CLIN CARE/EDUCATION/NUTRITION/PSYCHOSOCIAL

Diabetes-Related Distress, Insulin Dose, and Age Contribute to Insulin-Associated Weight Gain in Patients With Type 2 Diabetes: Results of a Prospective Study

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OBJECTIVE

The determinants of insulin-associated weight gain in type 2 diabetes mellitus (T2DM) are partly unknown. Therefore, we conducted a prospective study to identify predictors of insulin-associated weight gain.

RESEARCH DESIGN AND METHODS

In patients with T2DM, we assessed physical activity by accelerometry and measured diabetes-related distress by questionnaires before and 6 and 12 months after starting insulin therapy. Glycemic control (HbA$_{1c}$) and insulin dose were monitored.

RESULTS

After 12 months of insulin therapy, mean body weight had increased by 3.0 ± 2.5 kg ($P < 0.001$). The drop in HbA$_{1c}$ was correlated with insulin-associated weight gain. With the use of a multiple linear regression model, a cluster of variables was identified that significantly related to weight gain. Diabetes-related distress, initial insulin dose, and the increase of insulin dose during the course of the study as well as age appeared to be important predictors of weight gain after initiation of insulin therapy. Physical activity (measured as MET) decreased from 1.40 ± 0.04 at baseline to 1.32 ± 0.04 MET ($P < 0.05$) but was not significantly related to weight changes.

CONCLUSIONS

Diabetes-related distress, initial and titration of insulin dose, and age all significantly predict insulin-associated weight gain. After the initiation of insulin therapy, physical activity decreased significantly, but this did not determine weight gain over the first 12 months. Our study findings may have clinical implications.

Insulin therapy is frequently needed to achieve adequate glycemic control in patients with type 2 diabetes mellitus (T2DM) but often at the expense of weight gain. This is obviously a disadvantage of insulin therapy in an already obese population. The reported weight gain during the first year of insulin therapy ranges from ~2 to 6 kg (1). This weight gain shows large interindividual differences, with some patients

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experiencing substantial insulin-associated weight gain, while others do not show any weight gain at all or even lose weight.

Identification of clinical variables related to insulin-associated weight gain in T2DM would be valuable to predict or potentially prevent this side effect. While a number of putative mechanisms are postulated to explain this weight gain (2,3), formal prospective studies including these different clinical variables are lacking.

Improvement in glycemic control (change in HbA_{1c}) by itself seems to be related to insulin-induced weight gain, but the contribution appears to be rather small and even nonsignificant in the long term (4). Even so, a decrease in HbA_{1c} is inevitably related to insulin therapy. Insulin dose should therefore be regarded as a potential contributor to weight gain rather than changes in HbA_{1c}.

Insulin-associated weight gain may be related to a decrease in physical activity, but this possibility has received limited attention. In a cross-sectional study, we showed that patients with pronounced weight gain ("gainers") during insulin therapy performed less daily physical activity overall compared with those who did not gain weight ("nongainers") (5).

Diabetes mellitus is associated with a significantly increased risk for depressive symptoms (6). Depressive complaints and anxiety are related with larger weight gain and an increase in cumulative incidence of obesity in men and women (7). As a result, it can be reasoned that depressive complaints and anxiety in patients with T2DM incur weight gain.

In the current study, we first prospectively investigated whether baseline (i.e., at the start of insulin therapy) glycemic control, physical activity, insulin dose, and diabetes-related distress and also changes of these variables during the course of the study (changes over time) correlated with insulin-associated weight gain in patients with T2DM. Second, we modeled the relationship between baseline variables and changes over time in order to predict the amount of weight gain 1 year after the start of insulin treatment.

RESEARCH DESIGN AND METHODS
Patients
In this prospective, multicenter, observational study, patients with T2DM who

were starting insulin therapy were included. Patients were recruited from one university hospital (Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands), three nonuniversity teaching hospitals (Jeroen Bosch Hospital, 's-Hertogenbosch; Slingeland Hospital, Doetinchem; and Bernhoven Hospital, Oss, the Netherlands), and four large primary care practices (de Teselaar, Bemmel; de Vier Kwartieren, Boxtel; Hoevense Veld, Uden; and Berghem, Berghem, the Netherlands). The diagnosis of T2DM was made according to the diagnostic criteria of the World Health Organization. The decision to start insulin treatment was at the discretion of the responsible physician and was always based on a failure of glycemic control while on oral glucose-lowering agents and diet. All patients were treated according to national guidelines (8). The choice of insulin preparation, insulin regimen, dose, and titration was left to the responsibility of the treating physician. Patients were excluded if they already used insulin or had steroid-induced diabetes, latent autoimmune diabetes in adults (which was excluded by testing anti-GAD antibodies), or maturity-onset diabetes of the young. Furthermore, clinical evidence of psychiatric, renal, cardiovascular, liver, or other diseases and medication (prednisone) that may influence study results regarding glucose and weight, hormonal disorders that may influence weight (i.e., thyroid diseases, unless properly treated with stable hormonal levels), bariatric treatment, excessive alcohol consumption (>20 g/day), drug abuse, use of thiazolidine derivatives, and pregnancy or intention to become pregnant during the study were all considered exclusion criteria.

