Association of British Clinical Diabetologists

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ABSTRACTS

1 Efficacy and safety of insulin degludec/liraglutide (IDegLira) vs basal–bolus therapy in patients with type 2 diabetes: DUAL VII Trial

Billings LK; Oviedo A; Rodbard H; Tentolouris N; Grøn R; Halladin N; Walker M; Jodar E

Billings LK: NorthShore University HealthSystem Evanston, IL, USA; University of Chicago Pritzker School of Medicine, Chicago, IL, USA
Oviedo A: Santojanni Hospital and Cenudiab, Ciudad Autonoma de Buenos Aires, Argentina
Rodbard H: Endocrine and Metabolic Consultants, Rockville, MD, USA
Tentolouris N: National and Kapodistrian University of Athens, Medical School, Athens, Greece
Grøn R: Novo Nordisk A/S, Søborg, Denmark
Halladin N: Novo Nordisk A/S, Søborg, Denmark
Walker M: Novo Nordisk Ltd., West Sussex, UK
Jodar E: University Hospital Quiron Salud, Madrid, Spain

In this 26-week open-label trial, 506 patients with type 2 diabetes uncontrolled on metformin and 20–50 units (U) insulin glargine U100 (IGlar) were randomised 1:1 to IDegLira or basal–bolus therapy (IGlar + insulin aspart ≤4 times a day).
Mean HbA1c decreased from 8.2% at baseline to 6.7% at end of trial in both arms; non-inferiority for IDegLira with respect to HbA1c change (by <0.3%) was confirmed (p<0.0001). A similar proportion of patients achieved HbA1c targets with IDegLira vs basal–bolus (66.0% vs 67.0% for HbA1c <7%/49.6% vs 44.6% for HbA1c ≤6.5%). Total daily insulin dose was lower for IDegLira (40.4U) vs basal–bolus (84.1U) (p<0.0001). Body weight decreased with IDegLira by -0.93kg and increased with basal–bolus by 2.64 kg (estimated treatment difference -3.57 kg [-4.19; -2.95]95%CI p<0.0001); the rate of hypoglycaemia was lower with IDegLira vs basal–bolus (estimated rate ratio 0.11 [0.08; 0.17]95%CI p<0.0001). More patients achieved a triple composite endpoint (HbA1c <7% with no hypoglycaemia in the last 12 weeks and no weight gain) with IDegLira vs basal–bolus (38.2% vs 6.4%; odds ratio 10.39 [5.76; 18.75]95%CI p<0.0001). With regards to patient reported outcomes, TRIM-D (total scores) and SF-36 (mental component summary) improved more with IDegLira vs

basal–bolus ($p<0.0001$ and $p=0.0228$, respectively). Adverse event rates were similar in the two trial arms.
In conclusion, in patients with HbA1c >7% on metformin and IGlar, IDegLira vs basal–bolus resulted in similar HbA1c reductions, lower insulin dose, weight loss and lower risk of hypoglycaemia.

2 Modelling subcutaneous absorption of U100 and U300 insulin glargine in type 1 diabetes

Schiavon M (1); Visentin R (1); Dalla Man C (1); Klabunde T (2); Cobelli C (1)

1. University of Padova, Department of Information Engineering, Padova, Italy
2. Sanofi-Aventis Deutschland GmbH, Drug Design, Science and Medical Affairs, Frankfurt am Main, Germany

Background: Subcutaneous administration of long-acting insulin analogues are often employed in multiple daily injection (MDI) therapy of type 1 diabetes (T1D) to cover patients' basal insulin needs. Among these, U300 and U100 are formulations of insulin glargine indicated for once-daily subcutaneous administration of MDI therapy of T1D. U300 is a new formulation with different absorption kinetics from U100, resulting in less hypoglycaemia in clinical trials. Some models have already been proposed but were not assessed under controlled experimental conditions for both formulations. The objective is to develop a model of subcutaneous absorption of U100 and U300 glargine insulin formulations in T1D.
Methods: The database consists of 24 patients with T1D who underwent a randomized, 4-sequence, cross-over, double-blind, dose-response euglycaemic clamp study, receiving single subcutaneous injections of 0.4, 0.6 and 0.9 U/kg U300 and 0.4 U/kg U100 (NCT01195454). Plasma insulin concentrations were measured for 36 hours using a validated radioimmunoassay. Model identification was performed on U100 and U300 data using a Bayesian Maximum a Posteriori technique.
Results: The model fits the data well and provides precise parameter estimates for both insulin formulations. The model describes the gradual dissolution from the precipitate to soluble states and model parameters allow to characterize the different rates of absorption between U100 and U300.
Conclusions: The model will be incorporated into the UVA/Padova T1D simulator together with the joint parameter distributions. This will open the door to perform in silico clinical trials for testing novel up-titration and insulin glargine switching rules.
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3 Lower Glucose Variability and Risk for Hypoglycaemia on Insulin Glargine 300 U/mL Versus Insulin Glargine 100 U/mL, Evaluated by the Low Blood Glucose Index in Randomized Phase III Clinical Trials

