

ORIGINAL ARTICLE

Real-world effectiveness and safety of sensor-augmented insulin pump therapy in adults with type 1 diabetes: Long-term follow-up



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KEYWORDS

Sensor-augmented insulin pump therapy; Continuous insulin infusion systems; Continuous glucose monitoring; Glycated hemoglobin A1c; Type 1 diabetes mellitus; Type 2 diabetes mellitus

Abstract

Objective: To evaluate the effectiveness and safety of sensor-augmented insulin pump therapy (SAP) in addition to a comprehensive diabetes program on glycated hemoglobin (HbA1c), severe hypoglycemia, ketoacidosis, and the hospital admission rate in patients with type 1 diabetes under real-world settings during a 2-year follow-up.

Methods: This was a retrospective real-life study comparing diabetes control before and after SAP therapy initiation. Patients ≥ 18 years old with type 1 diabetes were included. They were followed for 2 years with clinical assessments at months 3, 6, 12, 18, and 24. Effectiveness was estimated by difference in medians of HbA1c from baseline and at each follow-up visit. Safety was assessed by comparing the annual rates of severe hypoglycemia, hyperglycemic crisis, and hospital admission related to diabetes.

Results: 162 patients were included, median age 32 years, women 73%). The main indication for SAP was poor metabolic control (51.2%). At 2 years HbA1c decreased from 8.4% to 7.5% (-0.9% , 95% CI: 0.5–1.2; $p < 0.0001$), HbA1c $\leq 7\%$ improved from 14.2% to 25.3% (11.1%, 95% CI: 19.7–2.5; $p = 0.006$), and severe hypoglycemia decreased from 22.2% to 14.1% (-8.1% , 95% CI: -16.5 to 0.3; $p = 0.03$).

Conclusions: SAP therapy improved glycemic control after the third month of use and for up to 2 years of follow-up, with lower rates of hospital admission and severe hypoglycemia. More studies are needed to assess the add-on impact of education programs and technologies for diabetes care.

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PALABRAS CLAVE

Terapia con bomba de insulina aumentada por sensor;
Sistemas de infusión continua de insulina;
Monitoreo continuo de glucosa;
Hemoglobina glicada A1c;
Diabetes mellitus tipo 1;
Diabetes mellitus tipo 2

Efectividad y seguridad en el mundo real de la terapia con bomba de insulina aumentada por sensor en adultos con diabetes tipo 1: Seguimiento a largo plazo

Resumen

Objetivo: Evaluar la efectividad y seguridad de la terapia con bomba de insulina aumentada por sensor (SAP), junto con un programa integral de diabetes en hemoglobina glicosilada, hipoglucemia severa, cetoacidosis y tasa de admisión hospitalaria en pacientes con diabetes tipo 1 bajo condiciones del mundo real durante el seguimiento a dos años.

Métodos: Este es un estudio retrospectivo de vida real comparando el control de la diabetes, antes y después de iniciar terapia SAP. Se incluyeron pacientes ≥ 18 años de edad con diabetes tipo 1. Fueron seguidos por dos años con evaluación clínica en los meses tres, seis, 12, 18 y 24. La efectividad fue estimada por diferencia en medianas de HbA1c entre la línea de base y en cada visita del seguimiento. La seguridad se evaluó comparando las tasas anuales de hipoglucemia severa, crisis hiperglucémica y hospitalización relacionada con diabetes.

Resultados: Se incluyeron 162 pacientes con diabetes tipo 1, mediana de edad 32 años, 73% mujeres. La indicación principal para terapia SAP fue el pobre control glucémico (51,2%). A los dos años, la mediana de HbA1c disminuyó de 8,4 a 7,5% ($-0,9\%$, IC 95%: 0,5 a 1,2; $p < 0,0001$), HbA1c $\leq 7\%$ mejoró del 14,2 al 25,3% (11,1%, IC 95%: 19,7 a 2,5; $p = 0,006$), y las hipoglucemias severas disminuyeron de 22,2 a 14,1% ($-8,1\%$, IC 95%: $-16,5$ a 0,3; $p = 0,03$).