Patients were followed for 12 months after the initiation of insulin therapy. Patient characteristics (age, sex, race, smoking habits) were noted, and clinical data were retrieved at baseline (i.e., prior to start insulin) and at 3-month intervals, which included body weight, blood pressure, HbA_{1c}, diabetes duration, comorbidities, number of hypoglycemic events, lipids, type of oral glucose-lowering medication, and insulin type and dose.

Before and at 6 and 12 months after the initiation of insulin therapy, physical

activity levels, diabetes-related distress and depressive complaints both measured by questionnaires, and caloric intake were assessed.

The inclusion and exclusion criteria were reviewed at a screening visit, where patients underwent a history taking and a complete physical examination. The study protocol was approved by the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, the Netherlands). All patients provided written informed consent.

Measures
Patients were studied in fasted-overnight conditions. Weight was measured with subjects wearing light underwear only. Scales were calibrated annually. Waist circumference was measured midway between the lower rib margin and the iliac crest at expiration and hip circumference over the greater trochanter; waist-to-hip ratio was calculated. Skin fold measurements at five specific sites (abdomen, next to the belly site; supra-iliac, just above the iliac crest of the hip bone; quadriceps, middle of the upper thigh; triceps, the back of the upper arm; and subscapula, beneath the edge of the shoulder blade) on the right site of the body were taken by using the Slim Guide Skinfold Caliper (Creative Health Products, Ann Arbor, MI). The scale of 0 to 85 mm is especially useful in assessing skin folds at the upper ranges, which are not accommodated by most other calipers. Accuracy may be interpolated to 0.5 mm. Measurements were taken twice and averaged. Body composition was assessed by using formulas described by Jackson et al. (9,10).

Blood pressure was measured twice by a manual sphygmomanometer in supine position after a minimum of 5-min rest at the right arm. The average blood pressure (mean systolic and diastolic blood pressure) was calculated. Furthermore, fasting blood samples were drawn to assess glucose, HbA_{1c}, thyroid hormone, and lipids.

Physical activity was objectively measured using a SenseWear Pro Armband (Body Media, Pittsburgh, PA) (11). The device was placed on the right upper arm over the triceps muscle for 4 consecutive days at baseline and at 6- and 12-month follow-ups. Measurements between 7:00 A.M. and 11:00 P.M.

were used for calculations if >90% of these data were available. Outcome variables from the activity monitor included average MET (1 MET = consuming 1 kcal/kg of body weight per hour), time (minutes/day) spent at different activity intensity categories averaged per day over the measurement period, and the number of steps per day. SenseWear InnerView Professional software 6.1 was used to analyze the data.

Dietary intake was measured by food records. Participants returned a hand-written food record (modified from Thompson and Subar [12]) in which self-reported detailed description of the types and amounts of food, beverage, and/or supplements was documented over a 3-day period. Some of the patients provided weighed diet records (i.e., participants weighed used food and beverages). Food records were obtained prior to the start of insulin therapy and at 6- and 12-month follow-ups. Food records were checked by a dietitian, and the intake of nutrients was calculated with a computer program (2008 Vodisys Medical Software b.v., the Netherlands). This computer program used a national database on the composition of foods (13).

Diabetes-related distress and depression was measured with the Problem Areas in Diabetes (PAID) scale questionnaire (14,15). PAID scores were calculated using a five-point Likert-scale with options ranging from 0, not a problem, to 4, serious problem. Summing all item scores and multiplying by 1.25 resulted in an overall PAID score. A minimum score of 0 indicated no diabetes-related distress. A maximum score of 100 indicated significant diabetes-related distress. The questionnaire was taken at baseline and at 6- and 12-month follow-ups.

Data Analysis

The sample size was based on data from a pilot study where physical activity was measured in nine patients with T2DM. This group showed a physical activity level of 1.31 MET and an SD of 0.30 MET. This study was powered to detect a difference in physical activity of 15% after 12 months of insulin therapy, with a power of 90% at a significance level of 0.05%. This translated to the inclusion of 65 subjects. It was estimated that 10–15% of the included

patients would drop out, resulting in the need for 72–75 patients to be included.

The results of the study are displayed as mean ± SD, unless otherwise indicated.

To study changes in clinical variables (insulin dose, body weight, HbA$_{1c}$, physical activity, caloric intake, and PAID score) during the course of the study, a general linear model for repeated measures was used.

To determine whether selected baseline variables were related to the change in body weight after the start of insulin treatment, a univariate approach by simple correlations was performed using the Pearson correlation coefficient for normally distributed variables and the Spearman correlation coefficient for non-Gaussian distributed data.

Relationships between changes in clinical variables during the course of the study (changes over time) were investigated by a linear mixed model for repeated measures (16).

Finally, a multiple linear regression model was designed in order to estimate the relationship between the dependent variable (insulin-associated weight gain) and different independent variables or predictors. Both baseline parameters (from the correlation analyzes) and the change in parameters over time (from the linear mixed model for repeated measures) were included in the model.

