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Original article

Early changes in respiratory quotient and resting energy expenditure predict later weight changes in patients treated for poorly controlled type 2 diabetes

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Abstract

Aim. – This study looked at whether early changes in resting energy expenditure (REE) and respiratory quotient (RQ) are correlated with later weight changes in patients with type 2 diabetes (T2D) being treated with insulin or GLP-1 analogues, or diet.

Methods. – A total of 67 patients (age: 57 ± 9 years; BMI: 33.7 ± 5.0 kg/m^2; HbA_{1c}: 9.9 ± 1.5%) began taking an insulin analogue at bedtime (INS, $n = 28$; initial dose: 0.2 IU/kg) or a GLP-1 analogue (GLP-1, $n = 23$), or only a dietary intervention (diet, $n = 16$; restricted carbohydrates and calories). Their respiratory exchanges were monitored on days 0, 1 and 2 before breakfast.

Results. – Two days after starting the bedtime insulin analogue, fasting glycaemia improved (INS: −65 ± 41 mg/dL; GLP-1: −29 ± 48 mg/dL; diet: −31 ± 46 mg/dL; $P < 0.05$), REE decreased (INS: −162 ± 241 kcal/24 h; GLP-1: 0 ± 141 kcal/24 h; diet: −41 ± 154 kcal/24 h; $P < 0.05$) and RQ increased (from 0.76 ± 0.04 to 0.80 ± 0.04; $P < 0.01$), whereas only RQ decreased with diet (from 0.79 ± 0.05 to 0.76 ± 0.04; $P < 0.05$) and remained unchanged with GLP-1 ($P < 0.005$ for ΔRQ across treatments). Only 33 patients attended the scheduled examination three months later. HbA_{1c} improved (INS, $n = 16$: −1.7 ± 1.4%; GLP-1, $n = 12$: −2.1 ± 1.4%; diet, $n = 5$: −1.7 ± 2.8%; NS), while weight changes differed (INS: +1.5 ± 4.3 kg; GLP-1: −2.8 ± 2.8 kg; diet: −2.2 ± 2.7 kg; $P < 0.005$). After three months, weight changes correlated with early changes in REE ($r = -0.37$, $P < 0.05$) and RQ ($r = +0.43$, $P < 0.01$), and remained correlated when both changes were included in a multivariate regression analysis ($r = 0.58$, $P < 0.005$).

Conclusion. – In poorly controlled patients with T2D and two days after the introduction of a bedtime insulin analogue, REE decreased by −9% while RQ increased by +5%, pointing to a reduction of lipid oxidation. These changes were predictive of later weight gain.

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

1. Introduction

Weight gain is a well-known effect of insulin therapy in type 2 diabetes (T2D). Although it may be more or less pronounced (with multiple injections or bedtime administration, respectively) [1], it still appears to be unavoidable, even when insulin is introduced early on in the course of the disease [2]. As it affects overweight and obese patients, it is undesirable [3] and, thus, opens up possibilities for alternative treatments such as glucagon-like peptide (GLP)-1 analogues [4]. Weight gain with insulin involves a change in energy balance, the mechanisms of which are not well understood. Increased energy intakes have been suspected to cause such weight gains, based on doubly labelled water studies [5], and it is also more likely to affect patients compensating for insulin-induced hypoglycaemia. Indeed, higher rates of hypoglycaemia were reported in the 'prandial' arm of the 4-T Study Group, which gained more weight after starting insulin [1]. Hypoglycaemia is, however, more frequent after five years of insulin, whereas the weight gain begins before that [6] and, based on animal studies, the proper effect of insulin should be a reduction, not an increase, in appetite [7]. On the energy-expenditure side, the fear of insulin-induced hypoglycaemia may lead some patients to reduce their

Abbreviations: BMI, body mass index; GLP-1, glucagon-like peptide-1; REE, resting energy expenditure; RQ, respiratory quotient; T2D, type 2 diabetes.

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activity levels. In fact, most insulin-using T2D patients have moderate levels of physical activity, with the majority of their energy expenditure occurring during rest, measured as resting energy expenditure (REE), which is 5–10% higher in T2D patients [8].

