The effect of terbutaline on the absorption of pulmonary administered insulin in subjects with asthma

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- People with mild and moderate asthma have been shown to absorb less inhaled insulin than healthy subjects.
- In people with moderate asthma, the administration of a bronchodilator before inhalation of insulin has been shown to lead to increased uptake of inhaled insulin compared with no prior administration of bronchodilator.

WHAT THIS STUDY ADDS

- This study is the first to show that in people with asthma, reduction of bronchoconstriction leads to increased absorption of inhaled insulin.
- This study illustrates that due to the effect of terbutaline on glucose metabolism, the effect of insulin on plasma glucose is complex when terbutaline is administered concomitantly.

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AIM

To investigate the effect of prior administration of a bronchodilator on the absorption of inhaled insulin in people with asthma treated with inhaled corticosteroids.

METHODS

A single-centre, randomized, open-label, two-period cross-over trial was carried out in 41 nondiabetic subjects with asthma treated with inhaled steroids, with reversible bronchoconstriction (Rev+; $n = 25$) or without reversible bronchoconstriction (Rev-; $n = 16$). A dose of 0.10 U kg^{-1} inhaled human insulin was administered on each dosing day with or without prior administration of the bronchodilator terbutaline (in random order).

RESULTS

Prior administration of terbutaline led to a 44% increase in absorption of insulin over 6 h for the Rev+ group compared with no prior administration of bronchodilator [ratio (95% confidence interval) 1.44 (1.13, 1.82), $P = 0.004$], whereas no effect was seen for the Rev- or the whole group. The maximum insulin concentration ($C_{\max}$) increased by 34% for the Rev+ group ($P = 0.018$) and 17% for the whole group ($P = 0.046$), whereas no significant effect of prior terbutaline administration was seen for Rev-. The time to $C_{\max}$ was not significantly different for the Rev+ group, whereas it was approximately 30% longer after bronchodilator administration for the Rev- group ($P = 0.044$) and the whole group ($P = 0.032$).

CONCLUSIONS

In people with asthma and reversible bronchoconstriction, the administration of a bronchodilator prior to administration of inhaled insulin led to increased absorption of insulin, whereas no effect on insulin absorption in subjects without significant reversibility could be detected.

Introduction

The inhaled route is useful for delivery of systemic active peptides and proteins [1]. As a result of the previous development of inhaled insulin by several companies, the compound most extensively evaluated is insulin, which due to the simple and valid methods for measuring pharmacokinetics and pharmacodynamics also serves well as a general model substance.

One of the crucial factors for deposition of drugs delivered to the lung is the linear flow velocity [2], which depends upon the diameter of the bronchial tree. In patients with asthma, bronchoconstriction leads to higher linear flow velocity, promoting more central airway deposition [3] and a less uniform distribution than in healthy people [4, 5]. This may lead to a lower blood concentration of the drug, as has been seen for locally active drugs (see [6] for review). Previous studies of inhaled human insulin have shown the total absorption to be reduced in patients with asthma compared with healthy subjects [7]. If a bronchodilator is administered and bronchoconstriction decreases, the deposition of the drug may be more peripheral, potentially leading to increased absorption. A recent trial with inhaled human insulin administered via the AIR inhaler has shown that in people with moderate asthma, administration of the bronchodilator salbutamol 1 h prior to administration of inhaled insulin leads to approximately 50% increase in the absorption of the inhaled insulin administered via the AIR inhaler [8]. Similar findings have been reported for inhaled human insulin administered via the Exubera inhaler by unmedicated people with moderate asthma [9]. In these studies, the effect of the bronchodilator has not been published, and the relation between the degree of bronchoconstriction at time of inhalation and the bioavailability of insulin is thus unknown. Furthermore, the use of inhaled corticosteroids by patients in previous studies is not known. This may be important, since airway inflammation potentially influences absorption across airway epithelium [10, 11].

The purpose of this trial was to investigate the effect of a bronchodilator on the absorption of inhaled insulin in people with asthma treated with inhaled corticosteroids. The hypothesis was that administration of bronchodilator prior to inhalation of insulin, leading to reduced bronchoconstriction, results in significantly increased absorption of inhaled insulin in people with reversible bronchoconstriction.