Conclusiones: La terapia SAP mejoró el control glucémico después del tercer mes de uso y hasta los dos años de seguimiento, con menores tasas de admisión hospitalaria e hipoglucemias severas. Se necesitan más estudios para evaluar el impacto adicional de los programas de educación en las tecnologías para el cuidado de la diabetes.

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Introduction

Continuous Subcutaneous Insulin Infusion (CSII) therapy and Continuous Glucose Monitoring (CGM) have been associated with better glycemic control without an increase in hypoglycemia when compared with multiple daily insulin injections (MDI) without CGM, mostly in Type 1 Diabetes (T1D).¹⁻³ Clinical practice guidelines recommend their use over MDI in patients with either type 1 or 2 diabetes who have not achieved an A1C goal or who have achieved their A1C goal but continue to experience severe hypoglycemia or high glucose variability.⁴⁻⁷ Among these technologies, Sensor-augmented insulin pump therapy (SAP) which combines CSII with CGM has demonstrated better glycemic control with a comparable reduction in hypoglycemic episodes than CSII alone in short-term studies, however, long-term efficacy has been less described.^{3,8-12} In Latin America there is very scarce evidence of the effectiveness and safety of the addition of SAP in a group of diabetic patients who are being followed in a structured diabetes program with continuous education and support.

This study is an up-date on the long-term follow-up of our real-world experience which was previously reported in 2016.¹³ The present study aimed to determine the long-term effectiveness and safety of SAP therapy within a comprehensive diabetes program in two specialized centers at Medellín, Colombia.

Methodology**Study design**

This is a retrospective real-life study analyzing effectiveness and safety of SAP therapy in two reference centers for

diabetes management at Medellín – Colombia (Clínica Integral de Diabetes – CLID and Endocrino SA), between January 2008 to December 2017.

Eligibility criteria

Patients ≥ 18 years old with type 1 diabetes who were using SAP for at least two years, were included. Patients with missing data or lost during the 2-year follow-up were excluded.

Intervention

Patients were on SAP (MiniMed® 640G or 530G, Guardian™ 2 Link transmitter and Enlite™ sensor; Medtronic, Northridge, CA), following standardized protocols for diabetes care. All the patients were using automation of insulin infusion depending on sensor glucose readings, individualized threshold for 530G users and predictive low glucose suspend feature on 640G pumps. Patients follow up included structured diabetes education, nutritional assessment, and psychological assistance. Structured education included a 6-month training course prior to SAP therapy and then continuing education with monthly out-patient appointments. The components of education and training comprise: instructions for managing daily living and sick-day rules, using CSII, adjusting insulin doses, carbohydrate counting, preventing and managing hypoglycemia and diabetic ketoacidosis, and understanding the role of either self-monitoring blood glucose (SMBG) or rtCGM. The indications for starting the insulin pump were established in accordance with institutional protocols: (1) poor glycemic control (HbA1c $> 7.5\%$) with MDI insulin regimen for the last six months at either institution, (2) dawn phenomenon, (3)

frequent and/or asymptomatic hypoglycemia, (4) diabetic gastroparesis, and (5) episodes of severe hypoglycemia. Clinical data was extracted from a prespecified and systematically registered electronic medical record, and included sociodemographic variables (age, sex, educational level), anthropometric (height, weight, body mass index), comorbidities (hypertension, dyslipidemia, micro and macrovascular complications, heart failure, coronary artery disease, peripheral artery disease and cerebrovascular disease), diabetes (duration, and treatment).

Follow-up

Patients were followed for 2 years since the initiation of SAP. Data on glycemic control and safety outcomes was analyzed retrospectively. Outcomes were analyzed at baseline, 3, 6, 12, 18, and 24 months by electronic medical record review.

