Improved Insulin Absorption by Means of Standardized Injection Site Modulation Results in a Safer and More Efficient Prandial Insulin Treatment A Review of the Existing Clinical Data

Journal of Diabetes Science and Technology
2015, Vol. 9(1) 116–122
© 2014 Diabetes Technology Society
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1932296814555400
dst.sagepub.com

Andreas Pfützner, MD, PhD¹, Itamar Raz, MD², Gabriel Bitton, PhD³,
David Klonoff, MD⁴, Ron Nagar³, Norbert Hermanns, PhD⁵, and Thomas Haak, MD⁵

Abstract

Temperature changes on the surface of the skin lead to modifications of subcutaneous microcirculation. This phenomenon is employed in a standardized way by the InsuPad device to stabilize skin conditions before injections, which is associated with enhanced prandial insulin absorption. Three programmed warming cycles to 40°C within 50 minutes are resulting in faster insulin appearance in the plasma. Early standardized meal tolerance studies indicated a substantial improvement in postprandial glucose control when the same short-acting insulin analog dose was applied using InsuPad, and a dose reduction by 20% resulted in comparable glucose excursions. Similar results were obtained when patients applied the device under real-world conditions for 1 month. The InsuPad device was also tested in a prospective, controlled, parallel 3-month real-world study with 145 well-controlled but insulin-resistant patients with type 1 or type 2 diabetes. Patients were treated to target in both treatment arms ($6.2 \pm 0.5\%$ in each group), with or without the device. However, patients with InsuPad needed 28% less prandial insulin, needed 12.5% less total insulin, and had 46% less confirmed hypoglycemic events (blood glucose < 63 mg/dL) as compared to the control group. Except for very few inflammatory or allergic skin reactions, there were no device-specific adverse events reported from these studies. In conclusion, use of InsuPad when applying prandial insulin doses may result in a safer and more efficient treatment of type 1 or type 2 diabetes.

Keywords

insulin treatment, InsuPad, injection site modulation, prandial insulin dose, hypoglycemia

Elevation of skin temperature leads to increased (sub)cutaneous vasodilatation, and local skin blood flow increases when the skin surface temperature goes above 37°C. It reaches a maximum when the skin temperature is held at 42°C.¹ This local temperature effect on microcirculation is mediated by an initial local activation of afferent cutaneous sensory nerves and by an additional local vascular nitric oxide secretion resulting in a prolonged plateau phase of increased blood flow.^{2,3} While already described in 1980 by Koivisto, who measured enhanced insulin absorption when using a finish sauna after insulin injection,⁴ the phenomenon was more thoroughly investigated and confirmed by Berger et al few years later.⁵ The InsuPad device employs this temperature effect on microcirculation locally at the injection site in a standardized way.

The InsuPad device (Figure 1) has 2 components, (1) a rechargeable flat warming control unit (29 × 44 × 12 mm) and (2) a disposable (42 × 60 mm) double plastic frame connected by a hinge that opens like a window. One part can be fixed to

the skin with an adhesive tape, while the warming block fits into the other frame part. The block contains the energy source and the device electronics. The patients inject through the frame that is large enough to allow the daily injection at sufficiently different locations to avoid development of lipodystrophy. After injection, the device is closed and exposes the skin surface at the injection site to the warming surface of the control unit. The closure automatically activates the device, which now applies 3 standardized warming intervals

¹Pfützner Science & Health Institute, Diabetes Center and Practice, Mainz, Germany

²Hadassah School of Medicine, Jerusalem, Israel

³Insuline Medical Ltd, Petach-Tikva, Israel

⁴Diabetes Center, Mills Peninsula Health Services, San Mateo, CA, USA

⁵FIDAM—Institute for Diabetes Research, Bad Mergentheim, Germany

Corresponding Author:

Andreas Pfützner, MD, PhD, Pfützner Science & Health Institute, Diabetes Center and Practice, Parcusstrasse 8, D-55116 Mainz, Germany.
Email: andreas.pfuetzner@pfuetzner-mainz.com

Figure 1. The InsuPad device.