Methods

Male and female subjects with a diagnosis of asthma (for at least 1 year), treated with inhaled corticosteroids for at least 4 weeks with or without concurrent use of bronchodilator therapy and a forced expiratory volume in 1 s (FEV_1) > 50% were included in the trial. Initially subjects were

required to have reversible bronchoconstriction (Rev+) (an increase in $FEV_1 \geq 12\%$ after administration of bronchodilator), but due to difficulties with recruitment this criterion was removed and analysis of the subgroups { FEV_1 increase <12% [without reversible bronchoconstriction (Rev-)] and FEV_1 increase $\geq 12\%$ (Rev+)} was included in the analysis (see statistical analysis below). Other inclusion criteria were age between 18 and 65 years (both inclusive), body mass index (BMI) $\leq 29 \text{ kg m}^{-2}$, and nonsmoker for at least 6 months (nonsmoking status confirmed by negative urine cotinine test). Subjects with any other past or present pulmonary disease were excluded, as were subjects that had been treated in emergency room for asthma within the last 3 months. Asthma severity was assessed at screening according to Global Initiative for Asthma (GINA) guidelines [12].

The study was approved by the Ethics Committee of Medical University Graz (Graz, Austria), where the study was carried out according to the principles of the Declaration of Helsinki [13] and Good Clinical Practice [14]. All subjects gave written informed consent before any trial-related activities.

Procedures

This Phase I, single-centre, open-label, randomized, two-period crossover trial consisted of a screening visit to evaluate the subject's eligibility for participation and two dosing days (visits 2–3). Screening procedures were carried out on more than 1 day. Follow-up procedures were performed at the end of visit 3.

Pulmonary function tests [FEV_1 , forced vital capacity (FVC) and FEV_1/FVC] were performed according to standard criteria in accordance with the European Respiratory Society [15] using a standard spirometer (MasterScope™; Viasys Healthcare GmbH/Erich JAEGER GmbH, Würzburg, Germany). In order to ensure standardization, the following medication and time schedule was followed for the course of the trial: at least 7 days before the screening pulmonary function test, any long-acting β_2 -agonist was replaced with a short-acting β_2 -agonist, and any combination of an inhaled steroid and β_2 -agonist was replaced by two single products. Before the pulmonary function tests with reversibility test (performed at screening, visit 2 and visit 3), inhaled steroids were withheld for 2 days, and inhaled short-acting β_2 -agonists were withheld for at least 12 h. There were 6–8 days between each occasion with pulmonary function test (i.e. between screening with pulmonary function test and visit 2, and between visit 2 and visit 3). At all three occasions, the bronchodilator (1.0 mg terbutaline in turbuhaler®; Astra-Zeneca GmbH, Wedel, Germany) was administered in two inhalations. The pulmonary function test to measure FEV_1 reversibility was performed 15 min after administration of the bronchodilator, when a near-maximal bronchodilator effect of terbutaline was to be expected [16, 17], and 15 min before administration of inhaled insulin, thereby minimizing any effect of the pul-

monary function manoeuvres that have been shown to effect absorption of inhaled substances [18, 19].

There were two treatments: (i) inhaled insulin with no prior bronchodilator (–B); and (ii) inhaled insulin with prior bronchodilator (+B). The inhaled insulin was administered 30 min after the bronchodilator to allow for a maximal bronchodilator effect at the time of insulin dosing [16, 17]. The two treatments were given to all subjects on separate dosing days in randomized order. Each treatment sequence was sealed until randomization.

At each visit, the subjects received a dose of 0.10 U kg^{-1} inhaled human insulin (1500 U ml^{-1} insulin human inhalation solution, $50 \mu\text{l}$ strip $^{-1}$; Novo Nordisk A/S, Bagsvaerd, Denmark) administered via the AERx[®] insulin Diabetes Management System (AERx[®] iDMS; version P3; Novo Nordisk A/S). One unit corresponds to approximately 1 IU insulin given subcutaneously. The dose was delivered in one inhalation. The mass median aerodynamic diameter of the aerosol was $2.4 \mu\text{m}$ with a geometric standard deviation of $1.3 \mu\text{m}$, measured using Andersen MK II Cascade impactor (Thermo Scientific, Waltham, MA, USA) [20]. No insulin was given subcutaneously or intravenously.