Outcomes

HbA1c was obtained at baseline and every 3 months to determine metabolic control. Safety outcomes included were: severe hypoglycemia (neuroglycopenic symptoms due to low blood sugar that require third party assistance), hospital admission related to diabetes (severe hypoglycemia, diabetic ketoacidosis and hyperosmolar hyperglycemic state defined by ADA standards), sensor or infusion set allergy or infection, or infusion set obstruction. At the end of follow-up additional information was obtained regarding the type of insulin, total daily insulin dose, basal/bolus percentage, type of bolus used (wizard or correction) and number of glucose readings per day. Adherence to real-time CGM was defined as the percentage of time using the sensor with its equivalence in days (i.e. 0–20% = 0–3 days, 21–40% = 3.1–6.1 days, 41–60% = 6.1–9.1 days, 61–80% = 9.1–12.7 days, and >80% = 12.7 days) was also estimated.

Statistical analysis

Qualitative variables were analyzed descriptively and presented as relative and absolute frequencies. For the quantitative variables, the mean and median were obtained, as well as the standard deviation and the interquartile ranges (IQR 25% to 75%) depending on whether the variable did or did not have normal distribution. A repeated measures analysis for HbA1c was applied with the Friedman test and Wilcoxon post hoc tests with Bonferroni adjustment. The difference in medians was estimated to assess the effectiveness in changing HbA1c of each period with respect to baseline, 95% confidence interval for the median was estimated with Bonett–Price test. The research protocol was approved by the institutional review board of the Universidad Pontificia Bolivariana and conducted in accordance with the ethical standards of the Declaration of Helsinki.

Results

Among 253 adults started on SAP, 162 patients were included for the long-term assessment. Baseline characteristics are presented in Table 1. In brief, 73% women, median age was

Table 1 Baseline characteristics of patients with type 1 diabetes prior to initiating SAP therapy.

Variables	n = 162
Women, n (%)	118 (72.8%)
Age – years, median (p25–p75)	32 (25–46)
<i>Education level, n (%)</i>	
Illiterate	3 (1.9)
Primary	2 (1.2)
High school	49 (30.3)
Technical	25 (15.4)
Academic (university degree)	83 (51.2)
<i>Weight – kg, median (p25–p75)</i>	62 (57–69)
<i>Body mass index – kg/m², median (p25–p75)</i>	23.7 (22–25)
<i>Type of diabetes, n (%)</i>	
<i>Diabetes duration – years, median (p25–p75)</i>	16.5 (11–25)
<i>Associated comorbidities, n (%)</i>	
High blood pressure	60 (37)
Dyslipidemia	53 (32.7)
Diabetic retinopathy	50 (30.9)
Diabetic nephropathy	27 (16.7)
Diabetic neuropathy	37 (22.8)
Coronary heart disease	5 (3.1)
Peripheral arterial disease	3 (1.9)
Cerebrovascular disease	1 (0.6)
Heart failure syndrome	0 (0)
<i>Clinical indications for SAP</i>	
Poor glycemic control	83 (51.2)
Severe hypoglycemia	36 (22.2)
Asymptomatic hypoglycemia	25 (15.4)
Dawn phenomenon	17 (10.5)
Diabetic gastroparesis	1 (0.6)
<i>HbA1C – %, median (p25–p75)</i>	8.4 (7.5–9.3)
<i>Ketoacidosis, n (%)^a</i>	4/139 (2.9)
<i>Hospital admission for diabetes, n (%)^a</i>	5/142 (3.5)
<i>Total daily dose of insulin – units/kg/daily, median (p25–p75)</i>	0.6 (0.5–0.7)
<i>Total daily dose of insulin – units/daily, median (p25–p75)</i>	36 (30–46)

^a The varying denominators are indicating the number of observations available for analysis.