For both the multiple linear regression model and the linear mixed model, estimated regression parameters are presented, with the appropriate SE and 95% CI. Details of both models are presented in the Supplementary Data.

All calculations were made using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL). A P value <0.05 was considered significant in all statistical comparisons.

RESULTS

A total of 79 patients were eligible to enter the study. Seventy-seven patients consented and underwent screening. Of these, 74 patients with T2DM enrolled in the study. We excluded nine patients (eight patients with missing follow-up data or withdrawal and one patient diagnosed with maturity-onset diabetes of the young). Finally, 65 subjects were included in the analysis. Table 1 displays the descriptive characteristics of the patients at baseline.

Patients started with a mean of 18 ± 2 units (0.21 ± 0.02 units/kg) of insulin per day. At 6 and 12 months, patients used a mean of 39 ± 3 units (0.42 ± 0.03 units/kg) and 46 ± 4 units (0.49 ± 0.04 units/kg) of insulin per day, respectively (P < 0.05 compared with baseline). In addition, at 6 months, a shift in the use of different types of insulin was observed: 9% of the patients who used long-acting insulin were switched to biphasic or prandial insulin. At 12 months, 46% of the patients used long-acting insulin, 14% used biphasic insulin, and 40% used basal/bolus insulin. Within the study period, no severe hypoglycemic episodes requiring a third party occurred.

Mean body weight increased from 89.4 ± 2.4 to 92.4 ± 2.5 kg at 12 months of insulin therapy (P < 0.001) (see Fig. 1A), and waist circumference increased from 106 ± 2 to 109 ± 2 cm at 12 months (P < 0.01). Seventy-one percent of the patients showed body weight gain, whereas 29% had stable body weight or even lost weight after 12 months of insulin treatment (Fig. 1B). Calculated lean body mass decreased from 70 ± 2 to 69 ± 2 kg at 12 months (P = NS), while calculated body fat increased from 21 ± 1 to 24 ± 1% at 12 months (P < 0.001).

Mean HbA$_{1c}$ decreased from 8.8 ± 0.2 (73) to 7.3 ± 0.1% (56 mmol/mol) after 12 months (P < 0.001).

After 12 months of insulin therapy, quantitatively measured physical activity was significantly reduced (Fig. 2A–E). Average MET decreased from 1.39 ± 0.04 to 1.32 ± 0.04 at the 12-month follow-up (P < 0.05), and time spent in sedentary physical activity level numerically increased, but this difference was not statistically significant. The amount of moderate physical activity (MET 3–6) at 12 months was significantly lower compared with 6 months of insulin therapy (P < 0.05). The average number of steps per day diminished significantly after the start of insulin therapy (from 6,441 ± 426 steps/day at baseline to 5,746 ± 343 steps/day after 12 months of treatment; P < 0.05).

Patients suffered from minor depressive complaints at baseline, and this did not change significantly over time (PAID scores: 10.0 ± 1.4 vs. 9.7 ± 1.3 vs. 9.4 ± 1.4 at baseline and after 6 months and 12 months, respectively; P = NS).

Table 1—Descriptive characteristics of the study patients at baseline

	Baseline
N	65
Age (years)	60 ± 1.3
Sex (% female)	46
Race (% Caucasian)	95
Duration diabetes (years)	9 ± 1
Weight loss prior start insulin therapy (kg)†	2.0 ± 0.5
BMI (kg/m^2)	30.8 ± 0.7
Systolic blood pressure (mmHg)	144 ± 2.5
Diastolic blood pressure (mmHg)	79 ± 1.3
Fasting glucose (mmol/L)	11.7 ± 0.5
HbA$_{1c}$ (%)	8.9 ± 0.2
Estimated average glucose (mg/dL)	209 ± 5.6
Total cholesterol (mmol/L)	4.5 ± 0.2
Triglycerides (mmol/L)	3.4 ± 0.8
HDL (mmol/L)	1.0 ± 0.04
LDL (mmol/L)	2.3 ± 0.1
Alcohol use (%)	28
Smoking (%)	20
Type of insulin (%)#	
Long-acting only	58
Biphasic	17
Short-acting only	0
Long-acting/short-acting (basal/bolus)	25
Concomitant use of oral glucose-lowering agents (%)	
Metformin	22
Sulfonylurea derivatives	9
Metformin + sulfonylurea derivatives	69
Diabetes-related complications (%)	
Nephropathy	15
Polyneuropathy	10
Retinopathy	10

Data are mean ± SE or percent. Baseline, prior to the start of insulin therapy. †Experienced weight loss within 12 months prior to the start of insulin therapy. #Type of initiated insulin after baseline measurement and type of insulin used at 6 and 12 months.

After insulin initiation, reported caloric intake decreased (from baseline 1,599 ± 72 to 1,392 ± 41 kcal/day at 12 months; $P < 0.05$), which cannot explain the insulin-induced weight gain.

Correlations of Baseline Variables and Insulin-Associated Weight Gain
Simple correlation coefficients were calculated between baseline variables and insulin-associated weight gain after 12 months of insulin therapy. These results are shown in Table 2. The baseline variables HbA$_{1c}$, insulin dose, and PAID score were positively correlated with weight gain. The baseline variables age and body fat were negatively correlated with weight gain.