A hand or antecubital vein was cannulated and kept in a thermo-regulated box (approximately 50°C) for the sampling of arterialized venous blood.

Arterialized venous blood samples for plasma glucose measurements were obtained on average every 5–15 min during the experiment, and plasma glucose was measured in duplicate using the Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA, USA). Except for the pulmonary function tests and the dosing period, the subjects were in supine position during the dosing day.

Blood samples for free plasma insulin and plasma C-peptide (for control of suppression of endogenous insulin) were drawn in intervals of 10–60 min [at time points –30 (before administration of bronchodilator), –20, –15, –10, 0 (immediately before administration insulin), 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, 210, 240, 300 and 360 min].

Immediate centrifugation of the blood samples and extraction of any insulin antibodies by polyethylene glycol precipitation were performed [21]. Free plasma human insulin was measured using a commercially available enzyme-linked immunosorbent assay insulin assay [Dako Ltd, Ely, UK; interassay coefficient of variation (CV) 5.2–17.8%] and plasma C-peptide was measured using a commercially available C-peptide kit (Dako Ltd; CV 6.1–11.5%) at Capio Diagnostik a.s. (Copenhagen, Denmark).

Safety assessments included adverse events (AEs), pulmonary function tests, physical examination, electrocardiogram, vital signs and standard laboratory safety parameters.

Statistical analysis

The sample size of 41 was based on ability to detect a 25% treatment difference in area under the curve (AUC) for

insulin from 0 to 6 h ($\text{AUC}_{\text{ins}(0-6 \text{ h})}$) with a two-sided significance level of 0.05 and a power of 0.80, based on a CV of 0.35.

All AUC and area over the curve (AOC) were calculated by means of the trapezoidal method. The primary end-point $\text{AUC}_{\text{ins}(0-6 \text{ h})}$ was naturally log-transformed and analysed by a mixed linear model including treatment and visit as fixed effect, and subject as random effect.

The maximal insulin concentration, C_{max} , was estimated together with t_{max} for the corresponding time point. The other end-points, extrapolated $\text{AUC}_{\text{ins}(0-\infty)}$, C_{max} and t_{max} , were analysed similar to $\text{AUC}_{\text{ins}(0-6 \text{ h})}$. For each subject, treatment and time point, the exogenous insulin concentration was derived as: $\text{insulin}_{\text{exogenous}} = \text{insulin}_{\text{measured}} - (\text{insulin}_{(-30 \text{ min})} / \text{C-peptide}_{(-30 \text{ min})}) \times \text{C-peptide}_{\text{measured}}$. All end-points were calculated from exogenous insulin. A significant effect of the FEV₁ reversibility covariate on $\ln\text{AUC}_{\text{ins}(0-6 \text{ h})}$ was found ($P = 0.049$). Thus, the statistical analyses were made for all subjects (All) and for the two subgroups (Rev– and Rev+) by inclusion of the reversibility by treatment interaction in the previously mentioned model.

The pharmacodynamic end-points, AOC for the plasma glucose from 0 to 6 h ($\text{AOC}_{\text{Glu}(0-6 \text{ h})}$), the maximal glucose reduction from baseline ($\text{GLU}_{\text{max,red}}$) and the time to the lowest plasma glucose concentration ($t_{\text{GLUmax,red}}$) were analysed similarly to the primary end-point.

For all analyses the (B+/B–) treatment ratio was estimated with the corresponding 95% confidence interval, and a significance level of 0.05 was used throughout.

Results

A total of 58 subjects were screened, and 41 subjects (18 women and 23 men; 40 White, one Asian/Pacific Islander), age 32.6 years (range 18.0–60.0 years) and BMI 24.6 kg m^{-2} (range 19.2–29.1) were randomized in the trial. All subjects completed the trial and were included in the analyses. The subjects had a mean duration of asthma of 13.5 years (range 1.2–53.8) and represented all GINA classes (four intermittent, eight mild persistent, 22 moderate persistent, and seven severe persistent) (Table 1).