32 years (IQR: 25–46). All the patients were covered by the government health-care system and 51% had university degree. Anthropometric characteristics were: median BMI 24 kg/m² and none were obese (BMI > 30 kg/m²). The insulin pumps were either MiniMed 640G or Minimed 530G, coupled to real-time CGM system (Enlite™ sensor, Medtronic). The main indications for SAP were poor glycemic control (51.2%) and severe hypoglycemia (22.2%). Median HbA1C of 8.4% (IQR 7.5–9.3%) and 16.5 years of diabetes duration (IQR 11–25); the main microvascular complications were retinopathy (30.9%), followed by neuropathy (22.8%) and nephropathy (16.7%).

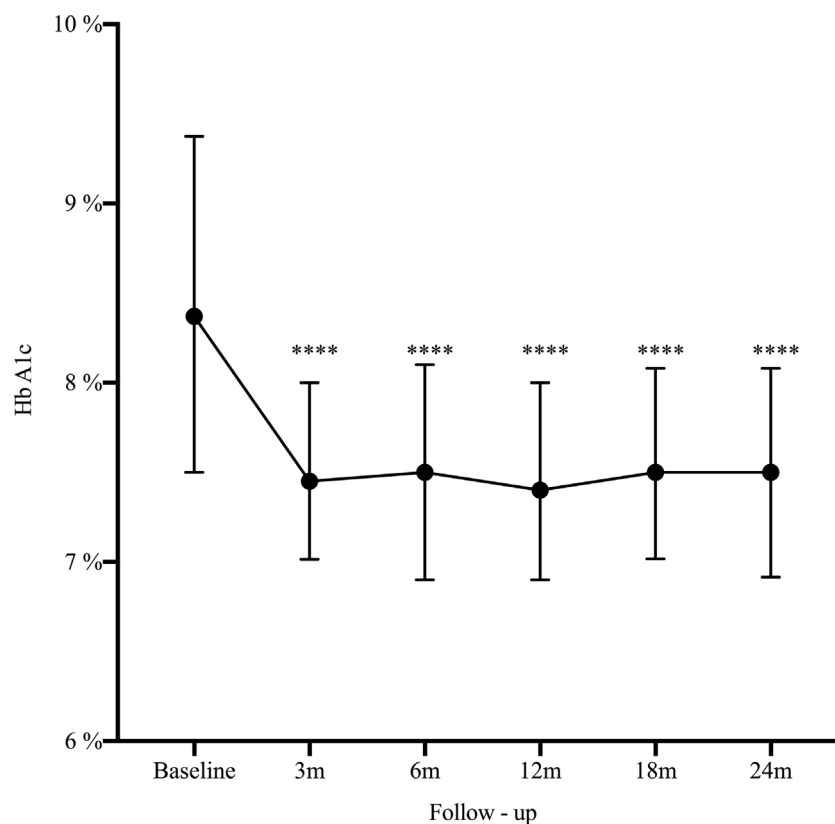


Figure 1 Effectiveness of SAP in 162 patients with type 1 diabetes during 2-year of follow-up. *p* values of the Wilcoxon signrank test for HbA1C difference in medians were statistically significant in all cases when comparing baseline versus each follow-up period (*****p* < 0.0001).

Clinical outcomes

Glycemic control

A statistically significant decrease in HbA1c was seen as early as the third month after SAP initiation ($\Delta -0.9\%$; $p < 0.0001$), and maintained during the long-term follow-up (Fig. 1). There was an increase in the percentage of patients who achieved glycemic control (HbA1C $\leq 7\%$) from 14.2% at baseline to 25.3% at 2-year follow-up ($\Delta -11.1\%$, 95% CI: -19.7 to -25.3 ; $p = 0.006$). By the end of follow-up, the median total daily insulin dose was 36 international units (IU) (IQR: 30–46) or 0.6 IU/kg/daily (IQR: 0.5–0.7). Lispro was the most common insulin used (42%), followed by Aspart (29.6%) and Glulisine (28.4%); the basal/bolus percentage was 40% for the basal rate (IQR 35–50%) and 60% for the prandial component (IQR 50–65%). The average glucose daily fingerstick testing was 5.4 times per day (SD ± 1.6). The proportion of patients who used the sensor based on percentage of time was: 0–20%, 21–40%, 41–60%, 61–80%, and $>80\%$ was 3.5%, 9.7%, 23%, 44.3%, and 19.5% respectively. Among given boluses, the mean of meal bolus wizard and correction wizard was 82% (SD ± 13.4) and 68.8% (SD ± 18.9), respectively.

