

Clinical Performance of a Device That Applies Local Heat to the Insulin Infusion Site: A Crossover Study

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Abstract

Background:

Fast-acting insulin analogs have been available since 1996. The absorption rate of these insulins is still too slow to mimic the physiological insulin action in healthy subjects. This study investigates the clinical performance of InsuPatch™, a local skin-heating device, on postprandial glucose excursion.

Methods:

Twenty-four type 1 diabetes mellitus subjects on continuous subcutaneous insulin infusion were included in this crossover study [10 male, 14 female, age: 43.5 ± 11.3 years, diabetes duration: 18.3 ± 10.5 years, glycosylated hemoglobin: $7.4 \pm 0.8\%$, body mass index: 25.0 ± 3.0 kg/m² (mean \pm standard deviation)]. The impact of local skin heating was measured by dividing the two-hour area under the curve by integration time (AUC/t₁₂₀) for blood glucose (BG) above baseline after two standardized breakfast and dinner meal pairs (with and without heating) per subject. For the first breakfast pair, venous insulin concentration was also measured.

Results:

A significant reduction was found for the AUC/t₁₂₀ after breakfast and after dinner meals (42 breakfast meal pairs, AUC/t₁₂₀ not heated 66.4 ± 32.8 mg/dl vs heated 56.8 ± 34.0 mg/dl, $p = .017$; 38 dinner meal pairs, AUC/t₁₂₀ not heated 30.8 ± 31.0 mg/dl vs heated 18.4 ± 23.9 mg/dl, $p = .0028$). The maximum venous insulin concentration with heating was 27% higher than without heating ($n = 23$). The number of hypoglycemic events on days with heating ($n = 9$) was similar to the number of days without heating ($n = 13$).

Conclusions:

Local heating of the skin around the infusion site significantly reduced postprandial BG by enhancing insulin absorption. The heating device was well tolerated, and it could facilitate development of closed-loop systems.

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Abbreviations: (ADE) adverse device effects, (AUC/t) area under the curve divided by integration time, (BG) blood glucose, (CHO) carbohydrate, (CSII) continuous subcutaneous insulin infusion, (HbA1c) glycosylated hemoglobin, (SD) standard deviation, (T1DM) type 1 diabetes mellitus

Keywords: blood glucose, continuous subcutaneous insulin infusion, insulin pump, postprandial excursion, skin heating

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Introduction

Near-normal glycemic control is an important goal for successful type 1 diabetes mellitus (T1DM) therapy.^{1,2} Rapid-acting insulin analogs were developed to meet prandial insulin requirements more effectively,³ however, an unambiguous improvement in glycosylated hemoglobin (HbA1c) could not be associated with the use of these new insulins.⁴⁻⁸ In comparison with the physiological postprandial insulin release in healthy subjects, rapid-acting insulin analogs are still absorbed more slowly.^{9,10}

Some studies have reported that smaller glucose excursions can reduce endothelial dysfunction and oxidative stress, and are therefore an important target for diabetes treatment, especially because the tools currently available are insufficient.^{11,12}

There are multiple approaches toward faster insulin action, especially to compensate for postprandial hyperglycemia. Sprinkler needles with multiple openings through which the insulin is delivered into multiple subcutaneous depots have been shown to increase insulin action,¹³ other studies have evaluated the use of inhaled insulins^{14,15} or intradermal insulin delivery.¹⁶ Some studies promote injection meal intervals¹⁷⁻²⁰ that do not accelerate the insulin action itself but reduce the time between meal consumption and maximum insulin action. The latter approach has disadvantages in terms of patient compliance or hypoglycemic risk if meals will be delayed or forgotten, e.g., in elderly subjects.

Faster-acting insulin also is essential in the development of closed-loop systems. In closed-loop systems, an algorithm uses glucose monitoring data to automatically control insulin delivered by an insulin pump. Current closed-loop systems incorporate continuous glucose monitors and insulin pumps, either for intraperitoneal or continuous subcutaneous insulin infusion (CSII).²¹ Systems that are used to achieve near-normal glycemic control still require human interaction, such as meal announcements, to provide efficient diabetes management,²² because insulin action does not occur fast enough.

