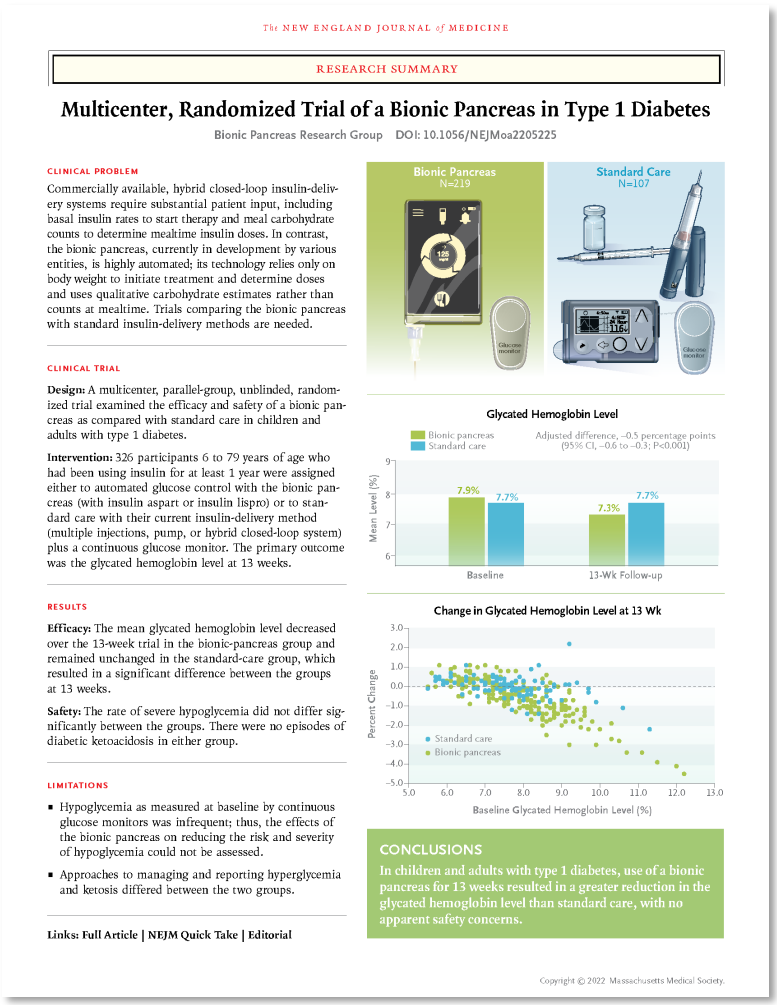
GRADE Study Research Group; Nathan DM, Lachin JM, Bebu I, et al. (2022). Glycemia Reduction in Type 2 Diabetes - Microvascular and Cardiovascular Outcomes. *N Engl J Med*. 387(12): 1075-1088. DOI: 10.1056/NEJMoa2200436

⇒	*Trial of Bionic Pancreas in type 1 diabetes*	2
⇒	*Is SMBG helpful in non-insulin treated type 2 diabetes?*	3
⇒	*Therapy App cut HbA1c, Drug intensification in diabetes*	4

Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes

BACKGROUND

Currently available semi automated insulin-delivery systems require individualized insulin regimens for the initialization of therapy and meal doses based on carbohydrate counting for routine operation. In contrast, the bionic pancreas is initialized only on the basis of body weight, makes all dose decisions and delivers insulin autonomously, and uses meal announcements without carbohydrate counting.



The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes

Bionic Pancreas Research Group DOI: 10.1056/NEJMoa2205225

CLINICAL PROBLEM

Commercially available, hybrid closed-loop insulin-delivery systems require substantial patient input, including basal insulin rates to start therapy and meal carbohydrate counts to determine mealtime insulin doses. In contrast, the bionic pancreas, currently in development by various entities, is highly automated; its technology relies only on body weight to initiate treatment and determine doses and uses qualitative carbohydrate estimates rather than counts at mealtime. Trials comparing the bionic pancreas with standard insulin-delivery methods are needed.

CLINICAL TRIAL

Design: A multicenter, parallel-group, unblinded, randomized trial examined the efficacy and safety of a bionic pancreas as compared with standard care in children and adults with type 1 diabetes.

Intervention: 326 participants 6 to 79 years of age who had been using insulin for at least 1 year were assigned either to automated glucose control with the bionic pancreas (with insulin aspart or insulin lispro) or to standard care with their current insulin-delivery method (multiple injections, pump, or hybrid closed-loop system) plus a continuous glucose monitor. The primary outcome was the glycated hemoglobin level at 13 weeks.

RESULTS

Efficacy: The mean glycated hemoglobin level decreased over the 13-week trial in the bionic-pancreas group and remained unchanged in the standard-care group, which resulted in a significant difference between the groups at 13 weeks.

Safety: The rate of severe hypoglycemia did not differ significantly between the groups. There were no episodes of diabetic ketoacidosis in either group.