Safety assessment

At baseline, annual rates of severe hypoglycemia, hospital admission related to diabetes, and ketoacidosis were reported in 22.2%, 3.5% and 2.9% of the patients respectively. After the 2-year follow-up of starting SAP, these safety

variables decreased to 14.1% ($\Delta -8.1\%$, 95% CI: -16.5 to 0.3 ; $p = 0.030$), 1.3% ($\Delta -2.2\%$, 95% CI: -5.7 to 1.3 ; $p = 0.101$), and 1.9% ($\Delta -1\%$, 95% CI: -4.5 to 2.5 ; $p = 0.298$). Rates of sensor or infusion set allergy, infection or infusion set obstruction were reported in 7.6%, 1.4%, and 10% respectively.

Discussion

The present study presents real-world evidence of the effectiveness and safety of SAP therapy. After 2 years of treatment, HbA1c decreased from 8.4% to 7.5% (-0.9% , 95% CI: 0.5–1.2; $p < 0.0001$), glycemic control defined by HbA1c $\leq 7\%$ improved from 14.2% to 25.3% (11.1%, 95% CI: 19.7–2.5; $p = 0.006$), and severe hypoglycemia decreased from 22.2% to 14.1% (-8.1% , 95% CI: -16.5 to 0.3 ; $p = 0.03$). These findings are consistent with our previous published data¹³ and is similar to the experience reported by another institution in Colombia.^{14–16} These results are not only related to SAP but most likely reflect the results of a multi-intervention approach. They are the reflection of continued education and training of patients in addition to the use of technology. The results are the effect of SAP therapy in addition to a comprehensive diabetes program.

An open-loop insulin delivery system like SAP requires patient input, i.e. carbohydrate counting, use of bolus wizard, adherence to sensor use, sensor calibration, alarm setting and threshold-suspend feature, there is also a moti-

vational factor involved among other variables that may fluctuate in time and depend on each patients behavior. The way to measure the impact of human behavior and its interaction with diabetes care technologies is difficult to assess by classic study designs and this might explain why the results of clinical trials and meta-analyses looking at glycemic control with CSII are conflicting and heterogeneous. Both the U.S. Food and Drug Administration and European Medicines Agency ask pump and CGM manufacturers to provide real-world evidence in combination with RCT to evaluate short- and long-term effectiveness and safety of new medical device submissions.^{17–19}

Meta-analyses have reported benefits of SAP therapy compared to MDI and self-monitoring blood glucose (SMBG),^{3,20} a statistically and clinically significant greater reduction in HbA1c from -0.68% to -0.7% . In addition, SAP therapy has shown to reduce the frequency of severe and non-severe hypoglycemic events when compared with use of continuous subcutaneous insulin infusion without real-time CGM.^{21–23} It is possible that the greater and sustained decrease in HbA1C levels and severe hypoglycemic annual rates observed during the 2-year follow-up in our study was due to the “add-on” effect of the comprehensive diabetes program. Structured education programs like DAFNE, INPUT or REPOSE have reported HbA1c reductions in the range of 0.2 and 0.7% over a sustained period of time.^{24–30} Similarly, real-world evidence from the COMISAIR demonstrated a significant HbA1c reduction from baseline and during the 3-year study period with a mean HbA1c difference of -0.99% (95% CI: -1.45 to -0.52).^{11,12} In concordance with these studies, our findings support that real time CGM and a structured education program are key elements for the effectiveness of SAP.