Several studies showed an influence of skin temperature on insulin absorption from the subcutaneous infusion site.²³⁻²⁵ Koivisto and colleagues²⁶ used 125I-labeled rapid-acting insulin to determine the influence of sauna visits on insulin disappearance rate and found an increase in insulin absorption, while Sindelka and colleagues²⁷ found a positive correlation between local skin temperature at

the injection site and serum insulin levels 45 min after injection for a skin temperature range of 30 °C to 37 °C. Yet another approach was reported by Dillon,²⁸ who showed improved insulin profiles after stimulation of the injection site with local massage.

Raz and colleagues²⁹ published results of a study in which a local skin-heating device was used to determine the effect of local skin heating on insulin and glucose pharmacokinetics. In their study, which included 17 T1DM subjects who consumed a standardized liquid meal and received a standardized insulin bolus, the AUC of the postprandial glucose excursion was reduced from 0 to 90, 0 to 120, 0 to 150, and 0 to 180 min after the meal.²⁹

Cengiz and colleagues^{30,31} presented preliminary data of a clamp study about the effect of a warming device.

In the clinical study reported here, the capability of a local skin-heating device in enhancing insulin action and lowering postprandial glycemic excursions by heating the skin surrounding the insulin infusion site was investigated. The study was specifically designed to show the pharmacodynamic effect in a more real-life setting, using meals that people with diabetes would consume at home.

Methods

Study Design

This single-center, single-arm crossover exploratory study was performed between February and June 2009 in compliance with the Good Clinical Practice (GCP) guidelines, International Organization for Standardization 14155, the Declaration of Helsinki (revised edition, Seoul 2008), and the German Medical Devices Act (MPG). The ethics committee at the University of Ulm, Germany, approved its study protocol and 24 out of 26 screened T1DM subjects were enrolled in the study after providing written consent. Subjects had to be on CSII for at least 3 months prior to the screening visit, and their HbA1c had to be below 10.0 %.

Individual therapy parameters [basal rate, insulin sensitivity, insulin to carbohydrate (CHO) factors] were obtained from data collected during a 5-day outpatient intensive monitoring phase prior to the clinical visit. Meal insulin boluses were standardized for each subject and for

breakfasts and dinners separately, using a standardized CHO amount and the subject's insulin-to-CHO ratio for the specific mealtime.

The main part of the study was a clinical visit of 6 days. Subjects were sequentially assigned to groups of six patients to use the local heating device on day 2 and day 5, or on day 3 and day 4, to minimize potential effects on insulin need caused by the duration of the in-house stay. An experiment number was assigned to every subject upon inclusion. Patients with odd experiment numbers were assigned to one group, and those with even numbers were assigned to the other.

Study Meals

Clinical staff prepared standardized continental breakfast and dinner meals composed of bread, cheese, sausage, and fruits, according to each subject's daily caloric need. The caloric need was determined according to the World Health Organization's guideline.³² Breakfast meals were composed of 65% CHO, 15% protein, and 20% fat (percentage of each component's caloric value in relation to the meal's total caloric value), amounting to 33% of the daily caloric need of the subjects. Dinner meals also amounted to 33% of the daily caloric need but were composed of 40% CHO, 20% protein, and 40% fat. All breakfast and dinner meals were cold meals and identical for each subject during the four experimental days. Breakfast and dinner meals were analyzed separately. For evaluation, the data gathered from these meals were compared pairwise. For each meal type, one pair consisted of the data of the specific meal type on day 2 and day 3, and the other pair of data was gained on day 4 and day 5.

Study Devices and Insulin

The study aimed to characterize the performance of the InsuPatch™-heating pad unit (InsuLine Medical Ltd., Petach-Tikva, Israel), a local skin-heating device (version R1.1). InsuPatch is a circular heating pad that can be attached to an insulin infusion set. After bolus delivery of at least 1 unit of insulin, the system increases the tissue temperature around the infusion site to about 38.5 °C for a period of 30 min. In this study, a steel needle infusion set, ACCU-CHEK® Rapid-D Link (Roche Diabetes Care AG, Burgdorf, Switzerland), and insulin pumps, ACCU-CHEK® Spirit Insulin Pump (Roche Diabetes Care AG) ($n = 23$), or ACCU-CHEK® Combo System (Roche Diabetes Care AG), were used. Subjects stayed with the rapid-acting insulin analog that they were already using (lispro $n = 21$, aspart $n = 2$,

glulisine $n = 1$) and injected the meal boluses at the time of meal start. Meal bolus doses were identical for days 2 and 3, and again for days 4 and 5, but they could be adapted between day 3 and day 4.

