Body Weight Changes Associated With Insulin Therapy

A retrospective pooled analysis of inhaled human insulin (Exubera) versus subcutaneous insulin in five controlled Phase III trials

PRISCILLA A. HOLLANDER, MD, PHD[1]
ALAN KRASNER, MD[2]
SOL KLIOZE, PHD[2]
PAMELA SCHWARTZ, PHD[2]
WILLIAM DUGGAN, PHD[2]

Weight gain is commonly seen when patients are started on subcutaneous (SC) insulin. In the UK Prospective Diabetes Study, those assigned insulin gained 4 kg more than those assigned conventional therapy at 10 years (1). Given that the majority of patients with type 2 diabetes are overweight or obese (2,3), additional weight gain is clearly a concern. Furthermore, while patients with type 1 diabetes were historically often underweight, the greater use of an intensified treatment approach to achieve the benefits of improved glycemic control is associated with greater weight gain than conventional treatment (4). Fear of weight gain, along with factors such as reluctance to self-inject and fear of hypoglycemia, is a frequent deterrent to initiating insulin therapy and has been linked to reduced treatment adherence in patients with both type 1 and type 2 diabetes (5).

In type 2 diabetes, the β-cell dysfunction that leads to impaired insulin secretion is progressive, and eventually patients will require a treatment strategy that includes insulin either alone or with oral agents (6). The aim of this pooled analysis was to compare weight changes in a large population of adult patients with type 1 or type 2 diabetes receiving a regimen involving inhaled human insulin (Exubera [rDNA origin] Inhalation Powder) versus an SC insulin–only regimen.

RESEARCH, DESIGN AND METHODS

— This was a retrospective analysis of pooled 6-month data from five controlled Phase III clinical trials conducted in North and South America to compare the effect of regimens involving Exubera (Exubera administered in combination with intermediate- or long-acting SC insulin) versus those involving only SC insulin on body weight in adult patients with type 1 or type 2 diabetes. The trials included studies from the Exubera clinical program of 6 months' duration or longer in patients with type 1 or type 2 diabetes in which SC insulin was used as the comparator regimen. The detailed study designs, clinical measurements, end point definitions, power calculations, and results of the studies used in the retrospective analysis have previously been published (7–11).

In summary, the trials had an open-label design. In general, target blood glucose values were 80–140 mg/dl (4.4–7.8 mmol/l) (premeal) and 100–160 mg/dl (5.6–8.9 mmol/l) (bedtime), with dose adjustments based on home-monitored blood glucose results. The primary outcome measure was change in A1C; secondary outcomes included fasting and postprandial glucose response, insulin dose, insulin antibodies, body weight, hypoglycemia, pulmonary function tests, and patient-reported outcomes. Patients who were smoking or had moderate to severe underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease) were excluded. Data from the five trials were pooled, and statistical methods repeated those used in the original trials, namely an ANCOVA model with model terms for baseline values, study, and treatment group.

RESULTS

— This analysis included 1,048 patients with type 1 diabetes (Exubera, $n = 527$; SC insulin, $n = 521$) and 912 patients with type 2 diabetes (Exubera, 460; SC insulin, 452). Baseline body weight and A1C levels were similar between the Exubera and comparator groups (Table 1).

Less weight gain was observed with Exubera regimens compared with SC insulin regimens in adult patients with type 1 or type 2 diabetes. The differences in the treatment effect on body weight were consistent across sex. In patients with type 1 diabetes, a 0.2-kg increase was noted with Exubera, compared with a 1.1-kg increase with SC insulin. Patients with type 2 diabetes gained only one-half as much weight on a regimen including Exubera than on regimens that only included SC insulin (0.7 vs. 1.6 kg, respectively). The adjusted mean change in weight was statistically different in patients treated with a regimen including Exubera versus an SC insulin–only regimen for both type 1 (−0.87 kg [95% CI −1.24 to −0.50]) and type 2 (−0.93 kg [−1.39 to −0.48]) diabetic subjects.