LIMITATIONS

- Hypoglycemia as measured at baseline by continuous glucose monitors was infrequent; thus, the effects of the bionic pancreas on reducing the risk and severity of hypoglycemia could not be assessed.
- Approaches to managing and reporting hyperglycemia and ketosis differed between the two groups.

Links: Full Article | NEJM Quick Take | Editorial

Bionic Pancreas N=219

Standard Care N=107

Glycated Hemoglobin Level

Bionic pancreas
Standard care

Adjusted difference, −0.5 percentage points (95% CI, −0.6 to −0.3; P<0.001)

Mean Level (%)

7.9% 7.7% 7.3% 7.7%

Baseline 13-Wk Follow-up

Change in Glycated Hemoglobin Level at 13 Wk

Percent Change

Standard care
Bionic pancreas

Baseline Glycated Hemoglobin Level (%)

CONCLUSIONS

In children and adults with type 1 diabetes, use of a bionic pancreas for 13 weeks resulted in a greater reduction in the glycated hemoglobin level than standard care, with no apparent safety concerns.

"In... adults and children with type 1 diabetes, use of a bionic pancreas was associated with a greater reduction in the glycated haemoglobin level than standard care."

METHODS

In this 13-week, multicentre, randomized trial, we randomly assigned in a 2:1 ratio persons at least 6 years of age with type 1 diabetes either to receive bionic pancreas treatment with insulin aspart or insulin lispro or to receive standard care (defined as any insulin-delivery method with unblinded, real-time continuous glucose monitoring). The primary outcome was the glycated haemoglobin level at 13 weeks. The key secondary outcome was the percentage of time that the glucose level as assessed by continuous glucose monitoring was below 54 mg per dl/3 mmol/l; the prespecified noninferiority limit for this outcome was 1 percentage point. Safety was also assessed.

RESULTS

A total of 219 participants 6 to 79 years of age were assigned to the bionic-pancreas group, and 107 to the standard-care group. The glycated haemoglobin level decreased from 7.9% to 7.3% in the bionic-pancreas group and did not change (was at 7.7% at both time points) in the standard-care group (mean adjusted difference at 13 weeks, −0.5 percentage points; 95% confidence interval [CI], −0.6 to −0.3; P<0.001). The percentage of time that the glucose level as assessed by continuous glucose monitoring was below 3 mmol/l did not differ significantly between the two groups (13-week adjusted difference, 0.0 percentage points; 95% CI, −0.1 to 0.04; P<0.001 for noninferiority). The rate of severe hypoglycaemia was 17.7 events per 100 participant-years in the bionic-pancreas group and 10.8 events per 100 participant-years in the standard-care group (P=0.39). No episodes of diabetic ketoacidosis occurred in either group.

CONCLUSIONS

In this 13-week, randomized trial involving adults and children with type 1 diabetes, use of a bionic pancreas was associated with a greater reduction in the glycated haemoglobin level than standard care.

(Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; ClinicalTrials.gov number, NCT04200313.)

Bionic Pancreas Research Group, Russell SJ, Beck RW, Damiano ER, Let al. (2022). Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes. *The New England Journal of Medicine*, 387(13), 1161–1172. DOI: 10.1056/NEJMoa2205225

Is blood glucose self-monitoring helpful in noninsulin treated type 2 diabetes?

TAKEAWAY

Self-monitoring of blood glucose (SMBG) aids in controlling blood glucose levels in people with type 2 diabetes not treated with insulin. An SMBG frequency of 8-11 times weekly appears optimal.

WHY THIS MATTERS

SMBG has been proven useful in the management of type 1 diabetes and in type 2 diabetes treated with insulin, but its efficacy in those with type 2 diabetes not treated with insulin is controversial.

Few diabetes management guidelines have defined an optimal SMBG regimen, and those that have are based on expert consensus rather than data.

STUDY DESIGN

Meta-analysis of 22 studies, with 17 (n=4375) comparing SMBG with no SMBG and 4 (n=1829) comparing SMBG with structured SMBG (S-SMBG), i.e., with defined timing and frequency.

KEY RESULTS

SMBG was associated with a significant HbA1c decrease compared with no SMBG (mean difference [MD], −0.30%; 95% CI, −0.42% to −0.17%).

S-SMBG was associated with lower HbA1c compared with SMBG (MD, −0.23%; 95% CI, −0.38% to −0.07%).

Compared with no SMBG, reductions in body mass index, weight, fasting plasma glucose, and waist circumference in the SMBG group were also significantly lower at −0.18 (95% CI, −0.31 to −0.04) kg/m2, −0.33 (95% CI, −0.62 to −0.05) kg, −0.27 (95% CI, −0.43 to −0.12) mmol/L, and −1.12 (95% CI, −2.17 to −0.06) cm, respectively.

