Environmental effects of ambient temperature and relative humidity on insulin pharmacodynamics in adults with type 1 diabetes mellitus

Ahmed Al-Qaissi MD1 | Maria Papageorgiou PhD1 | Zeeshan Javed MD1,2 | Tim Heise PhD3 | Alan S. Rigby PhD4 | Andrew T. Garrett PhD5 | David Hepburn MD6 | Eric S. Kilpatrick PhD7 | Stephen L. Atkin MD8 | Thozhukat Sathyapalan MD1

1Department of Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull, Hull, UK
2Pakistan Kidney and Liver Institute and Research Center, Lahore, Pakistan
3Profil, Neuss, Germany
4Department of Academic Cardiology, Hull York Medical School, University of Hull, Hull, UK
5Department of Sport, Health and Exercise Science, University of Hull, Hull, UK
6Department of Academic Diabetes, Endocrinology and Metabolism, Hull and East Yorkshire Hospitals NHS Trust and Hull York Medical School, University of Hull, UK
7Department of Pathology, Sidra Medicine, Doha, Qatar
8Weill Cornell Medicine in Qatar, Education City, Qatar

Correspondence
Thozhukat Sathyapalan MD, Department of Academic Diabetes, Endocrinology and Metabolism, Hull Medical School, University of Hull, UK.
Email: thozhukat.sathyapalan@hyms.ac.uk

Funding information
This study was supported by Hull and East Yorkshire Hospitals Charitable Funds.

Objective: This study aimed to explore the effects of ambient temperature and relative humidity on insulin pharmacodynamics in adults with type 1 diabetes.

Materials and methods: A three-way, cross-over, randomised study was performed in adults with type 1 diabetes mellitus (n = 10). The pharmacodynamics profile of a single dose of short-acting insulin (insulin lispro) was investigated, using a controlled environmental chamber, under three environmental conditions: (a) temperature: 15°C and humidity: 10%; (b) temperature: 30°C and humidity: 10%; and (c) temperature: 30°C and humidity: 60%. An euglycaemic glucose clamp technique ensured constant blood glucose of 100 mg/dL (5.5 mmol/L). The following pharmacodynamic endpoints were calculated: maximum glucose infusion rate (GIRmax), time to GIRmax (tGIRmax), total area under the curve (AUC) for GIR from 0-6 hours (AUCGIR.0-6h), and partial AUCs (AUCGIR.0-1h, AUCGIR.0-2h and AUCGIR.2-6h).

Results: Higher temperature (30°C) under 10% fixed humidity conditions resulted in greater GIRmax (P = 0.04) and a later tGIRmax (P = 0.049) compared to lower temperature (15°C). Humidity did not affect any pharmacodynamic parameter. When the combined effects of temperature and humidity were explored, tGIRmax occurred earlier, with a lower late insulin pharmacodynamic effect (AUCGIR.2-6h; P = 0.017) at a temperature of 15°C and humidity of 10% compared to a temperature of 30°C and humidity of 60%.

Conclusions: High ambient temperature resulted in a greater insulin peak effect compared to low ambient temperature, with the contribution of high relative humidity apparent only at high ambient temperature. This suggests that patients with type 1 diabetes mellitus who are entering higher environmental temperatures, with or without high humidity, could experience more hypoglycaemic events.

KEYWORDS
ambient temperature, environmental conditions, insulin pharmacodynamics, relative humidity, type 1 diabetes mellitus