Changes in Clinical Variables Over Time Related to Insulin-Associated Weight Gain
Using a linear mixed model for repeated measures, we assessed the relationship between changes in clinical variables over a 12-month period of insulin treatment and weight gain. Details from the outcome of the linear mixed model are described in Supplementary Tables 1–3. Both the change in HbA$_{1c}$ and insulin dose over time were significantly related with insulin-associated weight gain. A decrease in HbA$_{1c}$ and an increase in insulin dose contributed to weight gain. Changes in physical activity and diabetes-related distress over time were not related to weight gain.

Multiple Linear Regression Modeling
With a multiple linear regression model, we retrieved a cluster of clinical parameters consisting of baseline variables as well as variables that change over time that are related to weight gain. The change in HbA$_{1c}$ was omitted from the prediction model (see CONCLUSIO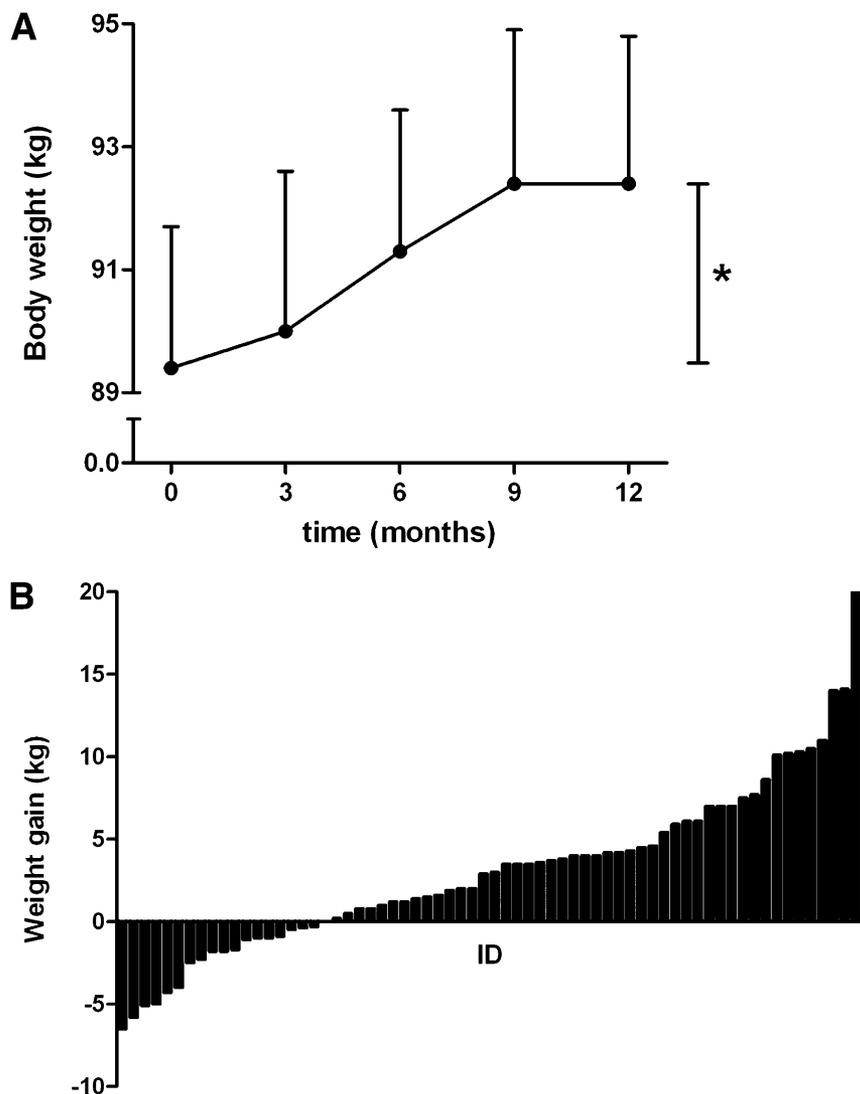NS). Table 3 shows that baseline diabetes-related distress as measured by PAID questionnaire/score, initial insulin dose, age, and change in insulin dose over time were the main contributors to the prediction model with respect to weight gain after the initiation of insulin therapy. In this model, a significant interaction between age and PAID score was observed. Hence this indicates that the aforementioned variables are significantly related to insulin-associated weight gain but should be corrected for the interaction between age and diabetes-related distress.

CONCLUSIONS
From our prospective study that was performed in a fairly large number of patients, we were able to predict insulin-associated body weight gain with the use of a cluster of clinical variables. Diabetes-related distress (PAID score), insulin dose at the beginning of insulin therapy, and age, together with the change in insulin dose during the study period (i.e., 12 months), are the main independent variables contributing to this prediction model. Physical exercise decreased after the initiation of insulin treatment but was not related to insulin-induced weight gain.

In this real practice-based study, most patients (58%) started with a basal insulin regimen. The uptitration of insulin and the corresponding decrease in HbA$_{1c}$ was well in line with the LANMET trial and other previous reports (1,17). The mean insulin-associated weight gain in our study patients was ~3 kg after 12 months of insulin therapy and is in line with previous reports (4,18).