Despite differences in weight changes, reductions in A1C were comparable in both treatment groups (Table 1) for both type 1 and type 2 diabetes. Similarly, rates of overall hypoglycemia (type 1 diabetes [$n = 1,048$]: Exubera 7.0 vs. SC insulin 6.8 events/subject-month; type 2 diabetes [$n = 912$]: Exubera 1.8 vs. SC insulin 2.1 events/subject-month) and severe hypo-

From the [1]Baylor Endocrine Center, Baylor University Medical Center, Dallas, Texas; and [2]Pfizer Global Research, New London, Connecticut.
Address correspondence and reprint requests to Priscilla A. Hollander, Baylor University Medical Center, 3600 Gaston Ave., Wadley Tower, Suite 656, Dallas, TX 75246. E-mail: priscilh@baylorhealth.edu.
Received for publication 9 October 2006 and accepted in revised form 18 May 2007.
Published ahead of print at http://care.diabetesjournals.org on 29 May 2007. DOI: 10.2337/dc06-2083.
Abbreviations: SC, subcutaneous.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Body weight and glycated A1C levels at baseline and mean adjusted change from baseline and insulin dose in patients with type 1 or type 2 diabetes randomized to inhaled human insulin (Exubera) or SC insulin for 6 months*

	Type 1 diabetes					Type 2 diabetes				
	Exubera	*n* or *n* (%)	SC insulin	*n* or *n* (%)	Difference between adjusted mean changes (95% CI)	Exubera	*n* or *n* (%)	SC insulin	*n* or *n* (%)	Difference between adjusted mean changes (95% CI)
Male		275 (55.4)		277 (54.3)			283 (66.9)		274 (64.0)	
Female		221 (44.6)		233 (45.7)			140 (33.1)		154 (36.0)	
Body weight at baseline (kg) (pooled analysis)	76.0 ± 14.0	496	75.0 ± 13.4	510		88.5 ± 14.9	423	88.5 ± 15.0	428	
Quattrin et al. (ref. 7)*	77.4 ± 14.9	135	76.4 ± 13.0	134						
Skyler et al. (ref. 8)*	76.0 ± 13.6	103	76.9 ± 14.1	104						
Skyler et al. (ref. 9)	75.1 ± 13.6	286	73.8 ± 13.1	285						
Hollander et al. (ref. 10)†						90.6 ± 14.5	147	89.0 ± 13.7	149	
Rosenstock et al. (ref. 11)						87.1 ± 14.8	312	88.4 ± 15.4	302	
Adjusted change from baseline in body weight (kg) (pooled analysis)‡§	0.2 ± 0.1	496	1.1 ± 0.1	510	−0.87 (−1.24 to −0.50)	0.7 ± 0.2	423	1.6 ± 0.2	428	−0.93 (−1.39 to −0.48)
Quattrin et al. (ref. 7)*	0.4 ± 0.3		1.1 ± 0.3		−0.72 (−1.48 to 0.04)					
Skyler et al. (ref. 8)*	0.4 ± 0.3		0.6 ± 0.3		−0.24 (−1.07 to 0.59)					
Skyler et al. (ref. 9) (6-month assessment)	0.01 ± 0.21	258	1.15 ± 0.24	272	−1.14 (90% CI −1.63 to −0.65)					
Skyler et al. (ref. 9) (24-month assessment)	0.9 ± 0.2	208	2.1 ± 0.3	217	−1.26 (90% CI −1.80 to −0.71)					
Hollander et al. (ref. 10)						0.1 ± 0.2		1.3 ± 0.2		−1.28 (−1.96 to −0.60)
Rosenstock et al. (ref. 11) (6-month assessment)						1.2 ± 0.23	276	1.9 ± 0.25	279	−0.75 (90% CI −1.27 to −0.22)
Rosenstock et al. (ref. 11) (24-month assessment)						1.97 ± 0.26	218	3.30 ± 0.27	224	−1.33 (90% CI −1.92 to −0.75)
A1C at baseline (pooled analysis)	7.6 ± 1.0	500	7.7 ± 1.0	509		7.8 ± 1.1	425	7.9 ± 1.1	437	
Adjusted change from baseline A1C (pooled analysis)‡§	−0.2 (0.03)		−0.3 (0.03)		0.09 (0.00 to 0.18)	−0.7 ± 0.05		−0.6 ± 0.04		−0.07 (−0.19 to 0.05)
Mean daily insulin dose at study end (short-acting insulin/intermediate- or long-acting insulin)¶										
Quattrin et al. (ref. 7)*	14.2/28.7		18.2/40.9							
Skyler et al. (ref. 8)*	12.0/37.7		28.1/37.9							
Skyler et al. (ref. 9) (6-month assessment)	11.3/31.1		25.0/35.5							
Skyler et al. (ref. 9) (24-month assessment)	14.7/31.8		25.4/36.2							
Hollander et al. (ref. 10)†						16.6/37.9		25.5/52.3		
Rosenstock et al. (ref. 11) (6-month assessment)						13.2/43.8		31.2/45.9		
Rosenstock et al. (ref. 11) (24-month assessment)						15.9/46.6		34.7/50.1		