1 INTRODUCTION

Type 1 diabetes mellitus is characterised by β-cell destruction and a lifelong requirement of exogenous insulin. Insulin requirements depend on insulin absorption from the injection site, the individual’s insulin sensitivity, body composition, inflammatory processes and environmental factors.1,2 Evidence from epidemiological research suggests seasonal differences in HbA1c3–5 and clinical onset of diabetes,6 with warmer temperatures (summer) favouring lower HbA1c and lower incidence of diabetes compared to cooler temperatures (winter). Conversely, there is a paucity of recent, well-controlled experimental studies employing technological advancements, such as an
environmental chamber,\(^7\) using the gold standard glucose clamp technique,\(^8\) to investigate the effects of ambient temperature on insulin action; such studies could provide evidence of a cause-effect relationship. Nevertheless, there is increasing evidence of the local effects of temperature on insulin pharmacodynamics and pharmacokinetics. For instance, local warming of the injection site as a result of local skin massage,\(^9\) application of an insulin infusion site heating device (InsuPatch),\(^10–13\) hot baths\(^14\) or sauna exposure\(^15\) has been shown to accelerate insulin absorption and improve insulin sensitivity in patients with diabetes, with these effects largely mediated by an increase in skin temperature which results in an increased perfusion at the injection site.

The effects of relative humidity on insulin pharmacodynamics and pharmacokinetics are largely unexplored. An epidemiological study conducted in the Mediterranean area suggested an increased prevalence of diabetes among the elderly population on islands with high relative environmental humidity when adjusted for ambient temperature.\(^16\) Notably, high relative humidity often occurs in the presence of high ambient temperature, making it challenging to unravel their individual effects.\(^17\) Individuals with diabetes appear to tolerate moist, warm air with more than 50% humidity less well than adults without diabetes.\(^18\) This may be explained by the fact that high humidity, when combined with high temperature, decreases the rate of cooling in the human body, leading to tiredness, exhaustion, reduction in alertness and, potentially, heat stroke,\(^17,19,20\) which may also affect glycaemic control.

In order to assess the independent and combined effects of ambient temperature and relative humidity, this study evaluated the insulin pharmacodynamic profile following a single injection of a short-acting insulin analogue.

2 | RESEARCH DESIGN AND METHODS

A single-centre, open label, three-way cross-over study was performed in the Diabetes Research Centre at Hull Royal Infirmary in adults with type 1 diabetes mellitus (\(n = 10\)). All participants provided written informed consent. The trial was approved by the Yorkshire and the Humber - Leeds West Research Ethics Committee (REC number: 14/YH/1129), registered at www.clinicaltrials.gov (NCT0 3102476) and conducted according to the Declaration of Helsinki. Individuals with type 1 diabetes mellitus were identified from databases of diabetes clinics and via advertisements placed at the Diabetes Centre of the Hull Royal Infirmary. Participants were included if they (a) were males, (b) aged between 18 and 55 years, (c) had been diagnosed with type 1 diabetes mellitus, and (d) had HbA1c ≤ 9.0% (75 mmol/mol) with a total insulin dose of <1.2 U/kg/day, and (e) had a body mass index (BMI) between 18.0 and 28.0 kg/m\(^2\). Exclusion criteria were (a) known or suspected allergy to insulin, (b) recurrent major hypoglycaemia or hypoglycaemic unawareness within the previous 6 months, (c) clinically significant diabetes neuropathy, (d) participation in clinical trials involving investigational drugs within 3 months prior to screening, and (e) supine blood pressure at screening outside the range of 90-140 mm Hg for systolic blood pressure or 50-90 mm Hg for diastolic blood pressure and/or resting supine heart rate outside the range 50-90 beats per minute.