Due to the observational nature the present study, the main limitations are lacking of a prospective control group and missing CGM data, hence it was not possible to control for potential confounding factors like non-severe hypoglycemia among others; as a result, these real-world findings related to effectiveness and safety need to be interpreted with caution. However, it is noteworthy that the results are consistent with those of controlled trials, meta-analyses, and real-world studies showing that SAP therapy along with an intensive and comprehensive approach to diabetes care can achieve long-term effective glycemic control with low risks of hypoglycemia and other complications.

Conflict of interest

All authors declare no conflicts of interest.

References

- Jeitler K, Horvath K, Berghold A, Gratzer TW, Neeser K, Pieber TR, et al. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. *Diabetologia*. 2008;51:941–51.
- Monami M, Lamanna C, Marchionni N, Mannucci E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 1 diabetes: a meta-analysis. *Acta Diabetol*. 2010;47:77–81.
- Yeh H-C, Brown TT, Maruthur N, Ranasinghe P, Berger Z, Suh YD, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157:336.
- Klonoff DC, Buckingham B, Christiansen JS, Montori VM, Tamborlane WV, Vigersky RA, et al. Continuous glucose monitoring: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2011;96:2968–79.
- Peters AL, Ahmann AJ, Battelino T, Evert A, Hirsch IB, Murad MH, et al. Diabetes technology-continuous subcutaneous insulin infusion therapy and continuous glucose monitoring in adults: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101:3922–37.
- Fonseca VA, Grunberger G, Anhalt H, Bailey TS, Blevins T, Garg SK, et al. Continuous glucose monitoring: a consensus conference of the American Association of Clinical Endocrinologists and American College of Endocrinology. *Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol*. 2016;22:1008–21.
- American Diabetes Association. 7. Diabetes technology: standards of medical care in diabetes – 2020. *Diabetes Care*. 2020;43:S77–88.
- Bergental RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med*. 2010;363:311–20.
- Danne T, Kordonouri O, Holder M, Haberland H, Golembowski S, Remus K, et al. Prevention of hypoglycemia by using low glucose suspend function in sensor-augmented pump therapy. *Diabetes Technol Ther*. 2011;13:1129–34.
- Nørgaard K, Scaramuzza A, Bratina N, Lalić NM, Jarosz-Chobot P, Kocsis G, et al. Routine sensor-augmented pump therapy in type 1 diabetes: the INTERPRET study. *Diabetes Technol Ther*. 2013;15:273–80.
- Šoupal J, Petruželková L, Flekač M, Pelcl T, Matoulek M, Daňková M, et al. Comparison of different treatment modalities for type 1 diabetes. Including sensor-augmented insulin regimens, in 52 weeks of follow-up: a COMISAIR study. *Diabetes Technol Ther*. 2016;18:532–8.
- Šoupal J, Petruželková L, Grunberger G, Hásková A, Flekač M, Matoulek M, et al. Glycemic outcomes in adults with T1D are impacted more by continuous glucose monitoring than by insulin delivery method: 3 years of follow-up from the COMISAIR study. *Diabetes Care*. 2020;43:37–43.
- Ramirez-Rincon A, Hincapie-García J, Arango CM, Aristizabal N, Castillo E, Hincapie G, et al. Clinical outcomes after 1 year of augmented insulin pump therapy in patients with diabetes in a specialized diabetes center in Medellín, Colombia. *Diabetes Technol Ther*. 2016;18:713–8.
- Gómez AM, Grizales AM, Veloza A, Marín A, Muñoz OM, Rondón MA. Factores asociados con el control glucémico óptimo en pacientes tratados con bomba de insulina y monitorización continua de glucosa en tiempo real. *Av En Diabetol*. 2013;29:74–80.
- Gómez AM, Marín Carrillo LF, Muñoz Velandia OM, Rondón Sepúlveda MA, Arévalo Correa CM, Mora Garzón E, et al. Long-term efficacy and safety of sensor augmented insulin pump therapy with low-glucose suspend feature in patients with type 1 diabetes. *Diabetes Technol Ther*. 2017;19:109–14.
- Gómez AM, Henao DC, Taboada LB, Leguizamón G, Rondón MA, Muñoz OM, et al. Impact of sensor-augmented pump therapy with predictive low-glucose management on hypoglycemia and glycemic control in patients with type 1 diabetes mellitus: 1-year follow-up. *Diabetes Metab Syndr*. 2019;13:2625–31.
- Katkade VB, Sanders KN, Zou KH. Real world data: an opportunity to supplement existing evidence for the use of long-established medicines in health care decision making. *J Multidiscip Healthc*. 2018;11:295–304.
- Khosla S, White R, Medina J, Ouwens M, Emmas C, Koder T, et al. Real world evidence (RWE) – a disruptive