"SMBG was associated with a significant HbA1c decrease compared with no SMBG"

NO DIFFERENCES IN TOTAL CHOLESTEROL OR SYSTOLIC BP

HbA1c was lower among people who used SMBG >7 times/week (MD, −0.39%; 95% CI, −0.54% to −0.23%) compared with ≤7 times/week (MD, −0.17%; 95% CI, −0.29% to −0.05%), with P=.03 between the 2 groups.

No significant difference in HbA1c between SMBG 8-11 times/week (MD, −0.35%; 95% CI, −0.51% to −0.20%) and ≥12 times/week (−0.40%; 95% CI, −0.65% to −0.15%); P=.75.

DISCUSSION

SMBG was effective for controlling HbA1c in non-insulin-treated T2D patients, although lacking detailed monitoring design. Better outcomes were seen with SMBG 8-11 times weekly and lifestyle adjustment based on SMBG results.

LIMITATIONS

Some factors not retrieved from the original trials could affect the analyses.

FUNDING: None disclosed.

Zou Y, Zhao S, Li G, & Zhang C (2023). The Efficacy and Frequency of Self-monitoring of Blood Glucose in Non-insulin-Treated T2D Patients: a Systematic Review and Meta-analysis. *Journal of general internal medicine*, 38(3), 755–764. DOI: 10.1007/s11606-022-07864-z

Therapy App Cut A1c, Drug Intensification in T2D

Previously reported results from the BT-001 trial showed that people randomized to use a Cognitive behavioural therapy (CBT) app had a significant average 0.4 percentage point reduction in haemoglobin A1c, compared with controls, after 90 days for the trial's primary endpoint, and a significant 0.29 percentage point reduction in A1c, compared with controls, after 180 days.

The new finding, that these incremental drops in A1c occurred while the control participants also received significantly more intensification of their diabetes medication, provides further evidence for the efficacy of the CBT app, said Marc P. Bonaca, MD, in a press conference organized by the American College of Cardiology in advance of its upcoming joint scientific sessions.

"the CBT app had a significant average 0.4 percentage point reduction in haemoglobin A1c, compared with controls, after 90 days for the trial's primary endpoint, and a significant 0.29 percentage point reduction in A1c, compared with controls, after 180 days."

The CBT app "significantly reduced A1c despite less intensification of ant hyperglycaemic therapy," noted Dr Bonaca, a vascular medicine specialist and executive director of CPC Clinical Research, an academic research organization created by and affiliated with the University of Colorado at Denver, Aurora.

Based on positive safety and efficacy findings from the primary-endpoint phase of the BT-001 trial, reported in *Diabetes Care*, the company developing the CBT app, Better Therapeutics, said in a statement that the U.S. Food and Drug Administration accepted the company's application for de novo classification and marketing approval of the app, also called BT-001. If the agency grants this classification and marketing approval, the company plans to sell the app on a prescription basis for use by people with type 2 diabetes.

CBT APP GIVES PATIENTS PROBLEM-SOLVING SKILLS

CBT gives people with type 2 diabetes a way to better understand their unhelpful behaviours and motivations and teaches them problem-solving skills. Providing this counselling via an app addresses the challenge of making the intervention scalable to a broad range of patients, Dr Bonaca explained.

"Clinicians are frustrated by trying to produce behavioural change" in patients. The BT-001 app "provides a new avenue to treatment," an approach that clinicians have been "very receptive" to using "once they understand the mechanism," Dr Bonaca said during the press conference. "The effect at 90 days was very similar to what a drug would do. It's not just drugs any more" for treating people with type 2 diabetes, he declared.

"It would be interesting to learn more about the adults who engaged with the app" and had a higher use rate "to provide more targeted care" with the app to people who match the profiles of those who were more likely to use the app during the trial, said Dr Shapira.

This "clear" dose-response relationship "was one of the most exciting findings. It helps validate the mechanism," Dr Bonaca said during the press conference. "We're now modelling which patients were the most engaged" with using the app, and "looking at ways to increase app engagement."

Better Therapeutics also announced, in December 2022, results from a separate, uncontrolled study of a similar CBT app in 19 people with non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. The findings showed that use of the tested app linked with an average 16% drop from baseline in liver fat content as measured by MRI, as well as other improvements in markers of hepatic function. The company said in a statement that based on these findings it planned to apply for breakthrough-device designation with the FDA for use of a liver-specific CBT app in people with non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

The BT-001 trial was sponsored by Better Therapeutics, the company developing the app. CPC Clinical Research receives research and consulting funding from numerous companies. Dr Bonaca has been a consultant to Audentes, and is a stockholder of Medtronic and Pfizer. Dr Shapira and Dr Grapsa had no disclosures.

MDedge.com/Cardiology (2023). ***Therapy app cut A1c, drug intensification in T2D.*** **Available at: https://www.mdedge.com/cardiology/article/261417/diabetes/therapy-app-cut-a1c-drug-intensification-t2d**