(40°C) of 10 minutes each followed each by 10-minute breaks. Thereafter, it shuts off automatically. For the next injection, the device has to be opened again. The energy pack can be used for 1 day and has to be recharged. Patients are provided with 2 control units to allow for recharging until each second consecutive day. Removal of the unit from the frame in the evening destroys the frame. Patients are trained to use a new frame at a different skin location in the following morning. A series of clinical trials has been performed with this new device to investigate the efficacy and safety of using the device for prandial insulin administration. A summary of these studies is shown in Table 1.

Meal Tolerance Studies

The device impact on prandial insulin doses has initially been investigated in several of controlled and standardized meal tests in a hospital setting.⁶ Sixteen patients with type 2 diabetes were enrolled and received a standardized liquid meal with an individually selected prandial insulin aspart dose (control experiment with original dose). In a second experiment, the same insulin dose was administered, but now using the InsuPad device. The postprandial glucose excursions are shown in Figure 2A. Use of InsuPad resulted in substantially lower glucose excursions and a much flatter glucose profile.⁷ Reducing the prandial insulin dose by 20% when using InsuPad lead to similar and overlapping glucose excursions as observed in the control experiment⁷ (see Figure 2B). In a final experiment, the original insulin aspart dose was administered 30 minutes after the meal uptake when using InsuPad. There was an earlier rise in the glucose levels after this delayed administration but the peak glucose levels were significantly lower with InsuPad indicating a still better postprandial glucose control with InsuPad use^{8,9} (see Figure 2C). The clinical implication of these findings for daily life conditions were investigated in an initial home-use

crossover study. The participating patients were randomized to the use of InsuPad when injecting bolus insulin before breakfast and dinner for 1 month and they measured their blood glucose 5 times daily (before and after breakfast and dinner and at bedtime). The other study group performed the same procedures but without using the InsuPad. A crossover to the other treatment arm took place after 4 weeks. In this study, 20 insulin-resistant diabetic patients could be included (age 53.7 ± 8.9 years, HbA1c $8.3 \pm 0.8\%$; total daily insulin dose: 0.97 ± 0.32 IU/kg body weight). Use of InsuPad resulted in a reduction of postprandial glucose excursions by 15.4 mg/dl (95% CI 9.7-21.2 mg/dl) after breakfast and dinner ($P < .05$) and a tendency for lower mean daily blood glucose levels (-8.8 mg/dl (95% CI 4.5-13.2 mg/dl; $P = .099$). In addition, the number of hypoglycemic (<60 mg/dL) and hyperglycemic (>300 mg/dL) events was slightly but not significantly reduced with device use. It was concluded from this initial home-use study that use of the InsuPad device for 4 weeks under daily life conditions resulted in improved glycemic control without negative side effects.¹⁰

The Real-World BARMER Study

In collaboration with one of the largest German health care cost carriers, the BARMER GEK sick fund, a prospective parallel controlled randomized study was designed and conducted to explore whether the improvements in postprandial control observed in the meal test studies can translate into clinical and economical advantages when InsuPad is used in daily life.¹¹

The primary objective of the BARMER study was to show a reduction of the prandial insulin dose by more than 10% when using InsuPad (InsuPad group), while achieving a similar glycemic control as compared to a control group not using the InsuPad device (control group). Inclusion criteria were type 1 or type 2 diabetes, intensive insulin therapy with insulin analogs, HbA1c $< 8.0\%$, and a total daily insulin dose > 60 IU. Prior to randomization to 1 of the 2 treatment arms, the basal insulin dose was optimized by means of titration algorithms to achieve normal fasting morning blood glucose levels. Patients were retrained about intensive insulin treatment and (if not randomized to the control group) on using the InsuPad device. To support the real-world character of the investigation, study visits took place only at baseline (randomization visit) and after 3 months (final visit). Patients were asked to try to treat themselves to a target HbA1c $< 6.5\%$ and target postprandial glucose levels < 160 mg/dL. Observation parameters included HbA1c, insulin dose, frequency of hypoglycemic events, body weight, and adverse events. To verify the documented prandial insulin dose information, a meal tolerance test procedure was performed in a subset of 32 participants in 1 study site at baseline and after 3 months.

All participating 145 patients (51 female, 94 male, 13 type 1, and 132 type 2 patients, age: 61.6 ± 8.4 years,

Table 1. Summary of the Clinical Studies Performed With InsuPad.

