Abstract

Aims. – In type 2 diabetes (T2D), insulin-induced weight gain may stem from a reduction in resting energy expenditure (REE). We sought to determine the early effects of insulin introduction on REE in 20 poorly controlled T2D patients.

Methods. – After improving the glycaemia, REE was measured on Day 0 and Day 4 during two treatment regimens: bedtime insulin (n = 10, group 1); and one off (3-day) intravenous insulin infusion (n = 10, group 2).

Results. – Both groups were similar in age, gender, BMI, C-peptide, HbA1c and initial REE. By Day 4, fasting glycaemia had similarly improved in both groups: group 1: −5.3 ± 2.7 mmol/L vs group 2: −5.8 ± 4.2 mmol/L. In group 2, the second REE was measured 12 h after stopping the intravenous insulin infusion, whereas subcutaneous insulin was maintained in group 1. REE did not change in group 2 (−1.3 ± 6.5%), whereas it decreased significantly in group 1 (−8.0 ± 7.0%; P < 0.05).

Conclusion. – Bedtime insulin led to an early and specific reduction in REE.

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Keywords: Insulin therapy; Resting energy expenditure; Type 2 diabetes

Résumé

Réduction précoce de la dépense énergétique de repos après introduction d’une insuline basale.

Objectifs. – Au cours du diabète de type 2, la dépense énergétique de repos est accrue. Sa réduction pourrait contribuer à la prise de poids lors de l’introduction de l’insuline. L’objectif de l’étude était de déterminer si cette réduction est décelable dès les premiers jours et si elle dépend de l’amélioration glycéémique.

Méthodes. – Chez 20 patients diabétiques de type 2 non contrôlés par une bithérapie antidiabétique orale, nous avons mesuré la DER pendant 30 minutes le matin à jeun, avant (j0) puis après quatre jours (j4) de traitement de leur hyperglycémie suivant deux modalités : une injection quotidienne au coucher d’un analogue lent de l’insuline (n = 10, group 1) et une insulinothérapie transitoire intraveineuse pendant trois jours (n = 10, groupe 2). À j4, la DER a été mesurée 12 heures après l’arrêt de l’insuline intraveineuse dans le groupe 2, alors que l’injection sous-cutanée quotidienne d’insuline basale a été poursuivie dans le groupe 1.

Résultats. – Les patients des deux groupes présentaient des caractéristiques initiales comparables (âge, sexe, IMC, C-peptide, HbA1c, et DER). À j4, l’amélioration de la glycéémie à jeun a été comparable dans les deux groupes – groupe 1 : −5.3 ± 2.7 mmol/L versus groupe 2 : −5.8 ± 4.2 mmol/L. De plus, la DER n’a pas varié dans le groupe 2 (−1.3 ± 6.5 %), alors qu’elle a significativement diminuée dans le groupe 1 (−8.0 ± 7.0 %, P < 0.05).

Conclusion. – L’introduction d’une insulinothérapie sous-cutanée de type basale entraîne donc une réduction précoce de la DER qui ne semble pas liée à l’amélioration glycéémique.

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Mots clés : Insulinothérapie basale ; Dépense énergétique de repos ; Diabète de type 2
1. Introduction

The mechanisms of weight gain during insulin therapy in type 2 diabetic (T2D) patients are not well understood. In two long-term studies [1,2], the decrease in resting energy expenditure (REE) contributed to insulin-induced weight gain and appeared to be independent of glycaemic control. Indeed, higher REEs have been reported in hyperglycaemic diabetic patients compared with non-diabetic subjects matched by body mass index (BMI) [3]. Gougeon et al. found that fasting plasma glucose is an independent determinant of REE in poorly controlled obese T2D patients [4]. Furthermore, previous data have shown that REE was decreased by 3–10% after 1 to 2 weeks of insulin therapy sufficient to improve glycaemia [5–7]. Nevertheless, it remains unclear whether or not this reduction could be detected sooner, and whether or not it is due to insulin itself or the improvement in glycaemia.

We assessed changes in REE over a 4-day period during which glycaemic control was improved in T2D patients with either once-daily subcutaneous insulin therapy (group 1) or a one-off (3-day) intravenous insulin infusion (group 2). To study the specific effect of insulin on REE, the only planned difference between the study groups was the presence of exogenous insulin on Day 4 in group 1, as intravenous insulin was stopped on Day 3 in group 2. The present study was designed to determine the early and specific effects of insulin introduction on REE in poorly controlled T2D patients.

2. Materials and methods

2.1. Subjects

Patients were recruited according to the following three criteria:

- HbA1c greater than 7%;
- previous oral therapy with a maximum tolerated dose (all patients were taking glibenclamide, nine in group 1 and eight in group 2 were also taking metformin, with three not taking metformin because of digestive intolerance; except for two patients in group 1 who stopped pioglitazone after inclusion, treatments continued as before during the study);
- normal renal function.