During the study, capillary blood glucose (BG) was measured each day using the ACCU-CHEK® Aviva BG meter (Roche Diagnostics GmbH, Mannheim, Germany). Two independent BG measurements were performed with distinct devices. If the values of the devices differed by more than 10%, then the measurement was repeated. After breakfast meals, capillary BG was measured every 10 min for the first hour and every 15 min for the second hour. After dinner meals, there were measurements every 15 min for the first hour and every 10 min for the second hour.

On days 2 and 3 of the clinical visit, venous blood was sampled nine times between 0 and 2 h after breakfast meals (at 0, 10, 20, 30, 40, 50, 60, 75, and 120 min after the meal), and insulin and BG concentrations were determined to investigate the impact of the skin-heating device on insulin absorption. Venous insulin concentrations were determined by the Central Department of Clinical Chemistry at the University Hospital in Ulm, Germany [fluorescence enzyme immuno-assay, AIA®-21 (NexIA), Tosoh Corporation, Tokyo, Japan]. Venous BG concentrations were measured in duplicates, using ACCU-CHEK Aviva BG meters.

Glycosylated hemoglobin was measured before enrollment, using a DCA 2000+ Analyzer (Bayer HealthCare LLC, Elkhart, IN).

Data Analysis

The primary endpoint of this study was the AUC/t of capillary BG above baseline, between 0 and 120 min after meals (AUC/t₁₂₀). The data of 24 subjects resulted in 96 values (48 pairs) for AUC/t₁₂₀ of BG above baseline during the clinical visit.

Secondary endpoints of the study included the capillary BG concentration above baseline 90 min after the meal, the AUC/t₆₀ above baseline insulin concentration, and assessment of hypoglycemia (BG values below 70 mg/dl or hypoglycemia symptoms).

Due to the exploratory nature of the study, descriptive statistics are presented using a paired *t*-test without adjusting *p* values to multiple testing for the primary end point.

The data of 24 subjects should result in 48 AUC/ t_{120} values during the in-house experiment. A sample size of 48 had 78% power to detect an effect size [expected difference in means divided by the within-group standard deviation (SD)] of 0.5 using a t -test with a 5% one-sided significance level. The sample size was calculated with the nQuery Advisor[®] 5.0 (Statistical Solutions, Saugus, MA). Data were expected to be normally distributed. The distribution of data was checked for normality using the Shapiro-Wilk test.

All AUC/ t was calculated using the linear trapezoid rule (results in mg/dl*min) and then divided by the integration time in minutes, which resulted in mg/dl as the unit for AUC/ t .³³ The last BG value obtained within 10 min before the meal was used as baseline value $T = 0$ min. Blood glucose measurement and venous blood sampling times could deviate up to 3 min from the planned time of measurement; in these cases, parameters were calculated from the interpolated curve.

Data sets were excluded from analysis of single parameters if there were catheter changes before meals, if heating was not triggered properly, or in case of hypoglycemia interventions with potential impact on the specific parameter investigated (per protocol analysis).

Results

Study Subject Demographics

Twenty-four T1DM subjects (10 male, 14 female) who were on CSII for 7.7 ± 4.0 years [1–15 years] [mean \pm SD (range)] were included in this study [age 43.5 ± 11.3 years (18–62 years), T1DM for 18.3 ± 10.5 years (8–52 years), body mass index 25.0 ± 3.0 kg/m² (20.8–32.2 kg/m²)]. The subjects' daily insulin need was 0.58 ± 0.15 units/kg/day [0.38–0.86 units/kg/day]. The quality of diabetes therapy ranged from moderate to good; the subjects' mean HbA1c was $7.4 \pm 0.8\%$ [6.4–9.7%].

Area Under the Curve Divided by Integration Time for Capillary Blood Glucose Concentration Above Baseline

This AUC/ t was evaluated separately for breakfasts and for dinners to account for the different meal composition. The difference between no heating and heating is statistically significant for both types of meal (breakfast not heated 66.4 ± 32.8 mg/dl vs heated 56.8 ± 34.0 mg/dl, 42 meal pairs, $p = .0170$; dinner not heated 30.8 ± 31.0 mg/dl vs heated 18.4 ± 23.9 mg/dl, 38 meal pairs, $p = .0028$) (Figure 1).