The pharmacodynamic profile of the short-acting insulin lispro dosed at 0.2 units/kg was investigated under three environmental conditions for each participant: (a) temperature, 15°C and humidity, 10%, (b) temperature, 30°C and humidity, 10%, and (c) temperature, 30°C and humidity, 60%. Participants attended six visits (Visits 1, 2a, 2b, 3, 4 and 5). Visits 1, 2a and 5 were conducted at the Diabetes Centre, Hull Royal Infirmary, whereas Visits 2b-4 were performed in the environmental chamber (Type SSR 60-20H, Design and Manufacture of Environmental Test Chambers, Gwent, Wales) located at the Department of Sport, Health and Exercise, University of Hull. During Visit 1, potential participants were screened against inclusion and exclusion criteria by medical history and clinical examination, routine blood tests (ie, HbA1c) and electrocardiogram (ECG). Visit 2a took place more than 72 hours prior to Visit 2b, to discuss and allow for any arrangements concerning insulin regimens and lifestyle (diet, exercise). More specifically, participants were switched from insulin lantus or detemir to neutral protamine hagedorn (NPH) insulin 48 hours before Visit 2b. The NPH insulin was discontinued 22 hours before Visits 2b-4, with the exception of short-acting insulin analogues which were discontinued 6-8 hours before that visit. Visits 2b-4 were the main experimental days, during which different environmental conditions were controlled and euglycaemic clamp was performed. Participants were weighed without shoes on a weighing scale (Marsden Weighing Machine Group Ltd, Rotherham, UK); height was measured barefoot using a wall-mounted stadiometer; and BMI was calculated as body mass (kg) divided by height squared (m\(^2\)). Blood pressure was measured using a sphygmomanometer (Datascope Duo Masimo Set, Mindray Ltd, Huntingdon, UK). Blood glucose was continuously monitored pre-administration and for the duration of clamp procedures. Standard safety parameters, including blood pressure, heart rate and temperature, were performed every 30 minutes throughout the study. A period of three to 21 days was allowed between Visits 2a, 3 and 4. Visit 5 included a follow-up examination within 14 days of the last experimental day (Visits 2b, 3 or 4) as well as a physical examination and a glycaemic management review.

2.1 | Euglycaemic glucose clamp procedure

Prior to the euglycaemic glucose clamp procedure, all participants fasted overnight and for the duration of the six-hour procedure. Water was allowed as required. In the clinic room, with the participant in a comfortable supine or semi-supine position, vital signs were recorded before two cannulas were inserted. One was inserted into the hand or forearm for venous sampling, with the hand heated to 55°C throughout the clamp procedure, allowing arterialization of the venous blood.\(^21\) The second was inserted into the opposite arm, at the cubital fossa, for a variable infusion of insulin (15 units of Humulin S in 49 mL saline and 1 mL of the participant’s own blood) or glucose (20% in saline). The infusion was initiated with a target blood glucose level of 5.5 mmol/L (100 mg/dL) ± 20% for 30–60 minutes prior to the participant being relocated to the environmental chamber where baseline glucose levels were taken followed by the injection of insulin lispro (NovoFine 32G Tip etw 0.23/0.25 × 6 mm, Novo Nordisk A/S, Denmark) on the left shoulder of the participants, equal to time 0.
In the environmental chamber, participants were instructed to wear light clothes to mimic real-life situations. The variable glucose infusion was used to maintain the target blood glucose level of 5.5 mmol/L (100 mg/dL) ± 20% guided by an algorithm and by the participants’ blood glucose concentration, measured within the preceding 5 minutes. Blood glucose concentrations were measured using a glucose analyser (HemoCue glucose 201+, Radiometer Ltd, Crawley, UK) and were recorded along with the glucose infusion rate every 5-10 minutes throughout the clamp procedure. Upon completion of the clamp procedure, vital signs were assessed and lunch was provided before discharge.

2.2 | Biochemical analysis

Venous blood samples were collected at Visit 1 as part of screening procedures. Plasma blood samples were centrifuged at 3500 x G for 15 minutes at 5°C and were analysed for HbA1c on a Menarini Diagnostics HB9210 premier (A.Menarini Diagnostics Ltd., Winnersh-Wokingham, UK).

2.3 | Statistical analysis

The exogenous glucose infusion rate (GIR) was analysed every 5 to 10 minutes throughout the clamp procedure. A weighted local regression technique (LOESS) with a smoothing factor (SF) of 0.1 for calculation of time-related parameters and maximum GIR in accordance with previous studies that investigated the pharmacodynamics of short-acting insulin. The pharmacodynamic endpoints calculated for each clamp study visit (Visits 2b, 3 and 4) were maximum glucose infusion rate (GIRmax) and time to maximum glucose infusion rate (tGIRmax). In addition to total area under the curve (AUC) for GIR from 0–6 h (AUCGIR.0-6h), partial AUCs from 0–1, 0–2 hours (AUCGIR.0-2h), 0–6 hours (AUCGIR.0-6h) and 2–6 hours (AUCGIR.2-6h) following insulin injection were also calculated to determine early and late insulin action. A two-way ANOVA with temperature, humidity and their interaction as fixed effects and the participant as random effect was used for determination of AUCGIR.0-1h, AUCGIR.0-2h, AUCGIR.2-6h, GIRmax (SF = 0.1) and tGIR.max(SF = 0.1). Data are presented as mean (1SD) and statistical significance was set at P ≤ 0.05. For graphical presentation (Figure 1) an SF of 0.3 was used and 10 data points with GIR-values of nearly 40 mg kg⁻¹ min⁻¹ in one participant were excluded in order to minimize random GIR-fluctuations. Statistical analysis was conducted using SAS, version 9.4.