Kovatchev BP (1); Meng Z (2); Breton MD (3); Leroy B (4); Cali A (4)

1. Center for Diabetes Technology, University of Virginia, Charlottesville, VA, USA
2. Sanofi, Bridgewater, NJ, USA
3. Université de Sherbrooke, Sherbrooke, Canada
4. Sanofi, Paris, France

Glucose variability (GV) and GV-based metrics such as the Low Blood Glucose Index (LBGI) can detect hypoglycaemia risk in T2D. Edition 2 (NCT01499095) and Edition 3 (NCT01676220) are 12-month studies comparing insulin glargine 300 U/mL (Gla-300) with insulin glargine 100 U/mL (Gla-100) in insulin-treated and insulin-naïve T2D patients, respectively.
GV and LBGI were computed using self-monitored blood glucose (BG) profiles recorded daily across the studies, and compared between Gla-300 and Gla-100. Total documented symptomatic hypoglycaemia (DSH) per patient, confirmed by BG readings <3 mmol/L, were stratified by LBGI.
LBGI and night-time LBGI were significantly lower with Gla-300 compared with Gla-100 ($p<0.001$ for both in Edition 2; $p=0.036$ and $p=0.005$ in Edition 3). These differences in LBGI were more apparent during the titration phase (mean 0.327 [Gla-300] vs 0.452 [Gla-100] [titration], 0.409 vs 0.497 [maintenance], respectively [Edition 2]; 0.199 vs 0.250 [titration], 0.375 vs 0.409 [maintenance], respectively [Edition 3]). The largest differences were observed overnight (mean LBGI 0.693 [Gla-300] vs 1.118 [Gla-100] [titration], 0.985 vs 1.238 [maintenance], respectively [Edition 2]; 0.394 vs 0.476 [titration], 0.729 vs 0.922 [maintenance], respectively [Edition 3]). LBGI correlated with the observed number of hypoglycaemic episodes ($r=0.35$ and 0.26, $p<0.001$ for both studies, respectively); patients who were at moderate risk (defined as LBGI ≥1.1) experienced six-fold more DSH than those at minimal risk (LBGI ≤1.1).
Use of Gla-300 versus Gla-100 showed significant reductions in GV as measured by LBGI and LBGI predicted hypoglycaemia risk reductions with Gla-300 and Gla-100 consistently, throughout both Edition studies.
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4 onset 1: efficacy and safety of mealtime fast-acting insulin aspart versus insulin aspart after 52 weeks

Mathieu C; Bode B; Franek E; Philis-Tsimikas A; Rose L; Graungaard T; Østerskov AB; Azizuddin, S; Russell-Jones D

UZ Leuven, Leuven, Belgium (CM); Atlanta Diabetes Associates, Atlanta, GA, USA (BB); Mossakowski Medical Research Center, Polish Academy of Sciences, Warsaw, Poland (EF); Scripps Whittier Diabetes Institute, San Diego, CA, USA (AP-T); Diabetes Research Center, Münster, Germany (LR); Novo Nordisk A/S, Søborg, Denmark (TG; ABQ); NovoNordisk Ltd, Gatwick, UK (SA); Department of Endocrinology & Diabetes, Royal Surrey County Hospital, Guildford, UK (DR-J)