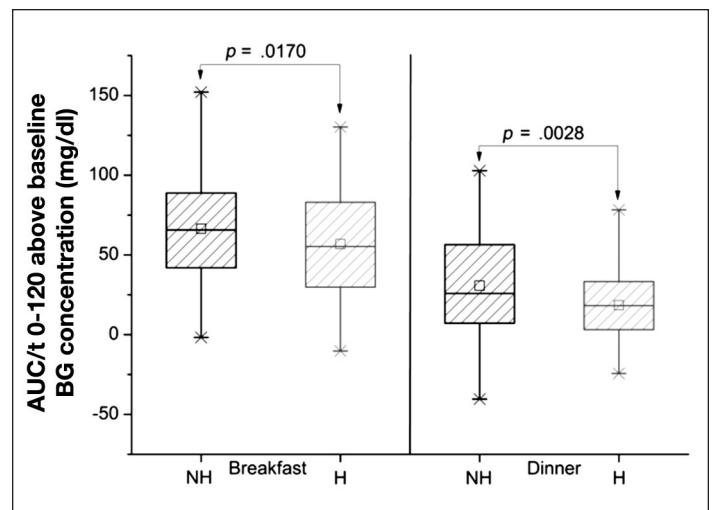


Figure 1. Box plots for AUC/ t_{120} min for capillary blood glucose concentration above baseline after breakfasts and dinners. For breakfast, data from 42 meal pairs were evaluated. For dinner, data from 38 meal pairs were evaluated. NH, not heated; H, heated.

For breakfast, baseline BG concentrations were 137.4 ± 35.7 mg/dl not heated and 138.1 ± 37.5 mg/dl heated. For dinner, they were 113.0 ± 38.6 mg/dl not heated and 123.5 ± 49.2 mg/dl heated.

Capillary Blood Glucose Concentration Above Baseline 90 Minutes After Meals

The BG concentration above baseline 90 min after breakfast and after dinner meals was significantly lower when the device was heated (breakfast not heated 83.0 ± 47.7 mg/dl vs heated 71.7 ± 51.3 mg/dl, 42 meal pairs, $p = .0392$; dinner not heated 41.1 ± 47.9 mg/dl vs heated 25.1 ± 37.2 mg/dl, 39 meal pairs, $p = .0091$). The BG₉₀ data for dinner not heated were slightly skewed to the left. Although using a t -test was formally incorrect, the result was kept for consistency. The statistical significance was confirmed by a Wilcoxon test. The capillary BG concentrations above baseline are displayed in Figure 2 (BG after breakfast) and Figure 3 (BG after dinner).

For breakfast, baseline BG concentrations were 137.4 ± 35.7 mg/dl not heated and 138.1 ± 37.5 mg/dl heated. For dinner, they were 112.4 ± 38.3 mg/dl not heated and 121.7 ± 49.8 mg/dl heated.

Venous Insulin and Blood Glucose Concentrations Above Baseline After Breakfast

Maximum venous insulin concentration above baseline was 27% higher with heating, but it was reached at the same time as without heating (not heated: 57.9 ± 32.7 mU/liter after 40 min; heated: 73.7 ± 38.5 mU/liter after 40 min,

maximum difference: 15.8 mU/liter at 40 min, 23 meal pairs; **Figure 4**).

Venous BG concentration above baseline remained at an elevated level for a longer time without heating, which led to an increasing difference in BG concentration (maximum difference: 17.0 mg/dl at 120 min, 23 meal pairs; **Figure 4**).

Baseline venous BG concentrations were 136.1 ± 39.9 mg/dl not heated and 147.3 ± 41.0 mg/dl heated. Baseline insulin concentrations were 14.9 ± 13.3 mU/liter not heated and 15.7 ± 15.1 mU/liter heated.

Technical Performance of the InsuPatch Heating Pad Unit R1.1

The local skin-heating device was worn by 24 subjects for 4 days, 2 days of which the device was used for local heat application. During this heating period, the heating was not triggered properly by bolus delivery on four occasions. In two of these cases, the cable connection loosened. However, in the two other cases, there was no apparent reason. Removing and reinserting the battery resolved the issue in all four cases, and the device started heating properly.

Safety Assessment

There were no serious adverse events or adverse device effects (ADE). Two skin reactions (both mild) and two abrasions (one mild and one moderate) were classified as ADE related to the study device.

The number of hypoglycemia interventions appeared to be similar with and without heating (9 vs 13).