3 | RESULTS

Demographic and clinical characteristics of participating adults with type 1 diabetes mellitus at baseline are presented in Table 1.

3.1 | Independent effects of ambient temperature

As illustrated in Figure 1 and Table 2, at a temperature of 30°C with 10% humidity, the time-action curve of insulin was shifted to the right, with a later tGIR.max (P = 0.049) and a significantly greater GIRmax (P = 0.04), compared to the condition at a temperature of 15°C and the same level of humidity, 10%. Although AUCGIR.0-1h, AUCGIR.0-2h and AUCGIR.0-6h did not differ significantly between the conditions with different temperatures, there was a trend towards higher AUCGIR.2-6h when comparing conditions at 30 and 15°C (P = 0.08) (Table 2).

3.2 | Independent effects of relative humidity

There was no effect of humidity on insulin pharmacodynamics, as indicated by the absence of significant differences in GIRmax, tGIR.max and AUCs for the time-action profile between the condition at 30°C with 10% humidity and the condition at 30°C with 60% humidity (P values between 0.21 and 0.95) (Table 2).
Abbreviations: AUC, area under the curve; GIR, glucose infusion rate; GIRmax, maximum glucose infusion rate; tGIR.max, time to maximum glucose infusion.

TABLE 1 Baseline characteristics of participants

|                          | Adults with type 1 diabetes (n = 10) |
|--------------------------|-------------------------------------|
| Age (y)                  | 28.3 ± 7.1                          |
| Weight (kg)              | 74.1 ± 12                           |
| Height (cm)              | 170.6 ± 5.7                         |
| BMI (kg/m²)              | 24.3 ± 2.9                          |
| Systolic BP (mm Hg)      | 124.2 ± 9.4                         |
| Diastolic BP (mm Hg)     | 75.6 ± 7.5                          |
| Duration of diabetes (y) | 18.8 ± 7.7                          |
| HbA1c (%)                | 7.9 ± 0.8                           |
| HbA1c (mmol/mol)         | 63 ± 6.7                            |

Abbreviations: BMI, body mass index; BP, blood pressure; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Data are presented as means ±1SD.

3.3 | Combined effects of ambient temperature and relative humidity

When exploring the combined effects of temperature and humidity, tGIR.max (SF = 0.1) (P = 0.008) occurred, on average, 44 minutes earlier (AUCGIR.0-2h, P = 0.017) at 15°C with 10% humidity compared to 30°C with 60% humidity (Figure 1, Table 2) with less glucose to be infused at a lower temperature and humidity, but no differences were seen in early effects (AUCGIR.0-1h, P = 0.48 and AUCGIR.0-2h, P = 0.87) and overall effects (AUCGIR.0-6h, P = 0.48) on insulin action (Table 2).

4 | DISCUSSION

Using the glucose clamp technique, the present study demonstrated that sudden changes in environmental conditions affect short-acting insulin analogue (insulin lispro) pharmacodynamics in adult men with type 1 diabetes mellitus. In response to higher temperature (30 vs 15°C) with fixed humidity, there was greater GIRmax and a trend towards greater AUCGIR.0-6h. High humidity affected insulin pharmacodynamics only when it was combined with high temperature. The mean time to GIRmax was prolonged at 30°C with 10% or 60% humidity compared to 15°C with 10% humidity, and GIRmax and late AUC (AUCGIR.2-6h) were greater, suggesting enhanced insulin absorption and peak effect.

