

Contribution of change in glycosylated haemoglobin to insulin-associated weight gain: results of a longitudinal study in type 2 diabetic patients

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Abstract To investigate the contribution of glycosylated haemoglobin change (HbA1c) on body weight in patients with type 2 diabetes after start of insulin therapy. We analysed 122 individual weight-profiles in relation to the change in HbA1c per se in these patients up to 36 months after the start of insulin therapy. Data were analysed separately for the first 9 months after commencement of insulin therapy and for the period thereafter. Within the first 9 months of insulin therapy mean body weight increased by 0.52 kg per month. HbA1c decreased from 9.9 ± 1.8 to $7.9 \pm 1.3\%$. Only 12% of the initial weight gain could be attributed to the change in HbA1c. Furthermore, the mean monthly increase in body weight gain was reduced by 0.006 kg for every 1 kg higher body weight at baseline. From 9 to 36 months after start of insulin therapy, body weight increased by 0.1 kg/month, which was independent of change in HbA1c. Improvement of glycaemic control per se contributes little to initial weight gain after start of insulin therapy in patients with T2DM. After 9 months of insulin treatment, weight gain is unrelated to change in glycosylated haemoglobin. Other factors have to be responsible for weight gain after start of insulin therapy.

Keywords Weight gain · Insulin therapy · Type 2 diabetes mellitus

Introduction

Insulin therapy is frequently needed to achieve adequate glycaemic control in patients with type 2 diabetes mellitus (T2DM), but often at the expense of significant weight gain [1–3]. This weight gain is obviously undesirable in an already overweight population and may negatively affect blood pressure, lipid levels, inflammatory and fibrinolytic parameters, and may also deter further optimization of insulin therapy [4–7]. Four putative mechanisms have been proposed for this weight gain: (1) Improvement of glycaemic control (HbA1c), (2) Anabolic effect of insulin increasing fat storage, (3) A decrease in metabolic rate and a fall in energy expenditure and (4) Defensive eating habits because of (fear of) hypoglycemia [8, 9].

Most authors view the improvement in glycaemic control per se (expressed as change in HbA1c) as the major determinant of weight gain. This conclusion is based on studies that usually relate the difference in body weight between two time-points to the difference in HbA1c in patients who initiated insulin therapy [8, 10]. Mäkimattila et al. [2] showed that after 12 months of insulin therapy a decrease in HbA1c by 2.5% is associated with a 5 kg weight gain (i.e. 2 kg/1% decrease in HbA1c). However, these studies do not show to what extent change in body weight may depend on change in HbA1c. The relationship between change in glycaemic control (i.e. change in HbA1c) and weight gain may vary over time. First, the change in HbA1c may primarily contribute to weight gain in the first months after the start of insulin therapy rather than later-on, when factors unrelated to glycaemic control

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become more important such as change in energy intake or physical activity, anabolic effects of insulin, and defensive eating behaviour probably [2, 8]. Second, patient's and physician's responses to changes in glycaemic control and body weight may affect the subsequent course of these variables.

Analysing data of HbA1c and body weight just at two time-points may negate these variations and lead to incomplete or even wrong conclusions. A more accurate evaluation of a relationship between change in HbA1c and weight after initiation of insulin therapy requires a longitudinal assessment with repeated measures of body weight and HbA1c in the same individuals. Therefore, we used a linear mixed model for repeated measures data to investigate the relationship between the changes in HbA1c and body weight at different time-points after commencing insulin therapy in patients with T2DM.

Methods

Subjects

Patients with T2DM, who all started biphasic insulin therapy in our academic center between March 2000 and November 2004, were included in this study. Patients who started biphasic insulin therapy were selected because most patients starting insulin therapy in this timeframe were assigned to this insulin regimen by their physician. Furthermore, to prevent confounding with respect to influences of different types of insulin on body weight we only included patients with biphasic insulin. All patients were seen at the diabetes clinic of the Radboud University Nijmegen Medical Center. The diagnosis of T2DM was made according to the diagnostic criteria of the WHO. The decision to start insulin treatment was at the discretion of the responsible physician and was always based on failure of glycaemic control on oral glucose-lowering agents and/or diet. Patients were excluded if they did not use biphasic insulin or had steroid-induced diabetes, latent auto-immune diabetes in adults (LADA) or maturity onset diabetes of the young (MODY). Patients were followed for a maximal of 36 months after start of insulin therapy. We conducted an observational study in which data of all patients starting biphasic insulin within the timeframe 2000–2004 were included.

