

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

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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 ± 0.6 kg, $p < 0.0001$) or type-2 (1.8 ± 0.8 kg, $p = 0.02$) 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 underestimation 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 HaemoglobinA_{1c}, 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 ($\alpha=0.05$, $\beta=90\%$) 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 vs. 32.3 ± 2.6 yr, mean \pm SEM, $p < 0.001$), had a greater BMI (32.4 ± 1.6 vs. 21.3 ± 0.8 kg.m², $p < 0.001$) and lower GHb (9.3 ± 0.2 vs. $12.4 \pm 0.6\%$). Weight gain was 4.7 ± 0.6 kg ($p < 0.0001$) in the type-1 and 1.8 ± 0.8 kg, ($p = 0.02$) in the type-2 diabetic groups, while the respective reductions in GHb were $-5.8 \pm 0.4\%$ ($p < 0.0001$) and $-1.5 \pm 0.2\%$ ($p = 0.0003$). 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

group at baseline (1726 ± 63 vs. 1559 ± 41 kcal/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 ± 1.2 g/d, $p=0.0003$) but not in the type-2 (2.8 ± 1.1 g/d to 1.3 ± 0.9 g/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 ± 82 kcal/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 ($+18$ kcal/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 under-reported (11). Calculated EI: REE was $0.95 \pm 0.04 \times \text{REE}$ at baseline and $0.97 \pm 0.05 \times \text{REE}$ at M6 in the type-2 diabetic group. Although $1.43 \pm 0.07 \times \text{REE}$ at baseline in the type-1 diabetic group, the ratio had significantly—($p=0.02$) decreased to

$1.23 \pm 0.05 \times \text{REE}$ 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 ($r^2=0.83$).

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

- (1) Ryan M, Livingstone MBE, Ritz P: Insulin treatment and weight gain in type 2 diabetes: Is our knowledge complete? *Curr Nutr Food Sci* 2:51-58,2006
- (2) UK Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837-852,1998
- (3) The Diabetes Control and Complications Trial Research Group : Weight gain associated with intensive therapy in the Diabetes Control and Complications Trial. *Diabetes Care* 11:567-573,1988
- (4) Welle S, Nair KS, Lockwood D: Effect of a sulfonylurea and insulin on energy expenditure in type 2 diabetes mellitus. *J Clin Endocrinol Metab* 66:593-597,1988
- (5) Franssila-Kallunki A, Groop L: Factors associated with basal metabolic rate in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 35:962-966,1992
- (6) Gougeon R, Lamarche M, Yale JF, Venuta T: The prediction of resting energy expenditure in type 2 diabetes mellitus is improved by factoring for glycaemia. *Int J Obes* 26:1547-1552,2002
- (7) Ryan M, Sallé A, Guilloteau G, Genetay M, Livingstone MBE, Ritz P: Resting energy expenditure is not increased in mildly hyperglycaemic obese diabetic patients. *Br J Nutr* 96:945-948, 2006
- (8) Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B : Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care* 29:1963-1972,2006
- (9) Henry RR, Gumbiner B, Ditzler T, Wallace P, Lyon R, Glauber HS: Intensive conventional insulin therapy for type 2 diabetes: Metabolic effects during a 6-mo outpatient trial. *Diabetes Care* 16: 21-31, 1993
- (10) Makimattila S, Nikkila K, Yki-Jarvinen H: Causes of weight gain during insulin therapy with and without metformin in patients with type 2 diabetes mellitus. *Diabetologia* 42 : 406-412, 1999
- (11) Goldberg GR, Black AE, Jebb SA, Cole TJ, Murgatroyd PR, Coward WA, Prentice AM: Critical evaluation of energy intake data using fundamental principles of energy physiology. 1. Derivation of cut-off limits to identify under-recording. *Eur J Clin Nutr* 45: 569-581,1991
- (12) Livingstone MB, Black AE: Markers of the validity of reported energy intake. *J Nutr* 133: 895S-920S, 2003
- (13) Samuel-Hodge CD, Fernandez LM, Henriquez-Roldan CF, Johnston LF, Keyserling TC: A comparison of self-reported energy intake with total energy expenditure estimated by accelerometer and basal metabolic rate in African-American women with type 2 diabetes. *Diabetes Care* 27: 663-669, 2004
- (14) Adams SJ: The dietary intake of people with non insulin diabetes (NIDDM): How valid is self-reported intake? *J Hum Nutr Diet* 11: 296-306, 1998
- (15) Prentice AM, Black A, Goldberg G : Diabetes and energy intake. *Am J Clin Nutr* 57: 596-598, 1993
- (16) Sallé A, Ryan M, Ritz P: Under-reporting of food intake in obese diabetic and non-diabetic patients. *Diabetes Care* 29:2726-2727, 2006
- (17) Van Strien T, Frijters JER, Bergers GPA, Defares PB: The Dutch eating behavior questionnaire (DEBQ) for assessment of restrained, emotional, and external eating behavior. *Int J Eat Disord* 5: 295-315, 1986
- (18) Stunkard AJ, Messick S: The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. *J Psychosom Res* 29: 71-83, 1985

(19) Rowlands AV, Thomas PW, Eston RG, Topping R: Validation of the RT3 triaxial accelerometer for the assessment of physical activity. *Med Sci Sports Exerc* 36: 518-524,2004

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 \pm SEM.