A limited number of studies have simulated the effects of environmental conditions on insulin pharmacodynamics. Ronnemaa and Koivisto investigated the acute effects of ambient temperature (10 and 30°C), with and without exercise, on insulin absorption and postprandial glycaemia in patients with type 1 diabetes mellitus, but in a different experimental protocol without using a glucose clamp procedure. They showed no significant effect of ambient temperature on total blood glucose AUC, calculated using glucose values from the time of insulin injection to the end of the study (195 minutes), but significant effects were revealed for partial AUC from 80 minutes post injection to 195 minutes. These results are in accord with those of the present study, in which there were no significant differences between the experimental conditions at 15°C and those at 30°C concerning AUCGIR.0-6h but there was a trend towards greater AUCGIR.0-6h with a higher temperature. The same study also assessed insulin pharmacokinetic parameters and showed a three- to five-fold higher AUC for plasma-free insulin at 30°C than at 10°C, regardless of exercise. We cannot provide comparative data on these aspects, given that our study is limited to insulin pharmacodynamics and does not include a pharmacokinetic profile. Furthermore, it is more challenging to detect differences in pharmacodynamic parameters than in pharmacokinetic parameters, as the former are often characterized by greater variability and, therefore, pharmacokinetic results would be expected to be in line with pharmacodynamic findings in our study.

TABLE 2 AUCGIR for 0–1, 0–2, 0–6 and 2–6 hours, GIRmax and tGIR.max

|                  | AUCGIR.0-3h (mg/kg) | AUCGIR.0-2h (mg/kg) | AUCGIR.0-6h (mg/kg) |
|------------------|---------------------|---------------------|---------------------|
| Mean ± SD        | 136 ± 251           | 347 ± 496           | 815 ± 764           |
| Min-max          | 0-835               | 12-1727             | 260-2823            |
| P values         | T15/H10 vs T30/H10  | 0.56                | T15/H10 vs T30/H10  | 0.96                |
|                  | T15/H10 vs T30/H60  | 0.48                | T15/H10 vs T30/H60  | 0.48                |
|                  | T30/H10 vs T30/H60  | 0.90                | T30/H10 vs T30/H60  | 0.51                |

|                  | GIRmax (mg/kg/min)  | tGIR.max (min)      |
|------------------|---------------------|---------------------|
| Mean ± SD        | 467 ± 319           | 107 ± 61.8          |
| Min-max          | 114-1096            | 10-205              |
| P values         | T15/H10 vs T30/H10  | 0.08                | T15/H10 vs T30/H10  | 0.049               |
|                  | T15/H10 vs T30/H60  | 0.008               | T15/H10 vs T30/H60  | 0.017               |
|                  | T30/H10 vs T30/H60  | 0.22                | T30/H10 vs T30/H60  | 0.65                |

Abbreviations: AUC, area under the curve; GIR, glucose infusion rate; GIRmax, maximum glucose infusion rate; tGIR.max, time to maximum glucose infusion rate.

P values <0.05 are indicated in bold italics. Statistical analysis was performed on the unsmoothed data.