Data are means ± SD unless otherwise indicated. *Data published in Quattrin et al. (ref. 7) and Skyler et al. (ref. 8) were combined adult and pediatric data, whereas the data reported in the table are from adults only. †Results in the table reflect the intent-to-treat population, whereas Hollander et al. (ref. 10) reported the per protocol population. Conclusions reached from these two populations are the same. ‡Means ± SE. §Least-squares means (±SE) based on the primary model with terms for baseline, treatment, and study. ¶Exubera was measured in milligrams and SC insulin in units; 1 mg Exubera is approximately equivalent to 2–3 units subcutaneously injected fast-acting human insulin.

glycemia (type 1 diabetes: Exubera 5.8 vs. SC insulin 5.2 events/100 subject-months; type 2 diabetes: Exubera 0.8 vs. SC insulin 1.1 events/100 subject-months) were also comparable.

CONCLUSIONS — Significantly less weight gain was observed at 6 months with regimens including Exubera therapy compared with SC insulin–only regimens in adult patients with type 1 or type 2 diabetes. Long-term data have confirmed that these differences in weight gain are sustained at 2 years (Table 1) (9,11). Compared with SC insulin, patients with type 1 diabetes receiving Exubera only gained a modest amount of weight; patients with type 2 diabetes gained one-half as much weight.

Comparable mean changes from baseline A1C were observed with Exubera and SC insulin–only regimens in both the type 1 and type 2 diabetes groups; thus, less weight gain with Exubera is not explained by differences in glycemic control. The incidence of hypoglycemia with Exubera regimens was consistent with that associated with SC insulin use. Both the frequency and nature of hypoglycemia with Exubera are comparable to those with SC insulin, with most events mild to moderate in severity (12).

The authors acknowledge that this was an analysis of 6-month data only, a relatively short time period given the lifelong need for insulin in patients with diabetes. However, in well-controlled animal studies comparing inhaled and matched intravenous insulin administration, inhalation of insulin was associated with markedly increased peripheral and decreased hepatic glucose uptake (13). Pending confirmation in humans, this finding may point to significant differences between routes of insulin administration potentially affecting metabolic energy balances.

For the patient, the clinical significance of less weight gain is important from a psychological standpoint and may also influence the likelihood of diabetes- and obesity-related complications. While there is no direct evidence that less weight gain reduces cardiovascular events or mortality, studies have shown beneficial effects of moderate weight loss on the cardiovascular risk factors associated with obesity (14,15). While speculative, any reduction in the amount of weight a patient gains with an insulin therapy may, therefore, have long-term benefits in reducing diabetes complications.

Acknowledgments — This study was funded by Pfizer, manufacturer of Exubera.

Editorial support was provided by J. Grice of PAREXEL.

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