Our study is the first to explore the relationship between the change in insulin-associated body weight and diabetes-related distress (PAID score). We showed that diabetes-related distress significantly contributed to the model that predicts the amount of weight gain after the initiation of insulin therapy. An increase in diabetes-related distress reflected by a higher PAID score before the start of insulin therapy is related to a more pronounced weight gain. The PAID scale is a reliable and validated questionnaire, which is able to assess emotional distress and significant motivational problems in patients related to their diabetes management (14,19). Although a relationship between emotional factors and BMI has

A

B

Figure 1—*A*: Change in body weight after the start of insulin therapy. *$P < 0.001$. *B*: Interindividual differences in absolute body weight gain (kg) after 12 months of insulin treatment. ID denotes study subject.

et al. (24) found in a large cohort of patients with T2DM starting on any type of insulin that starting insulin dose was associated with a greater weight gain, which is in agreement with our data. Their study did not investigate whether the dose escalation was also associated with weight gain. The reason why the initial insulin dose independently contributes to body weight gain after 12 months is unclear. The starting amount of insulin was established by the treating physician and may be partly based on the level of hyperglycemia and/or on the estimated insulin resistance. A separate analysis showed that HbA_{1c} and body weight at baseline were similar between patients starting with a low insulin dose compared with a high insulin dose, indicating that initial insulin dose was not determined by initial body weight or HbA_{1c}. Furthermore, it was shown that HbA_{1c} at the end of the study in patients who started with a relatively low insulin dose or high dose was well matched. This may suggest that a gradual decrease of HbA_{1c} compared with a steeper decrease has a favorable effect on ultimate weight gain. A possible explanation for this observation may be that patients suffering from a steep decrease of HbA_{1c} will experience more hypoglycemic episodes (which indeed was observed), leading to an increase in caloric intake. The change in reported caloric intake between these two groups, however, did not differ.

Age was shown to have a significant effect on insulin-associated weight gain. Older patients starting insulin therapy were prone to gaining more body weight. This could be related to a decrease in daily physical activity and fitness (25,26). Indeed, a subanalysis of changes in physical activity revealed that reduction in physical activity (MET and number of steps) was more pronounced in older patients.

As stated, physical activity did not seem to be related to insulin-associated weight gain in our study, i.e., it could not be identified as an independent predictor of insulin-associated weight gain. Age and physical activity are covariates. From the analysis, it was shown that only age was an independent variable. Nevertheless, it can still be viewed as an unfavorable finding from the perspective of general health. The decrease in energy expenditure after insulin

been described (20), no link has been identified between emotional distress per se and subsequent changes in weight after the initiation of insulin therapy. This study was not powered to investigate the influence of specific components of the PAID survey having an impact on body weight gain. It should be pointed out that patients with evident depressive disorders or on psychiatric medication, both known to have a significant impact on body weight, were excluded from the study. However, it can be hypothesized that diabetes-related distress contributes to an unhealthy diet or to physical inactivity (21). From the multiple linear regression analyzes, it was shown that diabetes-related distress (PAID scale) and age interact with each other. This means that
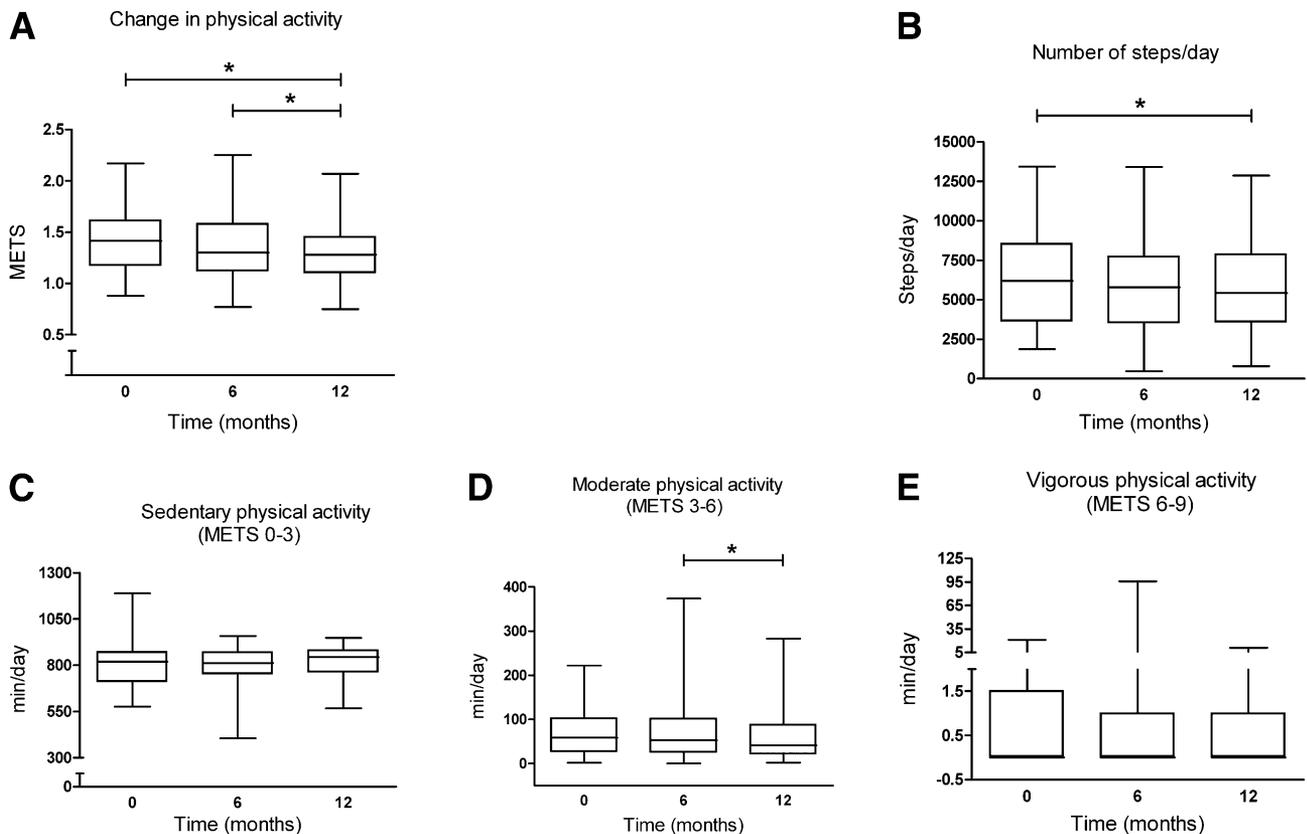
age negatively affected the strength of the relationship between PAID score and weight gain; in other words, the predictive value of diabetes distress with respect to insulin-associated weight gain will be less with increasing age.