Pharmacokinetics

The mean insulin concentration profiles are shown in Figure 1. For the whole group of subjects as well as the Rev– subgroup the absorption of insulin (measured as $\text{AUC}_{\text{ins}(0-6 \text{ h})}$) was not significantly different with and without prior administration of bronchodilator, whereas prior administration of bronchodilator led to a 44% increase in the insulin absorption in the Rev+ subgroup ($P = 0.004$) (Table 2). In a post hoc analysis no significant difference in absorption could be detected with or without prior administration of bronchodilator for the subgroup with intermittent or mild asthma [0.93 ($0.69, 1.25$), $P = 0.615$], nor for the

Table 1
Baseline characteristics

	All	Rev–	Rev+
Male/female	23/18	13/12	10/6
Ethnic origin			
White	40	24	16
Asian/Pacific islander	1	1	
Age (years)	32.6 (18–60)	32.2 (18–60)	33.4 (19–59)
Body mass index (kg m ⁻²)	24.6 (19.2–29.1)	24.0 (19.2–29.1)	25.5 (21.3–28.9)
Asthma diagnosis (years)	13.5 (1.2–53.8)	11.5 (1.2–41.7)	16.6 (1.6–53.8)
Asthma severity (GINA)			
Intermittent	4	4	0
Mild persistent	8	6	2
Moderate persistent	22	13	9
Severe persistent	7	2	5
Spirometry (pre-bronchodilator)			
FEV ₁ (% predicted)	85 ± 16	91 ± 14	76 ± 14
FVC (% predicted)	107 ± 16	105 ± 15	111 ± 17
FEV ₁ /FVC (% predicted)	79 ± 12	86 ± 7	68 ± 8
PEF (% predicted)	76 ± 14	82 ± 13	65 ± 9
FEV ₁ reversibility (%)	11.5 ± 9.5	5.3 ± 3.1	21.1 ± 7.8

Mean ± SD, mean (min–max). FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak flow; GINA, Global Initiative for Asthma.

Figure 1
Mean serum insulin concentration curves. (a) All subjects. (b) Rev– subgroup [subjects with forced expiratory volume in 1 s (FEV₁) increase <12% at baseline]. (c) Rev+ subgroup (subjects with FEV₁ increase ≥12% at baseline). Solid line, inhaled insulin with no prior administration of bronchodilator; dotted line, inhaled insulin with administration of bronchodilator 30 min before inhalation of insulin

Table 2

Pharmacokinetic end-points

	Group	n	+B Mean (SEM)	–B Mean (SEM)	Mean ratio (95% CI)	P
AUC_{ins0–6 h} (pmol h^{–1} l^{–1})	All	41	279.5 (0.07)	248.3 (0.07)	1.13 (0.96, 1.32)	0.145
	Rev–	25	259.0 (0.09)	270.4 (0.09)	0.96 (0.79, 1.16)	0.653
	Rev+	16	313.5 (0.11)	218.4 (0.11)	1.44 (1.13, 1.82)	0.004
AUC_{ins0–infinity} (pmol h^{–1} l^{–1})	All	41	298.3 (0.08)	273.1 (0.08)	1.09 (0.92, 1.30)	0.308
	Rev–	25	273.0 (0.10)	295.9 (0.10)	0.92 (0.75, 1.14)	0.438
	Rev+	16	340.9 (0.12)	242.2 (0.12)	1.41 (1.09, 1.82)	0.010
C_{max} (pmol l^{–1})	All	41	115.3 (0.07)	98.5 (0.07)	1.17 (1.00, 1.37)	0.046
	Rev–	25	116.1 (0.09)	108.6 (0.09)	1.07 (0.88, 1.30)	0.496
	Rev+	16	114.2 (0.11)	85.1 (0.11)	1.34 (1.06, 1.71)	0.018
t_{max} (min)	All	41	52.4 (0.09)	41.1 (0.09)	1.28 (1.02, 1.59)	0.032
	Rev–	25	55.5 (0.12)	41.2 (0.12)	1.35 (1.01, 1.80)	0.044
	Rev+	16	48.2 (0.15)	40.9 (0.15)	1.18 (0.83, 1.68)	0.354

All means are geometric means [exp(Least Squares Means)] based on ANOVA model. +B, with administration of bronchodilator 30 min before inhalation of insulin; –B, without prior administration of bronchodilator; Rev–, subjects with FEV₁ increase <12% at baseline; Rev+, group with FEV₁ increase ≥12% at baseline.

subgroup with moderate asthma [1.16 (0.92, 1.46), *P* = 0.191] (no analysis was performed for the very small group with severe asthma).