2.2. Experimental protocol

All patients were studied as hospital inpatients. REE was measured on entering the study (Day 0), the day after hospital admission. Two insulin regimens were then prescribed to improve glycaemic control. The second REE was measured on Day 4 in both groups (Fig. 1).

In group 1, patients (n = 10) were fed a weight-maintaining diet of fixed composition and caloric content throughout the study, and also received a once-daily subcutaneous injection of basal insulin analogues at bedtime (glargine, Lantus®; Sanofi–aventis, or detemir, Levemir®, Novo Nordisk). Insulin doses were adjusted according to fasting capillary glucose determinations (MediSense® Optium™, Abbott) with the objective of 5.5 mmol/L. Capillary glucose determination continued throughout the night. The bedtime insulin injection was maintained the night before the second REE.

In group 2, patients (n = 10) received a 72-h intravenous regular human insulin infusion to correct glucose toxicity [8]. Insulin was introduced at 2000 h and was infused intravenously via an electric syringe (Harvard Instruments, Les Ullis, France). To minimize postprandial glucose excursions, the patients were kept on an aglucidic diet until dinnertime on Day 3 (2000 h), while 150 g/day of glucose was infused at a constant rate with a pump. The insulin infusion rate was adjusted every 2 h according to capillary glucose determinations, with the objective of 5.5 mmol/L. Capillary glucose determination continued throughout the night. The insulin infusion was withdrawn on Day 3 at 2000 h, 12 h before the second REE measurement, to allow the exogenous insulin to dissipate. On Day 3, all patients ingested the same mixed, isoenergetic dinner.

2.3. Analytical procedures

Respiratory exchanges were monitored using a SensorMedics Vmax 29N apparatus. VCO₂ and VO₂ were determined over a 30-min interval, from 08 h 00 to 08 h 30, after an overnight fast, and REE was calculated according to Weir’s equation [9]. The coefficient of variation of the REE is about 10% [10].
Baseline characteristics and changes on Day 4 in the study patients.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 10)</th>
<th>Group 2 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 11</td>
<td>56 ± 12</td>
</tr>
<tr>
<td>Gender (female: male)</td>
<td>4:6</td>
<td>4:6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.1 ± 4.4</td>
<td>30.1 ± 3.7</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.6 ± 1.1</td>
<td>10.0 ± 1.7</td>
</tr>
<tr>
<td>C-peptide (ng/mL)</td>
<td>3.4 ± 1.5</td>
<td>4.1 ± 1.8</td>
</tr>
<tr>
<td>Fasting glycaemia (mmol/L)</td>
<td>12.0 ± 2.5</td>
<td>14.1 ± 3.6</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>6.6 ± 2.1*</td>
<td>8.2 ± 1.7*</td>
</tr>
<tr>
<td>Mean difference between Day 4 and baseline</td>
<td>−5.3 ± 2.7</td>
<td>−5.8 ± 4.2</td>
</tr>
<tr>
<td>Resting energy expenditure (Kcal/24h)</td>
<td>1880 ± 352</td>
<td>1810 ± 303</td>
</tr>
<tr>
<td>Baseline</td>
<td>1713 ± 252*</td>
<td>1782 ± 308</td>
</tr>
</tbody>
</table>

BMI: body mass index; HbA1c: haemoglobin A1c; data are expressed as means ± S.D.

Group 1: 4.2 in group 2. In group 1, REE decreased with bedtime insulin therapy. The only difference between the two groups at Day 4 was the presence of exogenous insulin in group 1. Although the absence of serum insulin level determination on Day 4 in this group is a study limitation, it is well known that glargine and detemir are long-acting insulin analogues [12]. Also, as the immunoradiometric assay we used has not been validated for assessing serum insulin glargine or detemir (≈ 30-fold higher) concentrations, we decided not to make any determinations of them. However, using slightly higher NPH insulin doses (≈ 40 IU/day), Maki-mattila et al. observed +5.5 μU/mL higher plasma insulin levels the morning after the bedtime injection [1], an increase probably similar in the present study patients.

Although the lack of randomization is another study limitation, our results favour the likelihood that the short-term reduction in REE stemmed from insulin itself, rather than the improved glycaemic control. The mechanism by which insulin affects REE independently of glucose is, however, uncertain, although some energy-expending processes not directly linked with glycaemia, such as proteolysis, are known to be inhibited by insulin [13].

The reduction in REE is not the only contributor to insulin-induced weight gain: hypoglycaemia, decreased glycosuria [1], and the anabolic effects of insulin are also implicated in increased fat deposition [14] and protein anabolism [13]. The early reduction in REE, however, supports its importance and may have practical implications. As changes in REE with subcu-
taneous insulin therapy may differ among T2D patients (range: −20 to +3.5% in our study), further studies are required to assess whether or not the early reduction in REE can predict the extent of insulin-induced weight gain, as a low REE is a known predictor of later weight gain in non-diabetic subjects [15]. Further work is also necessary to determine whether or not the reduction of REE might be detected even earlier (after a single insulin injection).

5. Conflicts of interests

Nothing to declare.

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References