Intriguingly, we found that a higher initial insulin dose at the start of the study significantly contributed to a more pronounced weight gain after 12 months of insulin therapy. Also, an increase in the insulin dose during the course of the study significantly contributed to the increase of body weight. Both an increase in total body lipid stores due to an increase in lipid synthesis and an inhibition of fatty acid release (lipolysis) (22) as well as fluid retention (23) may play a role in insulin-associated weight gain. In a recent article, Balkau

A

Change in physical activity

B

Number of steps/day

C

Sedentary physical activity
(METS 0-3)

D

Moderate physical activity
(METS 3-6)

E

Vigorous physical activity
(METS 6-9)

Figure 2—Physical activity. *A*: Change in physical activity levels after the start of insulin therapy (1 MET = consuming 1 kcal/kg of body weight per hour). *B*: Change in average number of steps per day after commencing insulin therapy. *C*: Change in sedentary physical activity (MET 0–3) after the start of insulin therapy. *D*: Change in moderate physical activity (MET 3–6) after the start of insulin treatment. *E*: Change in vigorous physical activity (MET 6–9) after the start of insulin therapy. The vertical box plots displayed represent summary statistics for the analyzed variables stated (*A–E*). The plot elements and the statistics represented are as follows: the length of the box represents the interquartile range (the distance between the 25th and the 75th percentiles), the horizontal line in the box interior represents the median, and the vertical lines issuing from the box extend to the minimum and maximum values of the analyzes variables. *$P < 0.05$.

initiation may be explained by a number of mechanisms. Patients who start insulin may experience (or at least fear) hypoglycemic episodes and, as a consequence, perform less physical activity in order to prevent hypoglycemia. In our patient cohort, the number of hypoglycemic episodes was low, and no severe hypoglycemia occurred. However, fear of hypoglycemia remains a potential explanation. Alternatively, a low physical exercise level may be a consequence of rather than a cause of body weight gain.

An increase in caloric intake is frequently mentioned as a determinant of weight gain. Especially after initiating insulin therapy, it can be reasoned that caloric intake may increase in relation to (the avoidance of) hypoglycemic events resulting in weight gain (27). In this current study, however, reported food intake did not increase, and even diminished significantly over time, arguing against increased food consumption

being an important determinant of body weight gain. It should be noted that reported calorie intake was lower than expected based on body weight and level of physical activity. Probably, substantial underreporting in food intake has occurred, as is often encountered with

food records and is quite typical in obese people. Several factors such as the intervals between the time points of taking the questionnaire, recall bias, true changes, and intrinsic feelings could have had an impact on reported caloric intake outcomes.

Table 2—Pearson correlation coefficients between baseline predictors and insulin-associated weight gain after 12 months of insulin therapy

Variable	r	P value
Age (years)	−0.27	0.03
Body fat (%)	−0.28	0.04
HbA$_{1c}$ (%/mmol/mol)	0.42	0.001
Insulin dose (units/day)*	0.43	<0.001
PAID score**	0.31	0.03

*Analysis performed with Spearman rank correlation. **Diabetes-related distress was measured by PAID scale. The other (nonsignificant) variables tested in simple correlation coefficients were sex (male/female), diabetes duration (years), presence of diabetes-related complications (neuropathy, nephropathy [microalbuminuria], retinopathy), body weight (kg), waist-to-hip ratio, skin fold measurement umbilicus (mm), body fat (%), use of metformin (yes/no), insulin dose (units/day), number of hypoglycemic episodes, physical activity (MET), thyroid hormone level (mU/L), PAID score, and center (patients treated in hospital versus treated by general practitioner).

