Is a failure to recognize an increase in food intake a key to understanding insulin-induced weight gain?

Miriam Ryan PhD\textsuperscript{1,2}, M. Barbara E Livingstone PhD\textsuperscript{2}, Pierre-Henri Ducluzeau MD PhD\textsuperscript{1}, Agnès Sallé MD PhD\textsuperscript{1}, Manon Genaitay BSc\textsuperscript{1}, Patrick Ritz MD, PhD\textsuperscript{1}\textsuperscript{*}

\textsuperscript{1}Department of Diabetes and Nutrition, CHU Angers F-49033, France
\textsuperscript{2}University of Ulster, Coleraine, N.Ireland

**Running title:** Insulin treatment and food intake

*Corresponding author:
Patrick Ritz MD, PhD
Pôle de maladies métaboliques et médecine interne, CHU
4 Rue Larrey
F-49033 ANGERS Cedex 09
France
patrick.ritz@wanadoo.fr

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ABSTRACT

The present study aimed to assess the contribution of energy intake (EI) to positive energy balance and weight gain with insulin therapy. Changes in EI (self-report, weighed food intake), dietary behaviour (auto-questionnaires), resting energy expenditure (REE, indirect calorimetry), physical activity (accelerometry) and glucosuria were monitored over the first 6 months of insulin therapy in 46 diabetic adults. No change in REE, activity or glucosuria could explain weight gain in the type-1 (4.1±0.6kg, p<0.0001) or type-2 (1.8±0.8kg, p=0.02) diabetic groups. An increase in EI provides the most likely explanation for weight gain with insulin. However it is not being recognized because of significant under-estimation of self-reported food intake, which appears associated with increased dietary restraint.
Weight gain can result from an increased energy intake (EI), or a decreased energy output or requirement, or for reasons that as yet remained unidentified. Meanwhile, gains during insulin therapy (1,2,3) are classically explained by decreases in resting energy expenditure (REE) and glucosuria (4,5). While the former may be applicable to patients with very poor metabolic control, in which REE is initially elevated (6), it appears less relevant to those with milder metabolic disturbances (7). This latter group represents most newly insulin-treated patients given current recommendations to lower GHb (8). Although glucosuria can contribute to weight change (4), it diminishes after a few days of insulin therapy, and therefore, is unlikely to invoke long-term gains. Only 2 studies in newly insulin-treated type-2 diabetic adults (9,10), have considered the role of EI. In one study(9), EI was restricted for weight maintenance. In the other (10), the authors found no change in ad libitum EI despite significant weight gain. However, reported EI at 12 months was extremely low (1.1xREE) suggesting food intake under-reporting (11). Under-reporting is widely acknowledged in non-diabetic people (12) but only alluded to in the type-2 diabetic population (13,14,15), despite being greater in the latter group (16). The issue has not been explored in the context of insulin-induced weight gain. We prospectively assessed contributors to positive energy balance (EB), with emphasis on EI, when starting insulin therapy.

**RESEARCH DESIGN AND METHODS**

Type-1 (n=23) and type-2 (n=23) diabetic adults beginning insulin therapy-participated in this study, approved by the local Ethical Committee. Patients' EB was assessed over 6 months.

**Hospital assessments.** Weight was measured when starting insulin (“baseline”), after 3 (“M3”) and 6 months (“M6”) to within 0.01kg. REE was measured by indirect calorimetry (7), fat and fat-free mass were assessed using a 3-compartment method (7), measurements of glucosuria were conducted—by glucose oxidase (Clinitek, Bayer Diagnostics, Germany) and of __GHb by HPLC (Varient HaemoglobinA1c, Bio-Rad, USA). At baseline, the quantities of food and beverages consumed were directly measured. The Dutch Eating Behavior (17) and Three-Factor Eating (18) Questionnaires assessed dietary behavior.