Discussion

This study was designed to investigate the effects of heating the insulin injection site after prandial bolus delivery under conditions similar to real life. Subjects enrolled in this study were adult men and women with T1DM on CSII with moderate to good overall glycemic control. While previous studies used standardized liquid meals to investigate the effect of increased skin temperature,²⁹ this study used continental breakfast and dinner meals in a structured clinical setting to investigate if the device also works in conditions similar to everyday use.

Postprandial AUC/ t_{120} for capillary BG above baseline and the BG concentration 90 min after the start of the meal were significantly reduced and venous insulin

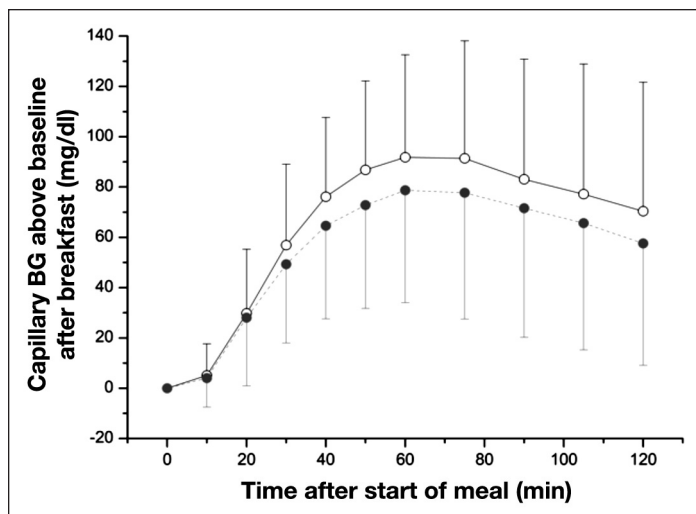


Figure 2. Capillary BG concentration above baseline (mean \pm SD) after breakfast without heating (open circles with solid line) and with heating (solid circles with dashed line) (42 meal pairs).

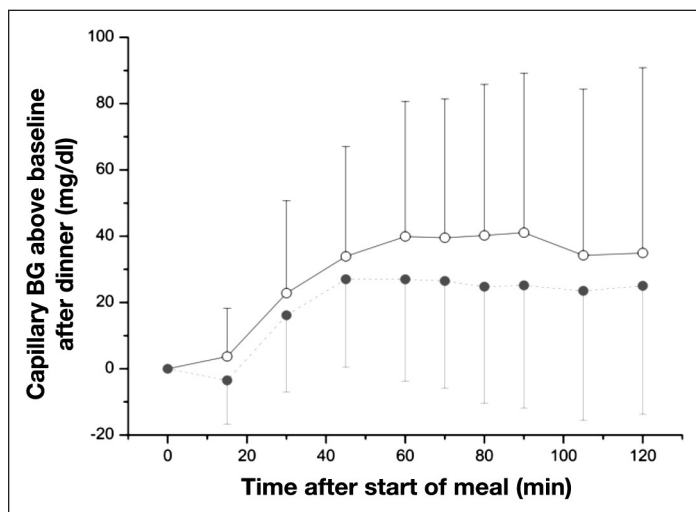


Figure 3. Capillary BG concentration above baseline (mean \pm SD) after dinner without heating (open circles with solid line) and with heating (solid circles with dashed line) (38 meal pairs).

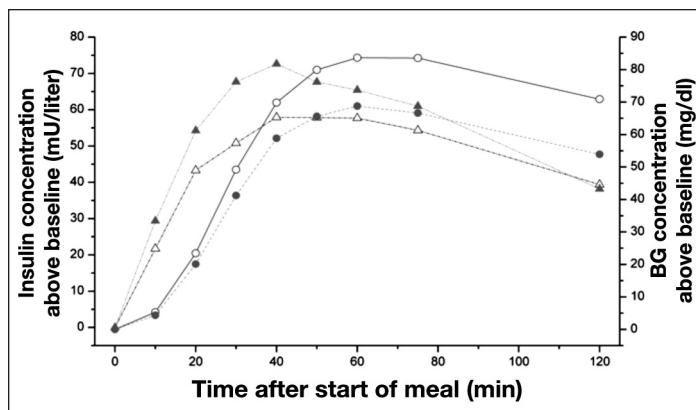


Figure 4. Overlay of venous blood glucose (circles) and venous insulin (triangles) concentrations above baseline (mean values) after breakfast (open symbols: no heating, solid symbols: heating) (23 meal pairs).

concentrations were higher with heating than without. The number of hypoglycemic interventions appeared to be similar with and without local heat application.