Study	Specifications
Standardized Meal Study	Type 2 patients, n = 14 Controlled prospective standardized meal experiments Not using InsuPad vs using InsuPad with different dosing conditions Same dose, 80% dose, and same dose postprandial administration Objectives: postprandial glucose excursions, insulin pharmacokinetics Safety objective: adverse events
Home Use Study	Type 1 and 2 patients, n = 20 Controlled prospective 2 × 4 weeks crossover Use of InsuPad vs not using InsuPad Objective: postprandial glucose excursions at breakfast and dinner
BARMER Study	Type 1 and 2 patients, n = 145 Controlled, prospective, parallel 3-month study Use of InsuPad vs not using InsuPad Objectives: prandial insulin dose, glycemic control Safety objectives: hypoglycemia, hyperglycemia, adverse events
BARMER Study, MTT Substudy	Type 1 and Type 2 patients, n = 32 Controlled prospective, parallel, standardized meal experiments Use of InsuPad vs not using InsuPad Objectives: verification of prandial insulin dose reduction Safety objective: adverse events
BARMER Study, Quality of Life assessment	Type 1 and 2 patients, n = 145 Controlled, prospective, parallel 3-month study Use of InsuPad vs not using InsuPad Objectives: quality of life questionnaires (PAID, DTSQ) Safety objectives: adverse events
BARMER Study Follow-up	Type 1 and 2 patients, n = 52 Uncontrolled follow-up questionnaire assessment after long-term use of InsuPad (18 months) Objectives: insulin doses, body weight Safety objective: device-related adverse events

HbA1c: 7.19 ± 0.50) were treated with intensive insulin glargine and short-acting insulin analog therapy. All of them were obese and insulin-resistant. HbA1c improved in both arms until study end (control group: $6.3 \pm 0.5\%$; InsuPad: $6.3 \pm 0.5\%$; both $P < .001$ vs baseline). To achieve this good control, patients in the control group needed to increase the daily prandial insulin dose by 8.1% (from 66 ± 31 U to 71 ± 38 U, $P < .05$) with stable basal insulin requirements. InsuPad patients required substantially less prandial insulin (70 ± 43 U to 55 ± 34 U; -19% , $P < .001$) and slightly more basal insulin ($+3.9\%$). Total daily insulin dose increased in the control group ($+3.7\%$) and decreased with InsuPad (-8.6% , $P < .001$). The number of hypoglycemic events (<63 mg/dL) during the observation period was higher in the control group (6.2 ± 9.9 /patient vs InsuPad: 3.3 ± 4.8 /patient, $P < .05$). There were no serious adverse events reported in the study that were considered to be related to the use of InsuPad and only few technical issues were observed.¹¹ From a subanalysis of the small group of the somewhat less obese type 1 patients in this study, it can be speculated that slim and more insulin-sensitive patients may rather benefit from the reduction in hypoglycemia and a

smoothing of the daily blood glucose profiles than from insulin dose reductions (see Figure 3). However, further and appropriately designed controlled larger studies are required to confirm this hypothesis.

The purpose of a consecutive post hoc analysis was to compare the outcome in patients who achieved a combination of 2 treatment targets (HbA1c $< 6.5\%$ and weight loss > 1 kg) with or without InsuPad, with respect to prandial insulin dose and hypoglycemic episodes (<63 mg/dL). All patients who completed the BARMER study and lost more than 1 kg of body weight in the 3-month observation period were included into this analysis. Mean values were calculated for HbA1c, body weight changes, changes in prandial and basal insulin dose, and changes in the number of reported hypoglycemic and hyperglycemic readings. Meeting the inclusion criteria were 22 patients in the InsuPad group (9 female, 1 type 1, age: 64 ± 8 years, weight: 106.7 ± 18.7 kg) and 17 patients in the control group (7 female, 3 type 1, 60 ± 10 years, 109.0 ± 18.4 kg). As predefined by the inclusion criteria, HbA1c treatment target ($<6.5\%$) was successfully met after 3 months in both groups (InsuPad: $6.2 \pm 0.5\%$ vs control: $6.3 \pm 0.5\%$, *ns*).