Data are presented as mean ± 1SD, (min) and maximum (max). Environmental conditions: T15/H10, 15°C with 10% humidity; T30/H10, 30°C with 10% humidity; T30/H60, 30°C with 60% humidity.
Exposure to temperatures higher than that investigated in this work, 30 °C, has been shown to have favourable effects on the time-action profiles of different types of insulin analogues. It is reported that sauna exposure, twice for 25 minutes at 85 °C with relative humidity of 30%-50%, accelerated insulin absorption by 110%, assessed by measuring the disappearance rate of 125I-labelled rapid-acting insulin, compared with room temperature, in eight participants with diabetes (type 1 diabetes mellitus, n = 7; type 2 diabetes mellitus, n = 1).15 Hot baths (water temperature ≥ 40 °C) increased serum insulin levels 90 minutes after injection.14 Other studies have shown the effects of temperature on insulin pharmacodynamics when heat is applied locally at the site of injection.10-13,24 When a local heating device at the injection site (InsuPatch, InsuLine Medical Ltd., Petach-Tikvah, Israel) was utilized to achieve a skin temperature of 38.5 °C, the time to maximal action of a 0.2 U/kg bolus dose of insulin aspart decreased from 125 to 90 minutes in adults with type 1 diabetes mellitus,13 and decreased similarly at 40 °C.12 Studies involving meal tolerance tests showed that local heat resulted in significant reductions in the time to maximal insulin action and lower postprandial excursion in patients with type 1 diabetes mellitus.11,24 These data suggest that high ambient temperature increases subcutaneous insulin absorption as the result of effects on blood perfusion at the injection site. In line with these findings, we showed enhanced insulin action and a prolonged time to maximum infusion rate with higher temperature compared to lower temperature. The findings concerning time to maximum infusion rate can be explained, at least in part, by the greater GIRmax observed with higher temperature; that is, greater GIRmax is expected to be reached later. Discrepancies between this study and previous studies may be largely explained by differences in exposure to heat (ie, extent, locality and duration). Although measurements of skin temperature were not undertaken in this study, the results are suggestive of a delayed thermoregulatory effect on subcutaneous tissue in the hotter environment (30 °C), which may explain the absence of earlier changes in the environment surrounding the insulin depot.

Conversely, we observed a shorter mean time to GIRmax under 15 °C with 10% humidity compared to 30 °C with 10% humidity and lower GIRmax and late AUC (AUCGIR2-6h). These results are in agreement with a previous study by Vallerand et al. which showed that, in response to an intravenous glucose tolerance test under nude exposure to cold (exposure: 3 hours at 10 °C), plasma glucose area under the curve was lower and plasma glucose levels returned to baseline levels within an hour compared to 2 hours under warm conditions (exposure: 3 hours at 29 °C) despite low insulin levels and enhanced carbohydrate metabolism.25 It is speculated that the marked effects of exposure to cold may be the result of enhanced insulin sensitivity and/or increased responsiveness for glucose uptake in peripheral tissues such as skeletal muscles.25-27 However, in the current study we cannot provide further insight into these mechanisms, given that subcutaneous insulin was used and, therefore, other factors (eg, visceral and subcutaneous tissues) may have differentially affected the pharmacodynamic parameters.

Short term exposure to different levels of relative humidity, 10% and 60%, under fixed temperature had no effect on the insulin time-action profile. However, exposure to high relative humidity in combination with high ambient temperature resulted in prolonged time to GIRmax and a greater insulin pharmacodynamic effect compared to responses to the low temperature-low humidity condition, suggesting that high humidity may augment the high-temperature effect on enhanced insulin absorption from the injection site, but has little effect in its own right.

In conclusion, high ambient temperature resulted in greater insulin peak effect compared to low ambient temperature, with the contribution of high relative humidity to insulin absorption apparent only at high ambient temperature. This suggests that patients with type 1 diabetes mellitus who are entering an environment with higher temperatures, with or without high humidity, could experience more hypoglycaemic events.

ACKNOWLEDGMENTS

We thank all study participants for their commitment to this study.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

Author contributions

A. A. Z. J., T. H., A. S. R., A. T. G., D. H., E. S. K., S. L. A. and T. S. participated in study conception and design. A. A. acquired the data. A. A., M. P., T. H., A. S. R., S. L. A. and T. S. participated in analysis and/or interpretation of data. M. P. prepared the first draft of the paper; all authors reviewed and approved the final manuscript. T. S. is the guarantor of the study.

ORCID

Tim Heise https://orcid.org/0000-0002-8346-2037
Stephen L. Atkin https://orcid.org/0000-0002-5887-7257
Thozhukat Sathyapalan https://orcid.org/0000-0003-3544-2231

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How to cite this article: Al-Qaissi A, Papageorgiou M, Javed Z, et al. Environmental effects of ambient temperature and relative humidity on insulin pharmacodynamics in adults with type 1 diabetes mellitus. *Diabetes Obes Metab.* 2019;21:569–574. [https://doi.org/10.1111/dom.13555](https://doi.org/10.1111/dom.13555)