onset 1 was a phase 3a trial evaluating fast-acting insulin aspart (FA) in adults with type 1 diabetes (T1D) over 52 weeks. Subjects were randomised to double-blind mealtime FA, insulin aspart (IAsp) or open-label post-meal FA, each with insulin detemir for the initial 26 weeks. Subjects on mealtime FA (n=381) and IAsp (n=380) continued to the additional 26-week period to assess long-term safety and efficacy.
After 52 weeks, HbA1c change from baseline (−0.08% [FA] vs. +0.01% [IAsp]) showed a significant estimated treatment difference (ETD) (95% confidence interval [CI]) favouring FA (ETD: −0.10% [−0.19;−0.00]). Change from baseline in 1-h postprandial plasma glucose (PPG) increment (meal test) was −1.05 mmol/L (FA) vs. −0.14 mmol/L (IAsp) (ETD: −0.91 mmol/L [−1.40;−0.43]); a similar trend toward better efficacy with FA versus IAsp was seen in 2-h PPG increment (ETD: −0.42 mmol/L [−1.11;0.27]). Change from baseline in mean 7-9-7-point self-measured plasma glucose profile was significant in favour of FA (ETD: −0.23 mmol/L [−0.46;−0.00]). Median total insulin dose was 0.77 U/kg (FA) vs. 0.83 U/kg (IAsp).

No difference was observed for body weight change (+1.18 kg [FA] vs. +1.05 kg [IAsp]; ETD: 0.13 kg [−0.38;0.65]). Adverse events were similar between treatments, and as expected for IAsp. There was no difference in overall severe or blood glucose-confirmed hypoglycaemia rates (plasma glucose <3.1 mmol/L) between treatments (estimated ratio: 1.01 [0.88;1.15]).
No long-term safety issues were identified with FA. Approaching a profile closer to physiology with FA significantly improved glycaemic control after 52 weeks in T1D versus IAsp.

5 Achievement of HbA1c Targets in the Diabetes Unmet Need with Basal Insulin Evaluation (DUNE) Real-World Study

Meneghini L (1,2); Mauricio D (3); Orsi E (4); Lalic N (5); Cali A (6); Westerbacka J (6); Stella P (6); Candelas C (6); Pilorget V (6); Perfetti R (7); Khunti K (8)

1. University of Texas Southwestern Medical Center, Dallas, TX, USA
2. Parkland Health & Hospital System, Dallas, TX, USA
3. Hospital Universitari Germans Trias i Pujol, Barcelona, Spain
4. Endocrine and Metabolic Diseases Unit, Fondazione Ca' Granda IRCCS, Milan, Italy
5. Faculty of Medicine University of Belgrade, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia
6. Sanofi, Paris, France
7. Sanofi, Bridgewater, NJ, USA
8. Diabetes Research Centre, University of Leicester, Leicester, UK

The association between achievement of individualized glycaemic targets and hypoglycaemia risk in the real-world setting is unknown. DUNE was a 12-week, prospective, observational, multinational, real-world study (conducted Feb 2015–Jul 2016) in adults with T2D newly (at time of enrolment) or recently (<12 months) initiated on basal insulin (Bl) therapy. The study aimed to assess individualized HbA1c target achievement and its association with symptomatic hypoglycaemia (occurrence/frequency).
Of 3139 evaluable participants from 28 countries, 99.7% were set individual HbA1c targets by their physicians (57% set at 7.0–7.4%). At week 12, both insulin-naïve (N=1716) and prior Bl (N=1423) participants showed a mean (SD) HbA1c decrease from baseline (–1.4% [1.3] and –0.8% [1.1], respectively) with limited up-titration of mean daily insulin dose from baseline to week 12 (+0.10 U/kg [0.13] and +0.06 U/kg [0.10], respectively); only 28% and 27% of participants, respectively, achieved individual HbA1c targets, with an average insulin dose of 0.31 U/kg/day at week 12. Overall, symptomatic hypoglycaemia, defined as any event associated with typical hypoglycaemic symptoms regardless of blood glucose measurement, was reported by 16% of participants (insulin-naïve: 14%; prior BI: 18%). Univariate logistic regression analysis showed a positive association between HbA1c target achievement and symptomatic hypoglycaemia occurrence (OR [95% CI]: 0.697 [0.568, 0.854]; p<0.001) and frequency of symptomatic hypoglycaemia (p=0.004).
To conclude, results from this real-world study show that while HbA1c levels fell substantially, most participants did not achieve individual HbA1c targets; participants who reached target were more likely to experience symptomatic hypoglycaemia.
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6 Longer acting basal insulin analogues - a therapeutic advance in selected patients