Figure 2. Glucose excursions during standardized meal experiments. (A) Same dose with and without InsuPad. (B) 20% dose reduction when using InsuPad. (C) Same dose with InsuPad injected 30 minutes after start of meal. In (B) and (C) error bars were omitted for better readability.

Mean weight loss was -2.6 ± 1.5 kg with InsuPad and -3.7 ± 4.4 kg without InsuPad (*ns*). InsuPad patients needed 28% less prandial insulin (control: +12%, $P < .001$) and 1% more basal insulin (control: -2%, *ns*) to reach this target. Overall number of glucose readings was similar in both groups. Mean number of hypoglycemic readings was 2.8 ± 4.4 /patient with InsuPad and 8.9 ± 16.0 /patient without InsuPad ($P < .05$), respectively. This reduction in hypoglycemia was by far more pronounced than the reduction in patients without change in body weight or with weight gain (see Figure 3). Treating obese patients to a combined treatment target (HbA1c <6.5% and weight loss > 1kg) with intensive insulin analog therapy was possible with and without use of the InsuPad device. However, patients using the device needed substantially less prandial insulin and had only a third of the frequency of hypoglycemic readings as compared to the control group not using the device.¹²

After the BARMER study, patients were supplied with the device and disposables and were allowed to continue with

Figure 3. Reduction in hypoglycemic events (symptomatic or asymptomatic readings < 63 mg/dL) as observed in different patient subgroups in the BARMER study.

device use if desired until a final reimbursement decision. A long-term follow-up investigation was performed in 52 patients (65 ± 8 years) who participated at 1 study site and who could be recontacted after a minimum of 13 months (mean usage time: 17.8 ± 2.5 months, range: 13-21 months). Only 2 patients (3.8%) had stopped to use the device because of persistent skin reaction to the adhesive. In the remaining patients, body weight had remained stable (3 months: 100 ± 23 kg vs 18 months: 100 ± 18 kg, *ns*), HbA1c was stable ($6.4 \pm 0.7\%$ vs $6.3 \pm 0.6\%$, *ns*), and total daily insulin dose was even further reduced as compared to baseline (3 months: -16.5% vs 18 months: -25.3% , $P < .001$). These results indicate that the benefits seen with InsuPad in the 3-month BARMER study were maintained even over a period of 18 months or longer.

It needs to be mentioned that the reported post hoc sub-analyses were performed with small subsets of the study population and the applied statistical models are quite basic. Therefore, further and appropriately designed and controlled larger studies are required to confirm these results.

The Meal Tolerance Test Substudy

The Meal Tolerance Test (MTT) substudy aimed to demonstrate noninferiority of the reduced insulin dose as seen in the BARMER study with InsuPad with respect to postprandial glucose and other metabolic parameters. The MTT was performed at baseline and after 3 months at 1 study site. The InsuPad-group was tested at baseline without InsuPad and at endpoint with InsuPad. The MTT dose was calculated based on the individually recorded prandial doses of the week before the test procedure. Blood was drawn for determination of glucose, insulin, C-peptide, proinsulin, triglycerides, free fatty acids, nitrotyrosine, and ADMA at multiple time points over 5 hours. A total of 32 patients were included into this substudy (8 female, 7 type 1 diabetes, age: 49.9 ± 12.5 years, HbA1c: $7.2 \pm 0.5\%$, body weight: 106.8 ± 17.5 kg, mean prandial insulin dose: 54.9 ± 20.4 U). During the 3-month BARMER study period, mean HbA1c was treated to target ($<6.5\%$) in both groups. Prandial insulin dose was decreased in the InsuPad group (-19.4% ; control: $+1.2\%$, $P < .001$). No change was seen for the basal insulin dose in both groups. Despite the lower dose at endpoint applied in the MTT, there were no differences between the groups with respect to the postprandial curves for glucose, C-peptide, intact proinsulin, free fatty acids, and triglycerides. Insulin absorption was faster with InsuPad ($T_{\text{Max}0.5}$: 17 ± 7 minutes, control: 26 ± 11 minutes, T_{max} : 60 ± 28 minutes vs 99 ± 46 minutes, $P < .05$ in both cases; see Figure 3). A decrease in both oxidative stress biomarkers (nitrotyrosine and ADMA) was more pronounced in the InsuPad arm. The MTT study confirmed that the observed prandial insulin dose reduction when using InsuPad had no negative impact on the entire postprandial metabolism. Biomarkers of oxidative stress indicated that use of InsuPad with short-acting insulin analogs might have the potential to delay the progression of macrovascular disease.¹³