Clinical data were retrieved from medical records at baseline and at 3-month intervals, which included body weight, HbA1c, age, gender, diabetes duration, blood pressure, lipids, doses of oral glucose-lowering medication, and insulin dose. We assumed that most of the weight gain that could be directly attributed to improvement in glycaemic control would appear within the first 9 months after start of insulin therapy. This was based on studies viewing

that most of the weight gain and change in HbA1c appears within the first 9–12 months after start of insulin therapy [8, 11]. After this period, weight gain tends to level off. Therefore, we studied the short-term weight-profiles (i.e. the first 9 months after start of insulin therapy) and the long-term weight-profiles (i.e. from 9 to 36 months after start of insulin therapy) separately. To analyse the short-term weight-profiles, data of baseline body weight and at least three subsequent weight measurements had to be available within the first 9 months. To study the long-term weight-profiles, data of at least four body weight measurements between 9th and 36th month after commencing insulin therapy had to be available.

Statistical methods

We studied the individual weight-profiles of patients with T2DM up to 36 months after the start of insulin therapy and the dependence on HbA1c with the use of linear mixed models for repeated measures [12]. At first, we found that the models were not statistically significantly improved when a quadratic term in time was included in the linear part of the models (Likelihood-Ratio test) in neither time period. The following initial model was used:

$$Y_i(t) = \mu + \beta_1 \times BBW_i + \beta_2 \times t + \beta_3 \times BBW_i \times t + \beta_4 \times \Delta HbA1c_{it} + \beta_4 \times \Delta HbA1c_{it} \times t + b_{1i} + b_{2i} \times t + \varepsilon_{it}$$

where Y refers to body weight, i to subject, t to the time (month) after start of insulin therapy, μ to the general mean, β to a fixed effect, b to a random effect, BBW to the baseline body weight, $\Delta HbA1c$ to the change in HbA1c since baseline and ε_{ij} to the normal distributed residual with mean zero.

We studied weight-profiles unadjusted and adjusted for change in HbA1c in each time period, separately. Note that in case of the unadjusted weight-profiles the terms related to $\Delta HbA1c$ were omitted from the model presented above. In total four models were designed.

Short-term linear mixed model (0–9 months; model I)

The dependent variable in this model was body weight. The independent continuous variables were: body weight at the start of insulin therapy and the time (t) since the start of insulin therapy (month). Furthermore, the interaction term between both variables ($BBW \times t$) was included in the model, representing different increase in body weight with higher initial body weight. The independent random variables were: intercept and the regression in time (representing weight gain or loss per month). This allows different regression lines for different patients, both in intercept and regression.

Short-term linear mixed model (0–9 months; model II)

The same dependent and independent (continuous and random) variables were entered into the model as in model I. Model II was designed to study the short-term weight-profile adjusted for change in HbA1c. Therefore, the independent continuous variables (time-dependent) change in HbA1c since the start of insulin therapy (ΔHbA1c) and the interaction term between time and change in HbA1c ($\Delta\text{HbA1c} \times t$) were included in the model.

Long-term linear mixed model (9–36 months; model III)

The same dependent and independent variables as in model I were entered in this model, except for the interaction term between baseline body weight and time ($\text{BBW} \times t$). The reason for this was that aforementioned interaction term did not significantly alter the outcome of the model.

Long-term linear mixed model (9–36 months; model IV)

The same dependent and independent variables as in model III were entered into this model. The independent continuous variables were: weight at the start of insulin therapy, and time since the start of insulin therapy (month). Model IV was designed to study the long-term weight-profile adjusted for change in HbA1c. Therefore, absolute change in glycosylated haemoglobin since start of insulin therapy (ΔHbA1c) was included as an independent variable. The interaction term between time and change in HbA1c was not included because of a non-significant contribution to the model.

Estimated regression parameters and mean profiles are presented, with the appropriate standard error (SE) and 95% confidence interval (CI). Statistical analyses were performed by using SAS[®] statistics 9.2 for Windows (SAS Institute Inc. Cary, NC, USA). $P < 0.05$ was considered statistically significant.