Administration of bronchodilator prior to inhalation of insulin led to an increase in *C*_{max} of 17% for the whole group of subjects (*P* = 0.046) and 34% for the Rev+ subgroup (*P* = 0.018), whereas no statistically significant difference in *C*_{max} could be detected for the Rev– subgroup (Table 2). The time to *C*_{max} was a little longer (approximately 11 min) in the whole group (*P* = 0.032) and the Rev+ (*P* = 0.044) subgroup when bronchodilator was administered prior to inhalation of insulin, but not significantly longer for the Rev+ subgroup (Table 2).

Pharmacodynamics

The mean glucose concentration profiles are shown in Figure 2. Administration of bronchodilator led to higher plasma glucose values, and influenced the pharmacodynamics of inhaled insulin. Prior administration of bronchodilator led to a 25% lower overall reduction in plasma glucose (measured as AOC_{0–6 h}) for the whole group of subjects (*P* = 0.033). In the Rev– subgroup a 33% lower overall reduction in plasma glucose was found (*P* = 0.021), whereas no significant difference could be detected for the Rev+ subgroup (Table 3). Prior administration of bronchodilator did not significantly reduce the maximal glucose reduction for the whole group of subjects (but tended to, *P* = 0.052) or the Rev+ subgroup, whereas it was significantly lower for the Rev– subgroup (*P* = 0.015). The time to maximal glucose reduction came 40–60% later with prior administration of bronchodilator (all, *P* = 0.002; Rev–, *P* = 0.028; Rev+, *P* = 0.017), corresponding to approximately 40 min (Table 3).

Safety

A total of 10 AEs were observed in eight subjects, with headache being the most frequent AE (six AEs in four subjects). All were mild, and no AEs were judged related to

inhaled insulin. There were no clinically relevant changes in any other safety parameters.

Discussion

This study has shown that in subjects with asthma treated with inhaled steroids having a reversible bronchoconstriction (FEV₁ increase ≥12%), prior administration of a bronchodilator leads to an increase in absorption of inhaled insulin, whereas there is no significant effect on absorption for subjects with little reversibility (FEV₁ increase <12%). No overall effect of bronchodilator prior to inhaled insulin was seen in the mixed asthma population, or in the subgroup of subjects with intermittent or mild asthma or the subgroup with moderate asthma.

In a recent study, Wolzt and coworkers [8] studied the absorption of human insulin inhaled with the AIR device in subjects with a clinical diagnosis of mild asthma (FEV₁ ≥ 80% predicted) or moderate asthma (daily asthma symptoms, daily use of short-acting β₂-agonists or exacerbations affecting daily activities, and FEV₁ values of >60 to ≤80% or a ≥12% increase in FEV₁ after bronchodilator). The authors found bioavailability of inhaled insulin to be reduced in both groups of asthmatic subjects compared with healthy subjects. They noticed an increase in inhaled insulin absorption of approximately 50% after administration of bronchodilator in the subgroup with moderate asthma. The degree of reversibility was not measured. Another difference between the study by Wolzt and coworkers and our study is that all subjects in our study had underlying treatment with inhaled corticosteroids.

This study indicates that the bioavailability of inhaled insulin is reduced by the presence of bronchoconstriction in asthmatic subjects. This is also supported by the findings by Wolzt and coworkers. The most likely explanation is that the deposition of the inhaled insulin is affected by bron-

Figure 2 Mean plasma glucose concentration curves. (a) All subjects. (b) Rev– subgroup [subjects with forced expiratory volume in 1 s (FEV₁) increase <12% at baseline]. (c) Rev+ subgroup (subjects with FEV₁ increase ≥12% at baseline). Solid line, inhaled insulin with no prior administration of bronchodilator; dotted line, inhaled insulin with administration of bronchodilator 30 min before inhalation of insulin