The effect of heating on the AUC/t_{120} after the slowly absorbed dinner was about three times stronger than after the fast-absorbed breakfast (14% for breakfast and 40% for dinner). Raz and colleagues,²⁹ who used a liquid meal tolerance test with 75% CHO content, reported a decrease of 33% in AUC/t_{120} when using the InsuPatch device. Postprandial glucose excursions are affected by several factors, such as meal composition^{34–36} and diurnal variations of the reaction to meal intake.^{37,38} Both are likely to have contributed to the larger effect observed after dinner.

Maximum venous insulin concentration was 27% higher with heating. Raz and colleagues,²⁹ who also investigated the InsuPatch device, also found an increase in maximum insulin concentration, although the increase was somewhat larger than in this study. If patients want to increase the available insulin, a typical approach would be to increase the meal insulin dose, but this increases the risk of late postprandial hypoglycemia and also increases insulin consumption. An alternative might be the use of a local skin-heating device.

According to some studies, for rapid-acting insulin analogs, the time to insulin peak action can be up to 90 min and more.^{15,39,40} Although this time frame is short enough for many patients to manage their diabetes, faster insulin action is one major criterion in developing an artificial pancreas. The major problem of an artificial pancreas is in compensating for meals and exercise. Current insulin analogs still act too slowly and too long for optimal regulation.²² The data presented here suggest that an augmented insulin action may be achieved by local application of heat to the skin.

In a published study, compared to bolusing at meal time, a prebolusing of insulin glulisine 20 min before the meal resulted in reductions of BG after 60 min of approximately 40 mg/dl and after 120 min of approximately 30 mg/dl.¹⁷ This reduction is more pronounced than the effect of the local skin-heating device without using an injection-meal interval, which is presented here. Injection-meal intervals do not change insulin action; they just shift the action profile so that insulin peak action may overlap better with the postprandial glucose excursion. There are studies reporting that many diabetes patients use no or very short injection-meal intervals¹⁹ and that using no injection-meal interval increases flexibility at meal

timing and quality of life.⁴¹ However, injection-meal intervals still are a beneficial therapy choice.¹⁷ Local skin-heating devices may offer an additional benefit when used in combination with injection meal intervals, but they could also be used by patients not able or willing to use injection-meal intervals.

Some technical issues with the heating device occurred during the 48 heating periods (2 days for each of the 24 subjects), especially with triggering of the heat application. However, these issues were resolved quickly, and use of the device was safe.

This study's findings have some limitations. This feasibility study took place in a controlled clinical environment. However, a clear effect could be demonstrated for meals that were composed in a way similar to everyday life. As stated earlier, meal composition and time of day might influence the device's effect. Lunch and snack meals were not investigated, but it seems likely that the heating device also has a beneficial effect on these kinds of meals. Although HbA1c was not investigated in this study, the observed change in glucose excursions might have an effect on HbA1c in a long-term study if the results are reproducible in a home-use setting.

Conclusions

This study has shown that applying local heat to skin has a beneficial effect on postprandial BG excursion by enhancing insulin absorption without increasing the risk of hypoglycemia. The slight increase in temperature at the infusion site had no impact on the subjects' well-being; nevertheless, it was powerful enough to enhance insulin absorption. The significance and role of individual factors, such as meal composition or time of day, should be investigated in future studies.

Local heating of the insulin infusion site is a step towards closing the loop, because overall insulin delivery is enhanced, which enables an adaptive model-based algorithm to compensate for a T1DM patient's post-prandial BG excursions in a much more flexible way. This would allow patients to be less affected by the restrictions of diabetes therapy in daily life.

Studies with a home-use setting, a larger number of patients, and longer duration should be conducted to investigate the beneficial effects of a local skin-heating device on postprandial blood glucose excursion, HbA1c, reliability, patient satisfaction, and hypoglycemic risk in long-term everyday use.

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Disclosures:

Guido Freckmann is general manager of the Institut fuer Diabetes-Technologie GmbH, in Ulm, Germany. This institute performs clinical trials in cooperation with different medical device companies. Guido Freckmann has received speaker's honoraria and travel support from such companies. Lars G. Krinelke and Andreas Buhr are employed by Roche Diabetes Care AG, in Burgdorf, Switzerland.

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