Results

A total of 146 patients who were assigned to biphasic insulin therapy were screened. Finally, 122 patients were included in our analysis. We excluded 24 patients (18 patients of whom no baseline HbA1c or body weight was available, in 6 patients the responsible physician changed the initiating insulin regimen (i.e. 4 patients started prandial insulin and 2 patients started basal insulin therapy instead of biphasic insulin)). All patients included started twice-daily biphasic human insulin/isophan insulin 30 (Mixtard[®] 30) or aspart 30 (Novomix[®] 30).

Table 1 Baseline characteristics of the study population ($N = 122$)

	Number	Median (range)/n (%)
Age (years)	122	64 (35–94)
Sex	122	
Male		63 (52%)
Female		59 (48%)
Diabetes duration (years)	122	9 (2–36)
Body weight (kg)	122	85.3 (47–157)
Body mass index (kg/m^2)	122	30 (21–48)
HbA1c (%)	122	10 (6–15)
Oral glucose-lowering Medication	122	
SU only		16 (13%)
MET only		18 (15%)
SU and MET		69 (57%)
TZD only		2 (2%)
SU and TZD		4 (3%)
SU and MET and TZD		1 (1%)
SU and MET and Acarbose		4 (3%)
None ^a		8 (6%)
Blood pressure (mmHg)	99	
Systolic		142 (100–190)
Diastolic		80 (62–105)
Anti-hypertensive therapy	122	
Yes		81 (66%)
No		33 (27%)
Unknown		8 (7%)
Statin use	122	
Yes		48 (39%)
No		61 (50%)
Unknown		13 (11%)
Smoking	122	
Yes		17 (14%)
No		72 (59%)
Unknown		33 (27%)
Alcohol	122	
Yes		9 (7%)
No		79 (65%)
Unknown		34 (28%)
Lipid profile (mmol/l)	90	
Total cholesterol		5.2 (2.5–8.2)
Triglycerides		2.5 (0.6–21.1)
HDL cholesterol		1.0 (0.5–2.4)
LDL cholesterol		2.9 (0.8–5.1)

HbA1c glycosylated haemoglobin, *SU* sulfonylurea derivatives, *MET* metformin, *TZD* thiazolidinedione derivatives, *HDL cholesterol* high-density lipoprotein cholesterol, *LDL cholesterol* low-density lipoprotein cholesterol

^a No use of oral glucose-lowering medication prior to the start of insulin therapy