Quality of Life Considerations

Another secondary objective of the BARMER study was to investigate the impact of InsuPad use on treatment satisfaction and diabetes-related distress during 3 months of device daily use. At endpoint, the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the Problem Areas in Diabetes (PAID) questionnaire were completed. Post hoc power analysis assessed the statistical power to detect differences of the observed magnitude in treatment satisfaction and diabetes-related distress. Patients of the intervention group were further asked to rate, if using the InsuPad would induce either less, the same or more pain at the injection site than not using the InsuPad. Overall diabetes treatment satisfaction was highly comparable between intervention (29.1 ± 6.7) and control group (29.6 ± 6.6 ; $p = .720$; post hoc power $1-\beta = 0.82$). Patients estimation of the frequency of unacceptable low blood glucose levels were lower when using the InsuPad (1.4 ± 1.2) than in the control group (1.9 ± 1.5 ; $P < .05$), which corresponds to the clinical hypoglycemia data (mean frequency of hypoglycemia/patient/3 months: 3.3 ± 4.8 with InsuPad and 6.2 ± 9.9 in the control group, $P < .05$). Self reported frequency of unacceptable high glucose values was slightly lower in the intervention than in the control group (1.9 ± 1.4 vs 2.2 ± 1.5 , $P = .12$). Diabetes-related distress was highly comparable in the intervention and control groups (19.3 ± 14.5 vs 18.8 ± 18.9 , $P = .85$, power $1-\beta = 0.85$). One-third of the intervention group (34.3%) reported reduced injection pain while using the InsuPad, 61.4% reported same pain intensity, and 4.2% reported increased pain sensation. The use of InsuPad induces an additional treatment effort for the patients (overnight recharging of the InsuPad, adhering the device to the body, opening and closing the dives for an injection). The analysis of patient-reported outcomes, however, did not indicate any negative impact of the InsuPad use on treatment satisfaction nor on diabetes-related distress. In summary, patient-reported outcomes suggest that use of the InsuPad seems to be perceived as beneficial by patients with regard to incidence of hypoglycemia and pain intensity, without reducing treatment satisfaction or increasing diabetes-related distress.¹⁴

Practical Recommendation for InsuPad Use

InsuPad is approved for marketing in Europe and has been commercially available in Germany since autumn 2013. It is approved for use with prandial insulin administration and without restriction in all adult patients with type 1 or type 2 diabetes. Practical recommendations about the most optimal way to use InsuPad have been developed in several advisory board meetings after the participating physicians had the opportunity to make their own experience with InsuPad in daily routine practice.

Table 2. InsuPad in a Nutshell.

InsuPad is a medicinal product that supports patients with intensive insulin therapy to reach treatment targets in a more efficient and safer way

InsuPad is useful for patients with

- High prandial insulin requirements
- High postprandial blood glucose excursions
- High blood glucose variability
- High risk of hypoglycemia

InsuPad may be useful in patients with

- Delayed gastric emptying
- Nephropathy
- Pregnancy

InsuPad may not be used

- When initiating prandial insulin treatment for the first time
- In patients with extensive abdominal hair growth and unwillingness to shave
- In patients with strong sweating
- In patients with allergy to the wound plaster
- In patients on anticoagulant combinations (risk of hematoma)

Topics to consider when using InsuPad

- Clear definition of intervention goal (insulin savings; prandial dose reduction vs better glycemic control; keep prandial dose)
 - Explain device action; patients do not always feel the warming process to 39.5°C
 - The daily use of new injection frames must be trained and explained
 - Injection to meal intervals have to be shortened (if applicable)
 - Initiation of InsuPad treatment should be associated with a higher frequency of glucose readings in the first days
-