Table 3—Multiple linear regression analysis to assess independent baseline factors of insulin-associated weight gain after 12 months of insulin therapy by including interaction terms and change in insulin dose over time

Variable	Unstandardized coefficients	SE	95% CI	*P* value
Constant	−8.635	5.023	−18.745 to 1.475	0.092
PAID score*	0.964	0.384	0.192 to 1.736	0.016
Initial (baseline) insulin dose (units/day)	0.165	0.060	0.044 to 0.285	0.008
∆ insulin dose**	0.048	0.019	0.009 to 0.087	0.017
Age (years)	0.106	0.082	−0.059 to 0.271	0.202
(Age × PAID score)	−0.015	0.006	−0.028 to −0.002	0.025

Linear regression analysis with weight gain after 12 months as dependent variable. Variables were selected using a manual backward selection method. The baseline variables considered for the model were age (years), body fat (%), HbA_{1c} (% or mmol/mol), insulin dose (units/day), PAID score, ∆ insulin dose (change in insulin dose at 12 months compared with baseline), and the interaction terms: (HbA_{1c} × PAID), (HbA_{1c} × body fat), (HbA_{1c} × initial insulin dose), (HbA_{1c} × age), (HbA_{1c} × ∆ insulin dose), (PAID × body fat), (PAID × initial insulin dose), (PAID × age), (PAID × ∆ insulin dose), (initial insulin dose × body fat), (age × body fat), (∆ insulin dose × body fat), (age × initial insulin dose), (initial insulin dose × ∆ insulin dose), and (∆ insulin dose × age). Only the variables that had a *P* value <0.05 remained in the final model (R^2 = 0.43, adjusted R^2 = 0.36). 95% CI, for unstandardized coefficients. In the formula, body weight gain = −8.635 + 0.106 × (age) + 0.964 × (PAID score) + −0.015 × (age × PAID score) + 0.165 × (initial insulin dose) + 0.048 × (∆ insulin dose). *Diabetes-related distress was measured by PAID scale. **∆ insulin dose is the change in insulin dose at 12 months compared with baseline.

We and several others reported that changes in HbA_{1c} are related to insulin-associated weight gain, although we found that this contribution was rather small (4). In the current study, we prospectively confirmed that an improvement in glycemic control is significantly related to insulin-associated weight gain. Nevertheless, the primary intention of insulin therapy is to improve glycemic control and decrease HbA_{1c}. As such, the change in HbA_{1c} is the consequence of insulin therapy. Therefore, although the change in $HbA1_c$ was related to weight gain in the linear regression model, we did not include this variable in the multiple linear regression model because it does not represent a true independent variable.

Importantly, ~30% of the patients did not gain or even lost weight after the initiation of insulin therapy. From the results of the multiple linear regression model, it can be concluded that a young patient with a low PAID score, starting on a low insulin dose, and in need of a more lenient uptitration of insulin to achieve adequate glycemic control will probably suffer from less body weight gain after 12 months of insulin treatment.

Our study has limitations. First, this study cannot assess whether the decrease in physical activity is a consequence or a cause of body weight gain. Second, between-center differences and treatment effects could have influenced outcomes but could not be tested because of the small numbers of participating centers and because the study involves a relatively small sample size.

Third, there was a discrepancy between reported caloric intake and body weight, which is probably explained by underreporting of food intake, a limitation of the use of food records. When filling in food records, subjects become more aware of their consumption and tend to report more socially preferred information. Given the increase in body weight together with a decrease in physical activity observed in our study, the underreporting seems to be more pronounced with the second measurement. Hence, the results of caloric intake should be interpreted with caution and do not allow us to conclude that caloric intake truly decreased. Finally, while our study provides predictors of insulin-associated weight gain, it cannot determine whether intervening on these factors, for example, a lower starting dose and a more lenient insulin uptitration, or interventions aimed at mood improvement will affect weight gain.

Our study results may have implications for clinical practice. The decrease in physical activity, although not related to insulin-associated weight gain in this study, is an unfavorable consequence of insulin therapy. Health education should be aimed at improving physical fitness in patients starting with insulin therapy, as this may be beneficial to reduce cardiovascular risk. The clinical importance of identifying emotional factors that might impact body weight gain in patients with T2DM adds value to understanding this novel relationship. Furthermore, it can be suggested that low initial insulin dose and a more gradual

titration of insulin over time may limit or even prevent body weight gain.

In conclusion, the initiation of insulin therapy in patients with T2DM is associated with weight gain and a decrease in physical activity. Although the reduction in physical activity was not associated with weight gain, it is an important issue for patients starting insulin therapy. A cluster of clinical variables predicts insulin-associated weight gain. This includes diabetes-related distress (PAID score), initial insulin dose, change in insulin dose, and age.

Further prospective studies are needed to investigate the exact role of emotional factors, types of insulin regimens, and strategies of insulin titration on weight gain.