Koh, WS; Shotliff, K; Feher MD

Beta Cell Diabetes Centre
Chelsea and Westminster Hospital, London

Hypoglycaemia, weight gain or high volume dose are unwanted management issues of insulin. In clinical trials, longer acting basal analogues insulin Glargine U300 (Toujeo) and insulin Degludec U100 (Tresiba), compared to Glargine U100, reduced hypoglycaemic events (HE) and weight gain, derived from formulation/pharmacokinetic/dynamic differences. Clinical utility of these insulins in selected patients requires evaluation.

Aim
To assess treatment effects of long acting basal insulin analogues when used for selected clinical reasons in routine practice.

Methods
Non-randomised, systematic audit of (Type 1, Type 2) diabetes patients requiring treatment change to long acting basal analogues. Demographics, disease profiles and reasons for new insulin were obtained from electronic databases. Weight, BMI, HbA1c, HE and insulin dose collected prospectively: 3-6 and 9-12 months.

Results
The study group, type 1(n=44) and type 2(n=15) diabetes, were switched to Toujeo (n=21) or Tresiba (n=38) for clinical reasons: hypoglycaemia (62.7%), glycaemic control (14.7%), high basal insulin dose (12.0%), weight control (5.3%), injection-site reaction(1.3%), injection frequency (2.7%), unspecified (1.3%). After 6 months, T1DM patients, HbA1c (-3.6%), weight (+0.5%), basal insulin dose (-9.3%), and in T2DM (Toujeo only), HbA1c (+1.9%), weight (+0.9%), and basal insulin dose (-6.8%). At follow-up, HE decreased in T1DM (-54%) , and T2DM (-36%).

Conclusions
In T1DM patients, switching to Toujeo or Tresiba may improve management of hypoglycaemia and insulin dose, without compromising glycaemic control. However, in T2DM on Toujeo, important reduction in hypoglycaemia was balanced by small change in glycaemic control. In selected patients, longer basal insulin analogues improve key therapeutic challenges of insulin therapy.

7 Day-to-day variability of fasting self-measured blood glucose associates with risk of hypoglycaemia in adults with type 1 and type 2 diabetes

Bailey TS; Bhargava A; DeVries JH; Gerety G; Gumprecht J; Heller S; Lane W; Wysham CH; Zinman B; Bak BA; Hachmann-Nielsen E; Walker M; Philis-Tsimikas A

Bailey TS: AMCR Institute, Escondido, CA, USA
Bhargava A: Iowa Diabetes and Endocrinology Research Center, IA, USA
DeVries JH: University of Amsterdam, Amsterdam, The Netherlands
Gerety G: Albany Medical College, Albany, NY, USA
Gumprecht J: Medical University of Silesia, Zabrze, Poland
Heller S: University of Sheffield, Sheffield, UK
Lane W: Mountain Diabetes and Endocrine Center, Asheville, NC, USA
Wysham CH: Rockwood Clinic, WA, USA
Zinman B: Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada

Bak BA, Hachmann-Nielsen E: Novo Nordisk A/S, Søborg, Denmark
Walker M: Novo Nordisk Ltd., West Sussex, UK
Philis-Tsimikas A: Scripps Whittier Diabetes Institute, CA, USA

The relationship between hypoglycaemia and day-to-day variability of glycaemic control has not been well established. A post hoc analysis was performed associating day-to-day variability of fasting self-measured blood glucose (SMBG) with hypoglycaemia in two double-blind, treat-to-target, crossover trials including insulin degludec U100 once daily (OD) and insulin glargine U100 OD in adults with type 1 diabetes (T1D, SWITCH 1, n=501) or insulin-experienced adults with type 2 diabetes (T2D, SWITCH 2, n=721). Available SMBG measurements were used to determine a weekly variance for each patient, using the log SMBG values to allow for relative comparisons. For each patient and treatment, the geometric mean of the weekly variance was calculated and these values were categorised into low, medium and high tertiles as a measure for day-to-day variability. The effect of having low or high variability compared with medium variability was analysed in relation to overall symptomatic (severe or blood glucose [<3.1 mmol/L] confirmed), nocturnal symptomatic (00:01–05:59), and severe (requiring third-party assistance and confirmed by a blinded adjudication committee) hypoglycaemia. Day-to-day fasting SMBG variability was significantly associated with the rates of overall and nocturnal symptomatic hypoglycaemia in patients with T1D or T2D (all p<0.0001). For severe hypoglycaemia, this significant association was also observed in patients with T1D (p<0.0001), whereas in patients with T2D, no significant difference was found across tertiles (p=0.1835). In conclusion, higher SMBG variability is associated with higher rates of hypoglycaemia. Treatment choices that reduce day-to-day fasting SMBG variability may contribute to a reduction in the risk of hypoglycaemia.