**Home assessments** were conducted 2 weeks prior to each hospital assessment (type-2 diabetic patients only pre-baseline). Physical activity (PA) was measured over 7 days by triaxial-accelerometry (RT3, Stayhealthy, USA) (19). Patients had ≥600 minutes of daily data and ≥4 days at each assessment. Food intake was self-reported using a 4-day (2 week, 2 weekend) food diary. All measured and self-reported data were analyzed for energy and macronutrient content using computerized software (Bilnut 4.0, Nutrisoft 95, France). The significance of 6-month changes was determined by repeated-measures ANOVA. Twenty patients per group was powerful enough (α=0.05, β= 90%) to detect a 10% difference in EI change between groups. Calculations were performed using Statview (Abacus concept, Berkeley, USA).

**RESULTS**

At baseline, compared to type-1 diabetic patients (16 M/7 F), type-2 diabetic patients (11 M/12F) were older (59.7±1.6 yr vs. 32.3±2.6yr, mean ± SEM, p<0.001), had a greater BMI (32.4±1.6 vs. 21.3±0.8kg.m⁻², p<0.001) and lower GHb (9.3±0.2 vs. 12.4±0.6%). Weight gain was 4.7±0.6kg (p<0.0001) in the type-1 and 1.8±0.8kg, (p=0.02) in the type-2 diabetic groups, while the respective reductions in GHb were -5.8±0.4% (p<0.0001) and -1.5±0.2% (p=0.003). Only the type-1 diabetic group reported weight loss (mean: 2.97kg) over the 6 months before starting insulin. REE, which was—higher in the type-2 diabetic patients...
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group at baseline (1726±63 vs. 1559±41kcal/d, p=0.03), remained unchanged by M6 (p=0.70), and increased by 8% (p=0.005) in the type-1 diabetic group. No change in weight/fat-free mass adjusted REE occurred in either group. No change in percentage time spent at low/moderate/high intensity activity was observed over 6 months. Hence, no component of energy expenditure could explain weight gain. Glucosuria diminished in the type-1 (12.6±2.2 to 2.1±1.2g/d, p=0.0003) but not in the type-2 (2.8±1.1g/d to 1.3±0.9g/d, p=0.25) diabetic group. Figure 1 shows that measured EI was significantly lower in the type-2 diabetic group (1634±67 vs. 2172±82kcal/d, p<0.0001). No significant change in self-reported EI was detected over 6 months in either the type-1 (-110 kcal/d, p=0.19) or type-2 (+18kcal/d, p=0.76) diabetic groups. Reported carbohydrate intake decreased in both groups, reciprocated by increased fat and decreased protein intake in the type-1 diabetic group. Six-month weight and EI changes were unrelated in both groups. An EI:REE ratio below a cut-off value of 1.395 identifies patients in whom EI is underreported (11). Calculated EI:REE was 0.95±0.04xREE at baseline and 0.97±0.05xREE at M6 in the type-2 diabetic group. Although 1.43±0.07xREE at baseline in the type-1 diabetic group, the ratio had significantly——(p=0.02) decreased to 1.23±0.05xREE by M6. Dietary restraint, which increased with therapy in both groups, was positively associated with EI:REE at baseline (p<0.01) and M6 (p<0.05). Weight gain, but not EI change, was significantly correlated with the number of hypoglycemic episodes in the type-1 diabetic group only (r²=0.83).

CONCLUSION

Present results show that no change in REE, physical activity or glucosuria could adequately explain insulin-induced weight gain; therefore increased EI is the only plausible mechanism. Accurate EI assessment was severely hampered by the under-reporting of food intake—with most EIs being insufficient to meet even basal energy requirements. Such under-reporting appears associated with increased dietary restraint, indicating that routine measures of restraint using self-report questionnaires could predict a patient’s potential to under-report. Although it is difficult to evaluate the effect of insulin per se, this comprehensive assessment of EB parameters shows that an increase in EI, associated with overeating in response to hypoglycaemia for example (3), provides the most likely explanation for positive EB during insulin therapy. The- under-reporting of food intake—requires more concerted effort to detect its presence and magnitude.
REFERENCES

FIGURE 1. Mean changes in energy intake in kcal/d (a), % protein intake/d (b), % carbohydrate intake/d (c) and % fat intake/d (d) in the type-1 diabetic patients (filled circles) and type-2 diabetic patients (filled squares) between baseline, month 3 (M3) and month 6 (M6). Values are expressed as means ± SEM.