- innovation or the quiet evolution of medical evidence generation? *F1000Research*. 2018;7:111.
19. Resnic FS, Matheny ME. Medical devices in the real world. *N Engl J Med*. 2018;378:595–7.
 20. Langendam M, Luijck YM, Hooft L, Devries JH, Mudde AH, Scholten RJP. Continuous glucose monitoring systems for type 1 diabetes mellitus. *Cochrane Database Syst Rev*. 2012;1:CD008101.
 21. Beato-Víbora PI, Quirós-López C, Lázaro-Martín L, Martín-Frías M, Barrio-Castellanos R, Gil-Poch E, et al. Impact of sensor-augmented pump therapy with predictive low-glucose suspend function on glycemic control and patient satisfaction in adults and children with type 1 diabetes. *Diabetes Technol Ther*. 2018;20:738–43.
 22. Bosi E, Choudhary P, de Valk HW, Lablanche S, Castañeda J, de Portu S, et al. Efficacy and safety of suspend-before-low insulin pump technology in hypoglycaemia-prone adults with type 1 diabetes (SMILE): an open-label randomised controlled trial. *Lancet Diabetes Endocrinol*. 2019;7:462–72.
 23. Abraham MB, Smith GJ, Nicholas JA, Fairchild JM, King BR, Ambler GR, et al. Effect of frequency of sensor use on glycaemic control in individuals on sensor-augmented pump therapy with and without Predictive Low Glucose Management System. *Diabetes Res Clin Pract*. 2020;159:107989.
 24. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ*. 2002;325:746.
 25. Speight J, Amiel SA, Bradley C, Heller S, Oliver L, Roberts S, et al. Long-term biomedical and psychosocial outcomes following DAFNE (Dose Adjustment For Normal Eating) structured education to promote intensive insulin therapy in adults with sub-optimally controlled Type 1 diabetes. *Diabetes Res Clin Pract*. 2010;89:22–9.
 26. Hopkins D, Lawrence I, Mansell P, Thompson G, Amiel S, Campbell M, et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. *Diabetes Care*. 2012;35:1638–42.
 27. Gunn D, Mansell P. Glycaemic control and weight 7 years after Dose Adjustment For Normal Eating (DAFNE) structured education in Type 1 diabetes. *Diabet Med J Br Diabet Assoc*. 2012;29:807–12.
 28. Cooke D, Bond R, Lawton J, Rankin D, Heller S, Clark M, et al. Structured type 1 diabetes education delivered within routine care: impact on glycemic control and diabetes-specific quality of life. *Diabetes Care*. 2013;36:270–2.
 29. Ehrmann D, Kulzer B, Schipfer M, Lippmann-Grob B, Haak T, Hermanns N. Efficacy of an education program for people with diabetes and insulin pump treatment (INPUT): results from a randomized controlled trial. *Diabetes Care*. 2018;41:2453–62.
 30. Group TRS. Relative effectiveness of insulin pump treatment over multiple daily injections and structured education during flexible intensive insulin treatment for type 1 diabetes: cluster randomised trial (REPOSE). *BMJ*. 2017:356.