

An Analysis of “No Effect of Insulin Pen with Memory Function on Glycemic Control in a Patient Cohort with Poorly Controlled Type 1 Diabetes: A Randomized Open-Label Study”

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Abstract

Missing meal bolus and nonadherence is an important barrier to achieving glycemic goals in type 1 diabetes (T1DM). In this issue of *Journal of Diabetes Science and Technology*, Danne and coauthors reported the results of a 24-week randomized-controlled study designed to evaluate if using an insulin pen with memory function, the HumaPen® Memoir™, might improve injection compliance and, therefore, overall glycemic control in T1DM. Patients treated with the pen device with memory function improved, albeit nonsignificantly, their mean HbA1c by 0.43%. Among the reasons to justify why this study was not positive, the most important is the high proportion of adult patients included in the study (87.9%)—children and adolescents being under-represented. I am convinced that pen devices with memory function might be helpful for forgetful patients (children, adolescents), as suggested in another recent study.

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Intensive insulin therapy prevents the onset or delays the progression of microvascular and macrovascular complications in type 1 diabetes mellitus (T1DM).^{1,2} However, poor adherence to insulin treatment has been reported as one of the major factors that contribute to long-term poor glycemic control, diabetes ketoacidosis, and brittle diabetes in adolescents and young adults with T1DM.³ In addition, in a survey on insulin-treated patients, mostly with type 2 diabetes, 33.2% of patients reported insulin omission/nonadherence at least 1 day in the past month.⁴ For young patients using continuous subcutaneous insulin infusion (CSII), missed mealtime insulin boluses have been recognized as a major cause

of suboptimal glycemic control.⁵ Patients who missed <1 bolus per week achieved a mean hemoglobin A1c (HbA1c) lower (~0.8%) than those who missed ≥1 bolus per week.⁵ A trend was found, albeit not significant, between lesser incidents of missing bolus and more self-monitoring of blood glucose (SMBG) tests per day.⁵ The consequences of missing bolus in adolescents with T1DM wearing insulin pumps are devastating. An audit in Sweden showed ~40% of adolescents missed >15% of doses on the previous day.⁶ These patients had higher HbA1c, took fewer SMBG measurements, were less satisfied with their treatment, and perceived medical treatment more negatively.⁶

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Abbreviations: (CSII) continuous subcutaneous insulin infusion, (HbA1c) hemoglobin A1c, (SMBG) self-monitoring of blood glucose, (T1DM) type 1 diabetes mellitus

Keywords: intensive insulin treatment, memory function, missing bolus, nonadherence, pen devices, type 1 diabetes

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The impact of poor adherence on insulin treatment efficacy has been quantified in some clinical scenarios. In adolescents using CSII, it has been calculated that HbA1c decreased by 0.2% for each additional SMBG ($p = .001$) and for each bolus event ($p < .001$).⁷ In addition, if patients took ≤ 2 meal boluses per day ≥ 1 day per fortnight, then HbA1c increased by 0.8% ($p = .001$).⁷ Reviewing medical literature, Randsløv and Poulsen,⁸ in a simulation study, suggested that forgetting 2.1 meal-related injections per week would increase HbA1c by at least 0.3–0.4%, confirming that missing injections are one of the main reasons for suboptimal treatment.

Regarding causes for insulin omission or nonadherence, the five most common reasons, as indicated by patients and providers in a survey, were as follow: too busy, travelling, skipped meals, stress or emotional problems, and/or public embarrassment.⁴ Insulin omission or nonadherence were more frequent among patients who were male, younger, had type 2 diabetes or more frequent hypoglycemia, were less successful with other treatment tasks, regarded insulin adherence as less important, had more practical/logistical barriers and difficulties with insulin adherence, were concerned that insulin treatment required lifestyle changes, or were dissatisfied with the flexibility of injection timing.⁹

Recognizing that missing meal bolus and nonadherence is an important barrier to achieving glycemic goals, different strategies have been tested with different success. In youth with T1DM wearing insulin pumps, Chase and coauthors¹⁰ evaluated if the use of meal bolus alarms would result in fewer missed boluses per week. Although the number of missed meal boluses significantly decreased after 3 months (from a mean of 4.9 to 2.5 missed meal boluses per week; $p = .0005$) and, therefore, HbA1c declined (from 9.32% to 8.86%; $p = .0430$), this beneficial effect of meal bolus alarms was not sustained after 6 months.¹⁰ The number of missed meal boluses increased by a mean of 0.8 per patient week between 3 and 6 months.¹⁰ The reasons for the weaning beneficial effect of the meal bolus alarms in these patients remain speculative.