InsuPad modifies the pharmacokinetic profile of the applied prandial insulin and makes it faster in the onset and shorter in duration of action. Despite this accelerating effect, all usual rules and considerations regarding insulin treatment remain still valid and in place. InsuPad should be regarded as another tool in the toolbox of the diabetologist, which was also successfully applied in cases of failure of the other established methods. Its efficacy can be seen directly with the first use and may therefore be helpful to motivate patients to improve their treatment. According to the experienced prescribers, there may be 3 patient groups that can particularly benefit from InsuPad use: patients with high prandial insulin doses, patients with substantial postprandial blood glucose excursions, and patients with high risk of hypoglycemic episodes.¹⁵ In the first and last case, patients may be educated to reduce their prandial insulin dose when initiating the InsuPad use by 20% with later dose changes trying to have postprandial values < 160 mg/dL. Patients seeking better postprandial control may keep their dose to see the immediate effect and adjust in the following days also to achieve postprandial target levels < 160 mg/dL. The option to use InsuPad to perform postprandial insulin treatment opens another field of therapeutic use, for example, in pediatric patients and in patients with delayed gastric emptying, unpredictable eating behavior, pregnancy, and renal insufficiency. An overview of the practical use recommendations is provided in Table 2. Starting InsuPad treatment should be handled like every insulin treatment intensification attempt and should be initially associated with a higher frequency of patient self-blood glucose measurements for fast correction of over- or underdosing. InsuPad is for use with prandial insulin

only. Injecting basal insulin through the device may result in unfavorable modifications of the basal insulin efficacy profile, although the clinical consequences are expected to be minimal.

Difficulties with InsuPad use may occur, if patients have a dense growth of hair on the belly and are reluctant to shave the skin clean. Hyperhidrosis may also impair the success rate with InsuPad especially at warm ambient temperatures. Measures to reduce sweating, such as antihidrosis rollers, have been successfully used in anecdotal cases. While a very tolerable dressing has been used to produce the disposable frames (the so called “Fenster”), skin reactions to this dressing have been reported in few cases. Because of the active mechanism of InsuPad and the morphologic appearance of the skin reaction, some of these cases were reported as “burns.” However, the respective devices were thoroughly investigated and proved to be functioning correctly, with temperature sensors preventing any overheating. In addition, some patients continued to use the device after the event without any further problems, which is contradictory to a contact allergy. These incidences are extremely rare, and no other device-related adverse events have been reported from the clinical studies or from routine use in daily practice.

Discussion and Conclusions

Using changes in physical conditions of the skin to enhance insulin absorption, for example by massaging the skin or warming the skin surface, is a well-known procedure to experienced patients, nurse educators, and physicians who

perform, teach, or initiate insulin treatment. The development of the InsuPad device makes it now possible to apply these conditions in a standardized way and stabilize skin conditions after insulin administration. The device has been tested in a comprehensive set of clinical studies and has shown to result in benefits for the patient with respect to treatment effectiveness and safety. When interpreting the study results for their transferability into daily clinical practice, their design and patient population have to be considered prior to drawing conclusions for the usefulness of the device for daily routine. It is certainly an advantage that the device has been tested several times with protocols trying to come as close as possible to real-life conditions. As usual, each study design has advantages and disadvantages, and certain patient populations have been excluded from each trial, which limits the transfer to the general diabetes population. Like every new treatment moiety, InsuPad is to be considered another treatment option, which may be suitable and beneficial for many but not for all patients with prandial insulin treatment. There have been astonishing and spectacular anecdotal results in the study and the marketing phases in individual patients, but there have also been patients for whom the extra effort and economical impact were not justified by the clinical outcome.

However, based on the study results and launch experience in Germany, it can be stated that InsuPad is a medical device that may be used to support prandial insulin treatment to improve glycemic control with less insulin requirements and a lower number of hypoglycemic events. InsuPad may therefore be useful to achieve treatment targets with a safer and more efficient basal bolus therapy in insulin-treated patients with type 1 or type 2 diabetes.

Abbreviations

ADMA, asymmetric dimethyl-adenin; DTSQ, Diabetes Treatment Satisfaction Questionnaire; HbA1c, hemoglobin A1c; MTT, Meal Tolerance Test; PAID, Problem Areas in Diabetes; Tmax, time to peak plasma concentrations; U, international unit.