8 Clinical Outcomes of Patients with Type 2 Diabetes (T2D) who Switched to Insulin Glargine 300 U/mL from Insulin Glargine 100 U/mL in Real-World US Treatment Settings

Ye F (1); Zhou FL (1); Xie L (2); Kariburyo F (2); Meneghini L (3)

1. Sanofi, Bridgewater, NJ, USA
2. STATinMED Research, Ann Arbor, MI, USA
3. University of Texas Southwestern Medical Center and Parkland Health & Hospital System, Dallas, TX, USA

To compare insulin dose changes in a real-world setting for adults with T2D on prior insulin glargine 100 U/mL (Gla-100) who either switched to insulin glargine 300 U/mL (Gla-300) or remained on Gla-100; retrospective patient data were extracted from the Optum Clinformatics database between 1 October 2014 and 31 March 2016. Data were assessed at baseline (≤6 months before inclusion) and follow-up (≤6 months after first Gla-300 claim or a randomly selected Gla-100 claim). Patients switching to Gla-300 were matched via propensity score matching. Endpoints included daily average consumption (DACON) of basal insulin and average percent change of DACON per patient from baseline to follow-up. Patients were considered persistent if they remained on index basal insulin during follow-up.
Matched patients for Gla-300 (n=443) and Gla-100 (n=1241) had comparable DACON at baseline (56.0 vs 53.6 U/day, respectively, p=0.2109) and follow-up (58.8 vs 55.0 U/day, respectively, p=0.0975), corresponding to comparable changes in DACON (13.8 vs 12.6%, respectively, p=0.753). In persistent patients, DACON also increased from baseline to follow-up (Gla-300: 56.45 to 59.2 U/day, n=346; Gla-100: 54.7 to 55.0 U/day, n=1090), with

no statistical difference between cohorts (Gla-300: 9.7%; Gla-100: 7.3%, p=0.467). For the subset of patients with available HbA1c measures, both cohorts showed comparable mean HbA1c at baseline and follow-up.
Switching from Gla-100 to Gla-300 was not associated with a higher basal insulin dose compared with continuing on Gla-100. Similar changes in DACON and HbA1c were observed. Despite the increase in DACON, mean HbA1c remained elevated.
Supported by Sanofi US, Inc.

9 Cost-Effectiveness of Insulin Glargine 300 U/mL (Gla-300) Versus Insulin Degludec 100 U/mL (IDeg) in Type 2 Diabetes

Murphy DR (1); Yu X (1); Fournier M (2); Klein TM (1); Fan T (3); Perk S (1); Preblick R (3); Zhou FL (3)

1. Medical Decision Modeling Inc., Indianapolis, IN, USA
2. Sanofi, Chilly-Mazarin, France
3. Sanofi, Bridgewater, NJ, USA