For patients using insulin pens, other tools have been developed for increasing patient compliance with insulin injections. In this issue of *Journal of Diabetes Science and Technology*, Danne and coauthors¹¹ reported the results of a 24-week randomized controlled study designed to evaluate if using an insulin pen with memory function, the HumaPen[®] Memoir[™], might improve injection

compliance and therefore overall glycemic control in a broad age range sample of inadequately controlled patients with T1DM (baseline HbA1c $\geq 8.0\%$). The HumaPen Memoir is a pen with memory function that records dose, date, and time of the past 16 injections.¹² Although patients treated with the pen device with memory function improved their mean HbA1c by 0.43%, there was not a significant difference from the decrease observed in the control group.¹¹ No differences were also found regarding hypoglycemic episodes or treatment satisfaction.¹¹

There are several reasons to justify why this study was unable to demonstrate superiority of the pen device with memory function against the conventional pen. Most of the arguments have been discussed by the authors in the original manuscript. In principle, such a device will be of most profit for forgetful patients, mostly youths, who sometimes do not inject the insulin before meals and then, when they remember, administer the bolus after meals. However, the majority of patients in this study were adults (87.9%), with a mean age of 39.8 years, with children and adolescents underrepresented. Although the reasons for poor diabetes control may be diverse, it could be assumed that adults with poor diabetes control (HbA1c = $\sim 9.1\%$) may also be too noncompliant to administer insulin after meals. In addition, there was no information about the overall number of missed bolus injections, the number of corrective actions based on the memory, and, also importantly, blood glucose profiles, essential information to understand exactly the causes for the unexpected results. It is plausible that either corrective insulin injections started too late after a forgotten preprandial injection or there were, in fact, too few to have an impact on overall glycemic control.

Adolfsson and coauthors¹³ evaluated safety and patient perception of a new insulin pen with simple memory function in a sample of children and adolescents with T1DM. The tested pen device showed only the last dose and was able to deliver insulin in 0.5 U steps. They found that this new pen device increased the proportion of children who injected insulin themselves, missing fewer injections and reporting greater confidence in managing their insulin injections.

In conclusion, missed meal boluses or insulin injections occurs frequently, especially in pediatric patients, and are a major cause of poor glycemic control in these patients. Therefore, any strategy designed to increase compliance in these patients is welcome. Pen devices with memory function might be helpful for forgetful patients, mostly

children and adolescents, as shown by Adolfsson and coauthors.¹³ Consequently, there is still a need for more studies with such devices with memory function to establish their value in selected populations.

References:

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329(14):977–86.
2. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med.* 2005;353(25):2643–53.
3. Morris AD, Boyle DI, McMahon AD, Greene SA, MacDonald TM, Newton RW. Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus. The DARTS/MEMO Collaboration. *Diabetes Audit and Research in Tayside Scotland. Medicines Monitoring Unit. Lancet.* 1997;350(9090):1505–10.
4. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. *Diabet Med.* 2012;29(5):682–9.
5. Burdick J, Chase HP, Slover RH, Knievel K, Scrimgeour L, Maniatis AK, Klingensmith GJ. Missed insulin meal boluses and elevated hemoglobin A1c levels in children receiving insulin pump therapy. *Pediatrics.* 2004;113(3 Pt 1):e221–4.
6. Olinde AL, Kernell A, Smide B. Missed bolus doses: devastating for metabolic control in CSII-treated adolescents with type 1 diabetes. *Pediatr Diabetes.* 2009;10(2):142–8.
7. O’Connell MA, Donath S, Cameron FJ. Poor adherence to integral daily tasks limits the efficacy of CSII in youth. *Pediatr Diabetes.* 2011;12(6):556–9.
8. Randle J, Poulsen JU. How much do forgotten insulin injections matter to hemoglobin a1c in people with diabetes? A simulation study. *J Diabetes Sci Technol.* 2008;2(2):229–35.
9. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. Factors associated with injection omission/non-adherence in the Global Attitudes of Patients and Physicians in Insulin Therapy study. *Diabetes Obes Metab.* 2012. Epub ahead of print.
10. Chase HP, Horner B, McFann K, Yetzer H, Gaston J, Banion C, Fiallo-Scharer R, Slover R, Klingensmith G. The use of insulin pumps with meal bolus alarms in children with type 1 diabetes to improve glycemic control. *Diabetes Care.* 2006;29(5):1012–5.
11. Danne T, Forst T, Deinhard J, Rose L, Moennig E, Haupt A. No effect of insulin pen with memory function on glycemic control in a patient cohort with poorly controlled type 1 diabetes: a randomized open-label study. *J Diabetes Sci Technol.* 2012;6(6):1992–7.
12. Venekamp WJ, Kerr L, Dowsett SA, Johnson PA, Wimberley D, McKenzie C, Malone J, Milicevic Z. Functionality and acceptability of a new electronic insulin injection pen with a memory feature. *Curr Med Res Opin.* 2006;22(2):315–25.
13. Adolfsson P, Veijola R, Huot C, Hansen HD, Lademann JB, Phillip M. Safety and patient perception of an insulin pen with simple memory function for children and adolescents with type 1 diabetes - the REMIND study. *Curr Med Res Opin.* 2012;28(9):1455–63.