Acknowledgments

The authors would like to thank all patients and the staff members of the involved institutions for the commitment and efforts made to develop InsuPad and successfully bring it to the market.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: InsuPad is a device marketed and sold by Insulin Medical, Petach-Tikva, Israel. RN and GB are employees and shareholders of Insuline-Medical. AP, IR, DK, NH, and TH have received consultancy fees, speaker fees, travel support, and research grants from Insuline-Medical in the context of the device development.

References

1. Magerl W, Treede RD. Heat-evoked vasodilatation in human hairy skin: axon reflexes due to low-level activity of nociceptive afferents. *J Physiol.* 1996;497(pt 3):837-848.
2. Minson CT, Berry LT, Joyner MJ. Nitric oxide and neurally mediated regulation of skin blood flow during local heating. *J Appl Physiol.* 2001;91:1619-1626.
3. Kellogg DL Jr. *In vivo* mechanisms of cutaneous vasodilation and vasoconstriction in humans during thermoregulatory challenges. *J Appl Physiol.* 2006;100:1709-1718.
4. Koivisto VA. Sauna-induced acceleration in insulin absorption from subcutaneous injection site. *Br Med J.* 1980;280:1411-1413.
5. Berger M, Cüppers HJ, Hegner H, Jörgens V, Berchtold P. Absorption kinetics and biologic effects of subcutaneously injected insulin preparations. *Diabetes Care.* 1982;5:77-91.
6. Bitton G, Raz I, Pfützner A, et al. Reduced postprandial glucose excursion in type 2 diabetic subjects using the InsuPad device. *Diabetologia.* 2012;55(suppl 1):A98.
7. Pfützner A, Feldman D, Bitton G, et al. Effect of the InsuPad device on postprandial glucose excursion in type II diabetic subjects. *Diabetes Technol Ther.* 2013;15(suppl 1):A167.
8. Bitton G, Feldman D, Alon T, Nagar R, Pfützner A, Raz I. Effect of the InsuPad device on post meal glucose level with delayed insulin bolus injections. *Diabetes.* 2013;62(suppl 1):A217-A364.
9. Pfützner A, Hermanns N, Funke K, et al. Die standardisierte Erwärmung der Injektionsstelle nach Insulingabe mit InsuPad: ein einfaches physikalisches Phänomen führt zu einer effizienteren und sichereren Insulintherapie. *Diabetes Stoffw Herz.* 2013;22:295-230.
10. Pfützner A, Hermanns N, Kulzer B, Funke K, Haak T. The impact of local warming at the insulin injection site by the use of the InsuPad device on treatment satisfaction and diabetes related distress. In: Proceedings from the IDF World Diabetes Congress; December 2-6, 2013; P1729; Melbourne. <http://conference2.idf.org/MEL2013/WorldDiabetesCongress2013/data/HtmlApp/main.html#open-sessions>
11. Pfützner A, Hermanns N, Funke K, et al. The BARMER Study: impact of standardized warming of the injections-site to enhance insulin absorption and to reduce insulin requirements and hypoglycemia in obese patients with diabetes mellitus. *Curr Med Res Opin.* 2014;30:753-760.
12. Pfützner A, Segiet T, Behnke T, Haak T, Bitton G, Nagar R. Obese patients on intensive insulin analog therapy losing body weight particularly benefit from using the InsuPad device with respect treatment safety and insulin. *Diabetes.* 2014;63(suppl 1):2371.
13. Pfützner A, Dissel S, Forkel C, et al. Reduced prandial insulin dose after 3 months with InsuPad results in similar metabolic control than the original dose at baseline in a meal tolerance test [published online ahead of print 2014]. *Curr Med Res Opin.*
14. Pfützner A, Hermanns N, Kulzer B, Funke K, Haak T. The impact of local warming at the insulin injection site by the use of the InsuPad device on treatment satisfaction and diabetes related distress. Paper presented at: IDF Conference; December 2-6, 2013; Melbourne, Australia.
15. Behnke T, Segiet T, Funke K, Pfützner A. Aus der Praxis für die Praxis: Empfehlungen für den InsuPad-Einsatz. *Diabetes Stoffw Herz.* 2014;23:43-44.