Crude data

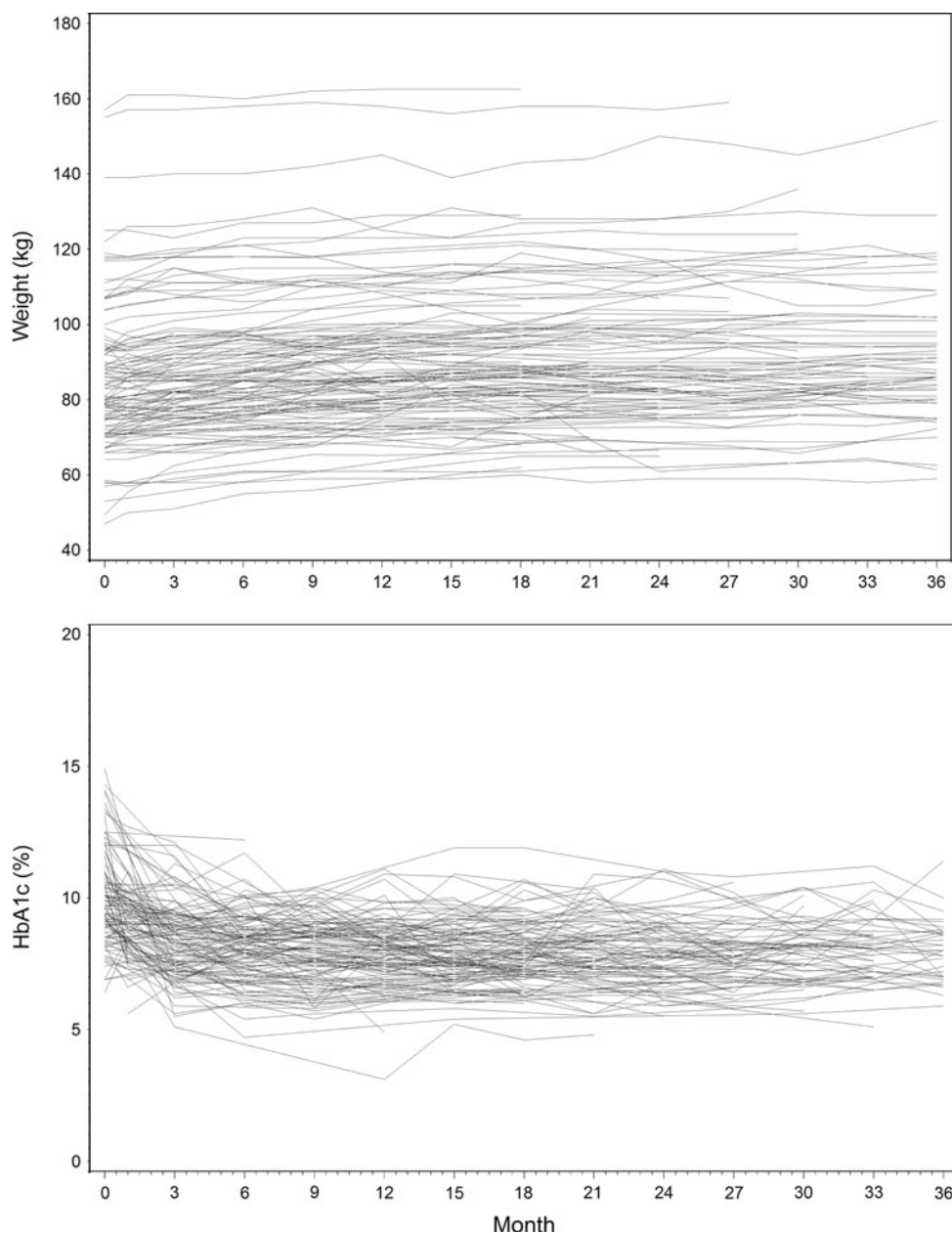
Baseline characteristics of the study population are shown in Table 1. Median follow-up was 33 months and 90% of all study subjects had a minimum follow-up of 18 months. Patients had a median age of 64 years and a median diabetes duration of 9 years. At baseline, mean body weight was 85 kg (range 47–157 kg) and HbA1c averaged 10%. After 9 and 36 months of insulin therapy, mean body weight was 90.6 ± 18.6 (SD) and 91.1 ± 17.2 kg, respectively (both $P < 0.001$ for mean change in body weight compared to baseline body weight). Furthermore, mean HbA1c after 9 months of insulin therapy was $7.9 \pm 1.3\%$, and after 36 months $8.1 \pm 1.3\%$ (both $P < 0.001$ for mean change in

HbA1c compared to baseline HbA1c). At the time of data collection, the median insulin dose was 56 units insulin per day (0.7 U/kg). Figure 1 shows the interpolation of crude data of body weight and change in HbA1c after start of insulin therapy. The mean increase in body weight was more pronounced in the first 9 months after start of insulin than from 9 months further onwards (0.52 vs. 0.10 kg/month, $P < 0.05$). HbA1c decreased steeply in the first 3 months after the start of insulin, followed by a more gradual decline.

Fit of linear mixed models to crude data

Figure 2 visualizes the fit of the short-term weight model to the crude data. In this figure the crude data (stars) and

Fig. 1 Interpolation of crude data of body weight (*top panel*) and HbA1c (*bottom panel*) after start of insulin therapy