This cost-effectiveness modelling analysis simulated a cohort of patients receiving Gla-300 (EDITION 2 and 3) or IDeg using the IMS Core Diabetes Model (lifetime [50 years]; n=1,000,000; age ≥62 years). Efficiency parameters, HbA1c reduction and hypoglycaemia event (HE) rates were estimated using a network meta-analysis: for Gla-300 vs IDeg, HbA1c reduction over 24 weeks was 1.00 vs 0.98%; HE rates were estimated as 2.5 vs 4.0 (severe HEs [SHEs]) and 446 vs 555 (non-SHEs [NSHEs]) per 100 patient years, respectively. The cost/unit of Gla-300 was set to US$0.22 to maintain dose-adjusted price parity with insulin glargine using data from the EDITION trials; the cost/unit of IDeg was set to $0.296 from its US wholesale acquisition cost. Treatment costs were $1,561/SHE and $13.65/NSHE (2015 $). Utilities to estimate quality-adjusted life years (QALYs) for multiple comorbidities were applied using the minimum utility approach; a disutility of –0.0118 was applied for SHEs and a method of diminishing marginal disutility was applied for NSHEs.
Compared with IDeg, Gla-300 provided a total cost reduction per patient of $8,998 ($162,288 vs $171,286) and a QALYs gain of 0.035 (7.677 vs 7.642) for lifetime in base-case analysis. One-way sensitivity analysis showed that 10% change in HbA1c, SHE/NSHE rates and treatment costs did not change the incremental cost-effectiveness ratio dominance for Gla-300. Probabilistic sensitivity analysis found that Gla-300 was less costly in 95.4% of cases and more effective in 60.1% of cases vs IDeg; real-world data need to confirm this finding.
Supported by Sanofi US, Inc.

10 Audit: Assessment of appropriate dosing of diabetic medications in people with type 2 diabetes and renal impairment

Zaman S; Corallo C; Martineau M

West Middlesex Hospital, Chelsea and Westminster Hospitals NHS Foundation Trust, London

Introduction: Chronic kidney disease (CKD) can be found in up to 23% of people with diabetes.1 However, treatment options for people with type 2 diabetes and CKD are limited as reduced glomerular filtration rate results in accumulation of certain drugs and/or

their metabolites. Therefore, it is extremely important to review diabetic medications in people with renal disease.
Objectives: To audit the optimal and safe dosing of diabetic medications in patients with type 2 diabetes and CKD.
Methods: Data was collected retrospectively through paper and electronic medical records of patients with type 2 diabetes and CKD stage 3 or below (eGFR < 60) who attended diabetes clinics from 01/01/2015 to 31/07/2016. It was recorded and analysed on MS Excel.
Results: Total number of patients was 162. Out of these, 69% had safe and optimal dosing, 30% had non-optimal dosing and 0.6% patient's records were unavailable. Non-optimal dosing was further divided into 2 groups; patients on doses of oral diabetic medications that were not appropriately adjusted according to their renal functions (33%) and patients at risk of hypos with HbA1c < 53 mmol/mol (67%).
Recommendations: To ensure there is a plan to optimize medication dosing for patients approaching CKD3 and 4 in the clinic letters. Hypos should be actively addressed and doses need to be optimized in patients with tight diabetes control even if they do not report hypos.
References:
1) Diabetes Management Issues for Patients With Chronic Kidney Disease; Kerri L.Cavanaugh, MD: Clinical Diabetes 2007 Jul; 25(3): 90-97. http://dx.doi.org/10.2337/diaclin.25.3.90

11 World travel with type 1 diabetes: a review (and experience of a couple with type 1 diabetes)

Charlton, AR; Charlton JR.

University Hospitals of Leicester NHS Trust; Camp Charnwood.

Living with type 1 diabetes and using insulin pump therapy (IPT), the authors travelled together for four months through 11 countries. Travelling with type 1 diabetes presents various added challenges. These are reviewed along with personal experience of the authors.
Air travel
Flying at altitude causes increased insulin resistance; a condition that is compounded by prolonged periods of inactivity during air travel.
Another consideration is that unintended insulin delivery from IPT occurs during ascent, and bubbles can form or increase in size within the insulin chamber.
Insulin must not be subjected to low temperatures, and therefore must be carried in hand luggage, and the risk of hold luggage becoming lost or delayed, meant that we carried all paraphernalia for IPT and glucose monitoring with us.
Crossing time zones
Using IPT allows insulin to be infused in correlation with the circadian rhythm; matching insulin infusion to insulin resistance through a 24-hour period. This is an important consideration when crossing time zones.
Airport security
Damage to insulin pumps can be caused from exposure to x-ray or full body scanner technology while negotiating airport security. This, combined with increasingly stringent security and a lack of knowledge among security staff, results in a negative experience for IPT users.
Altitude

Physiological changes at altitude lead to increased insulin resistance and risk of diabetic ketoacidosis, and altitude sickness can mask symptoms of hypoglycaemia, making altitude potentially hazardous for type one diabetics.

Climate

Tropical climates increase insulin sensitivity, risk of fever, and cause temperature-related insulin failure.