References

1. Holman RR, Thorne KI, Farmer AJ, et al.; 4-T Study Group. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med 2007;357:1716–1730

2. Heller S. Weight gain during insulin therapy in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2004;65(Suppl. 1):S23–S27

3. Sallé A, Ryan M, Guilloteau G, Bouhanick B, Berrut G, Ritz P. 'Glucose control-related' and 'non-glucose control-related' effects of insulin on weight gain in newly insulin-treated type 2 diabetic patients. Br J Nutr 2005;94:931–937

4. Jansen HJ, Hendriks JC, de Galan BE, Penders G, Tack CJ, Vervoort G. Contribution of change in glycosylated haemoglobin to insulin-associated weight gain: results of a longitudinal study in type 2 diabetic patients. Endocrine 2011;39:190–197

5. Jansen HJ, Vervoort G, van der Graaf M, Tack CJ. Pronounced weight gain in insulin-treated patients with type 2 diabetes mellitus is associated with an unfavourable cardiometabolic risk profile. Neth J Med 2010;68:359–366

6. Rotella F, Mannucci E. Diabetes mellitus as a risk factor for depression. A meta-analysis of longitudinal studies. Diabetes Res Clin Pract 2013;99:98–104

7. Brumpton B, Langhammer A, Romundstad P, Chen Y, Mai XM. The associations of anxiety and depression symptoms with weight change and incident obesity: The HUNT Study. Int J Obes (Lond) 2013;37:1268–1274

8. Bouma M, Rutten GE, Wiersma T. [The practice guideline 'Diabetes mellitus type 2' (second revision) from the Dutch College of General Practitioners; a response from the perspective of general practice]. Ned Tijdschr Geneeskd 2006;150:2339–2340

9. Jackson AS, Pollock ML. Generalized equations for predicting body density of men. Br J Nutr 1978;40:497–504

10. Jackson AS, Pollock ML, Ward A. Generalized equations for predicting body density of women. Med Sci Sports Exerc 1980;12:175–181

11. Fruin ML, Rankin JW. Validity of a multisensor armband in estimating rest and exercise energy expenditure. Med Sci Sports Exerc 2004;36:1063–1069

12. Thompson FE, Subar AF. Dietary assessment methodology. In *Nutrition in the Prevention and Treatment of Disease*. 2nd ed. Coulston AM, Boushey CJ, Eds. San Diego, Academic Press, 2008, p. 3–39

13. Westenbrink S, Jansen-van der Vliet M. In NEVO Kwaliteitshandboek 2012 *[internal document]*. Bilthoven, RIVM, 2012, p. 1–24

14. Welch G, Weinger K, Anderson B, Polonsky WH. Responsiveness of the Problem Areas In Diabetes (PAID) questionnaire. Diabet Med 2003;20:69–72

15. Hosoya T, Matsushima M, Nukariya K, Utsunomiya K. The relationship between the severity of depressive symptoms and diabetes-related emotional distress in patients with type 2 diabetes. Intern Med 2012;51:263–269

16. Verbeke G. *Linear Mixed Models in Practice: A SAS-Oriented Approach*. New York, Springer-Verlag, 1997

17. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia 2006;49:442–451

18. Turner RC, Cull CA, Frighi V, Holman RR; UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA 1999;281:2005–2012

19. Snoek FJ, Pouwer F, Welch GW, Polonsky WH. Diabetes-related emotional distress in Dutch and U.S. diabetic patients: cross-cultural validity of the problem areas in diabetes scale. Diabetes Care 2000;23:1305–1309

20. Miller ST, Elasy TA. Psychometric evaluation of the Problem Areas in Diabetes (PAID) survey in Southern, rural African American women with type 2 diabetes. BMC Public Health 2008;8:70

21. Forman-Hoffman VL, Yankey JW, Hillis SL, Wallace RB, Wolinsky FD. Weight and depressive symptoms in older adults: direction of influence? J Gerontol B Psychol Sci Soc Sci 2007;62:S43–S51

22. DeFronzo RA. Insulin and renal sodium handling: clinical implications. Int J Obes 1981;5 (Suppl. 1):93–104

23. Wolfe RR. Effects of insulin on muscle tissue. Curr Opin Clin Nutr Metab Care 2000;3:67–71

24. Balkau B, Home PD, Vincent M, Marre M, Freemantle N. Factors associated with weight gain in people with type 2 diabetes starting on insulin. Diabetes Care 2014;37:2108–2113

25. Ekelund U, Brage S, Franks PW, et al. Physical activity energy expenditure predicts changes in body composition in middle-aged healthy whites: effect modification by age. Am J Clin Nutr 2005;81:964–969

26. St-Arnaud-McKenzie D, Payette H, Gray-Donald K. Low physical function predicts either 2-year weight loss or weight gain in healthy community-dwelling older adults. the NuAge Longitudinal Study. J Gerontol A Biol Sci Med Sci 2010;65:1362–1368

27. Ryan M, Livingstone MB, Ducluzeau PH, Sallé A, Genaitay M, Ritz P. Is a failure to recognize an increase in food intake a key to understanding insulin-induced weight gain? Diabetes Care 2008;31:448–450