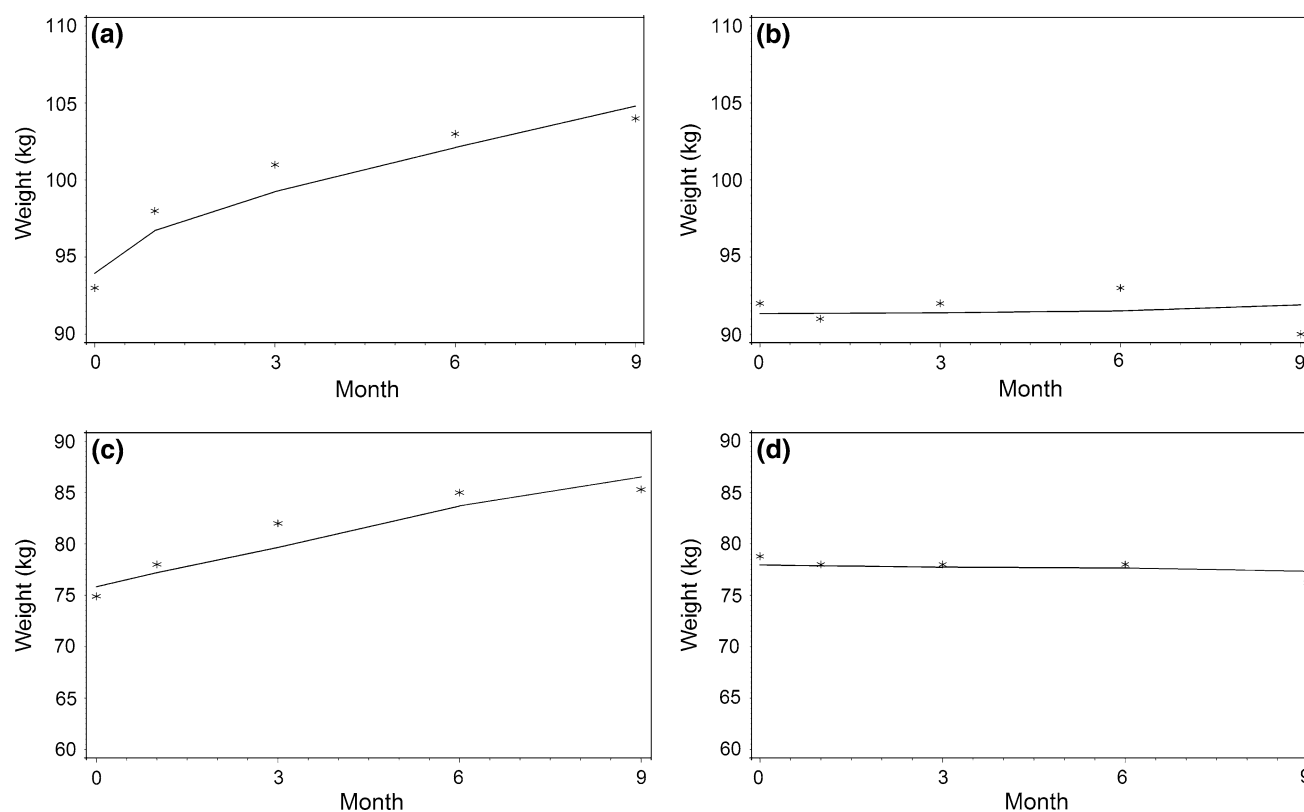


Fig. 2 The crude data (stars) and estimated profiles (line) of four different patients with complete data up to 9 months after start of the insulin therapy

estimated profiles (line) of four different patients with complete data up to 9 months after start of the insulin therapy are displayed. This figure shows that this model is sufficiently flexible to obtain a good fit in all cases: high (top panels) or low (bottom panels) values of the weight-profile as well as increasing (left panels) or non-increasing (right panels) weight-profiles. A similar good fit was obtained using the long-term weight model.

Outcome of linear mixed models (short-term and long-term profiles)

Figure 3 shows the mean weight-profile in the 36 months after insulin therapy (mean baseline body weight 85.3 kg, baseline HbA1c of 9.9%, decrease of HbA1c 2.0%). Table 2 shows the regression parameters for the weight-profiles.

Short-term weight-profiles

Estimated mean body weight increased from 85.6 kg (95% CI: 85.4–85.9 kg) to 90.3 kg (89.3–91.2 kg) after 9 months of insulin therapy. When expressed as percentage of baseline body weight, the average increase in weight was 5.5% after 9 months of insulin therapy. Estimated mean HbA1c decreased from 9.5 (9.4–9.6) to 7.6% (7.3–7.9).