Long-term studies using indirect calorimetry have reported −5 to −10% reductions in REE one year after introducing insulin in T2D patients [9,10], but by this time, the patients' body composition will have changed and their weight stabilized, so REE reductions have to happen earlier to contribute to weight gain and early REE reductions with a bedtime insulin regimen have so far not been demonstrated. Gougeon [11] reported only a −3% reduction after eight days with multiple insulin injections, which could not be associated with later weight gain as the patients were following a very-low-calorie diet the subsequent month. Studies of insulin action on energy expenditure over shorter time periods have been reported, but have failed to offer any information on the true effects of insulin as they used the glucose clamp technique with an associated glucose infusion, which has a thermic effect [12]. This raises the question: do bedtime long-acting insulin analogues influence REE in patients with T2D? And if so, how soon? Also, does their effect differ compared with non-weight-gaining alternatives such as GLP-1 analogues and dietary interventions? In addition, would early changes in REE predict the later course of weight changes in these patients?

To answer these questions, it was hypothesized that changes in REE, and perhaps also in respiratory quotient (RQ), might be detectable only a few days after the introduction of insulin in patients with T2D compared with patients taking treatments not favouring weight gain, and that they might also be related to the patient's later weight changes. For this reason, the respiratory exchanges in 67 patients with poorly controlled T2D who started a bedtime insulin analogue or a GLP-1 analogue, or a dietary intervention, were monitored. Also, any REE and RQ changes were compared and correlated with any changes in body weight three months later.

2. Patients and methods

Patients with T2D were recruited into our study on admission to our clinical ward based on the following criterion: uncontrolled diabetes ($HbA_{1c} > 7\%$) despite taking the maximum tolerated doses of oral therapy with metformin and sulphonylureas, which were continued throughout the study. The exclusion criterion was the presence of any intercurrent conditions, such as infections (including diabetic foot ulcer), inflammation or cancer, or thyroid diseases that might affect energy expenditure. All patients gave their written informed consent to participate in the study.

2.1. Treatments

These were selected according to a patient-centred approach [3] that was primarily based on the following findings:

- recent body-weight course with an increase favouring diet or GLP-1 instead of insulin;
- glucose profile with postprandial rises favouring GLP-1;
- long duration of diabetes, suggesting insulin deficiency and favouring insulin;
- acceptability of injections for either GLP-1 or insulin.

In all relevant cases, patients were instructed and informed on diet during a visit with a dietitian, self-monitoring of blood glucose, and/or how to inject insulin or GLP-1, or adjust insulin doses according to fasting glucose levels.

In the insulin group, patients ($n = 28$) received once-daily subcutaneous injections of basal insulin analogues at bedtime [either Lantus® insulin glargine (sanofi-aventis) or Levemir® insulin detemir (Novo Nordisk)]. Insulin doses started at 0.2 IU/kg body weight and over the following days were adjusted, using fasting capillary glucose determinations, to achieve plasma glucose < 120 mg/dL (6.6 mmol/L).

In the GLP-1 receptor agonist group, patients ($n = 23$) received subcutaneous injections of 0.6 mg once daily before breakfast (Victoza® liraglutide, Novo Nordisk) or 5 μg twice daily before breakfast and dinner (Byetta® exenatide, Eli Lilly). These starting dosages were maintained throughout the following days, and patients were asked to double the doses at home one month later if tolerability was acceptable.

In the dietary group, patients ($n = 16$) were put on a low-carbohydrate, very-low-calorie diet (20 g of carbohydrates, 800 kcal/day) for three days. Thereafter the diet was modified according to their measured REE, with 40–55% of calories coming from carbohydrates.

A follow-up clinical visit was proposed three months after hospitalization to all study patients to check their body weight and HbA_{1c} levels.

2.2. Respiratory exchange monitoring

All study patients were inpatients. REE was measured on the first morning after admission (day 0), then every morning before breakfast on day 1 and day 2 in the diet and GLP-1 groups. In the insulin group, respiratory exchanges were monitored every morning for the next few days until the goal value (capillary glucose < 120 mg/dL) was achieved twice, after which the patients were discharged. Respiratory exchanges were monitored using a Sensor Medics Vmax 29 N apparatus. VCO_2 and VO_2 were determined during a 30-min interval (from 0800 to 0830 h) after an overnight fast, and REE was calculated according to the Weir equation [13]. HbA_{1c} was measured by high-performance liquid chromatography (A. Menarini Diagnostics, Florence, Italy).

2.3. Statistical analysis

Results are expressed as means ± SD, and the group comparisons were by analysis of variance (ANOVA) with Bonferroni correction or chi-square tests. Regression analysis was performed to test whether the patients' initial REE and RQ values correlated with their later weight course. The analyses were