Table 3 Pharmacodynamic end-points

	Group	n	+B Mean (SEM)	–B Mean (SEM)	Mean ratio (95% CI)	P
AOC (mg h ^{–1} dl ^{–1})	All	41	55.55 (0.11)	73.73 (0.11)	0.75 (0.58, 0.98)	0.033
	Rev–	25	47.7 (0.17)	70.7 (0.17)	0.67 (0.48, 0.94)	0.021
	Rev+	16	70.25 (0.23)	79.12 (0.23)	0.89 (0.59, 1.33)	0.557
GLU _{max,red} (mg dl ^{–1})	All	41	19.82 (0.08)	24.17 (0.08)	0.82 (0.67, 1.00)	0.052
	Rev–	25	17.68 (0.13)	24.34 (0.13)	0.73 (0.56, 0.94)	0.015
	Rev+	16	23.58 (0.18)	24.01 (0.18)	0.98 (0.72, 1.34)	0.907
t _{GLUmax,red} (min)	All	41	123.4 (0.10)	83.83 (0.10)	1.47 (1.16, 1.86)	0.002
	Rev–	25	130.8 (0.15)	92.84 (0.15)	1.41 (1.04, 1.91)	0.028
	Rev+	16	112.9 (0.21)	71.31 (0.21)	1.58 (1.09, 2.30)	0.017

All means are geometric means [exp(Least Squares Means)] based on ANOVA model. +B, with administration of bronchodilator 30 min before inhalation of insulin; –B, without prior administration of bronchodilator; Rev–, subjects with FEV₁ increase <12% at baseline; Rev+, group with FEV₁ increase ≥12% at baseline.

choconstriction, being more central and/or focal. Confirmation of this mechanism would require the use of radiolabelled insulin aerosol. Reduced bioavailability of inhaled insulin may depend not only on bronchoconstriction but also on inflammatory changes in the airway mucosa. Since we had no group of healthy controls, this study provides no information concerning the effects of asthma *per se*. Reduced bioavailability in asthmatic sub-

jects has, however, been reported by Henry and coworkers [7] and by Wolzt and coworkers [8], even in subjects with normal FEV₁. One cause of this may be inflammatory changes in the peripheral airways. Reduced absorption of solutes has previously been shown in subjects with allergic rhinitis [10, 11]. Since the mucosal changes in allergic rhinitis and asthma are quite similar [22], corresponding reduction in bioavailability may occur in the small airways.

The condition of asthma is characterized with a varying degree of bronchoconstriction from day to day and, compared with healthy subjects, large within-subject variation in the absorption has been observed for inhaled insulin [7, 23]. This variability as well as the effect of reversible bronchoconstriction on the absorption of inhaled insulin observed in this study shows that in people with asthma it will be difficult to predict the exact systemic dose of the inhaled dose, and probably further so in daily life, as study conditions usually limit the variability. Considering these findings, general for other inhaled drugs, it is clear that in the case of inhaled drugs for systemic use with a bioavailability of <100% and where large variations in plasma concentrations cannot be tolerated (e.g. morphine [24]), the use in people with asthma should be avoided. For drugs where larger plasma variations are tolerable, it should be considered if such variations are consistent with the best treatment for the patient.

Terbutaline and other β_2 -agonists increase blood glucose via adrenergic stimulation, and have even been tested as prevention of hypoglycaemia in people with diabetes [25–27]. Due to this glucose-increasing effect of terbutaline, the insulin-induced drop in plasma glucose was not as pronounced on the days with terbutaline administration compared with the pharmacokinetic response. Thus, this study confirms that especially people with asthma and diabetes should be aware of a potential glucose-increasing effect when taking terbutaline, and adjust diabetes treatment accordingly.

In summary, the present study has shown that in those with asthma and reversible bronchoconstriction, the administration of a bronchodilator prior to administration of inhaled insulin leads to increased absorption of insulin, whereas no effect in subjects without significant reversibility could be found. Furthermore, because of the observed glucose-increasing effect of terbutaline, patients with diabetes and asthma should be aware of this potential effect and monitor glucose accordingly.

Competing interests

A.H.P. has received funds for research from Novo Nordisk A/S, which developed the AERx® iDMS. A.H.P., T.S. and J.R. are employees of Novo Nordisk A/S. A.H.P. and T.S. have shares in Novo Nordisk A/S. P.W. has received reimbursement for attending a symposium, fees for speaking, funds for research, and fees for consulting from Novo Nordisk A/S. P.W. has previously been an employee of Novo Nordisk A/S. T.R.P. has received reimbursement for attending a symposium, a fee for speaking, funds for research, funds for a member of staff, and fees for consulting from Novo Nordisk A/S. S.K., G.K., A.W. and H.O. have no competing interests to declare.

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