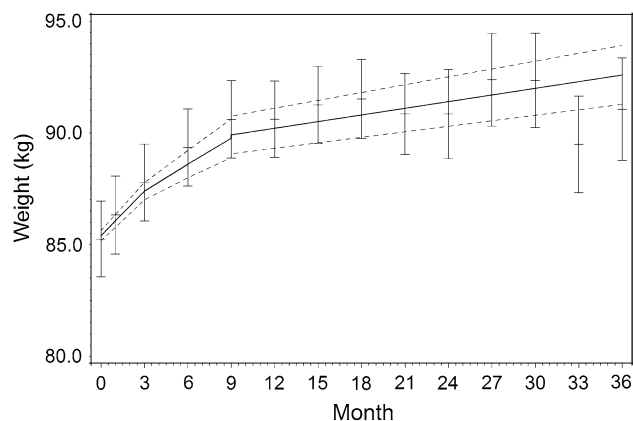


Fig. 3 The estimated mean weight-profile (solid line) with the appropriate 95% confidence bands (dashed lines) in the 36 months after start of insulin therapy (mean baseline body weight of 85.3 kg and baseline HbA1c of 9.9%). The decrease in HbA1c since baseline at 3rd, 6th and 9th month is 1.6, 1.8 and 2.0%, respectively. The vertical bars indicate the crude data (mean with one standard error)

We found that the monthly increase in body weight decreased by 0.006 kg per kg of higher body weight above mean body weight at baseline (85.6 kg). Thus, with the use of model I it was calculated that a patient with a baseline body weight of 50 kg increased 0.70 kg per month, whereas for a patient with a baseline body weight of

Table 2 The estimated regression parameters with the 95% CI of the crude data on body weight and the HbA1c adjusted weight-profiles by period using a linear mixed model

Effect	Model I		Model II	
	Estimate	(95% CI)	Estimate	(95% CI)
0–9 months				
Intercept	85.643	(85.399;85.887)	85.400	(85.167;85.634)
BBW [#]	1.000	(0.987;1.013)	1.000	(0.988;1.012)
t (month) [#]	0.516	(0.420;0.613)	0.462	(0.350;0.574)
BBW $\times t$ ^{\$}	−0.006	(−0.011;−0.001)	—	—
Δ HbA1c [#]	—	—	0.510	(0.336;0.684)
Δ HbA1c $\times t$ ^{\$}	—	—	−0.050	(−0.09;−0.001)
Effect	Model III		Model IV	
	Estimate	(95% CI)	Estimate	(95% CI)
9–36 months				
Intercept	90.452	(89.450;91.455)	89.918	(89.066;90.771)
BBW [#]	0.931	(0.878;0.985)	0.954	(0.909;0.999)
t (month) [#]	0.099	(0.055;0.143)	0.099	(0.056;0.143)
Δ HbA1c ^{\$}	—	—	0.548	(0.060;1.036)

Model I and III represent the estimated regression parameters of the crude data on body weight for the short (0–9 months after start of insulin therapy) and long-term (9–36 months after start of insulin therapy) period, respectively. Model II and IV represent the HbA1c adjusted weight-profiles for the short and long-term period, respectively

All variables entered into the models contributed significantly to the change in weight-profiles ([#] $P < 0.001$ and ^{\$} $P < 0.05$)

BBW baseline body weight, Δ HbA1c absolute change in HbA1c after start of insulin therapy —denotes not applicable

100 kg this was 0.40 kg per month. Table 2 also shows that 0.46 kg/month (0.350–0.574 kg/month) of weight gain within the first 9 months after start of insulin therapy was independent of the change in HbA1c (model II). Thus, only 12% of the total monthly increase of 0.52 kg per month could be attributed to the change in HbA1c.

Furthermore, we found that the effect of a decrease in HbA1c on weight gain diminished later in time after start of insulin therapy. The effect of HbA1c change on body weight after 3rd month was 0.37 kg/month ($= 0.510 - 3 \times 0.050$) per absolute percentage decrease in HbA1c and after 9th month this was only 0.1 kg/month ($= 0.510 - 9 \times 0.050$) per absolute percentage decrease in HbA1c. Figure 4 shows the short-term mean weight-profiles with various decreases in HbA1c and the effects on weight gain.

Long-term weight-profiles

Table 2 shows that the estimated increase in body weight from 9th to 36th month after start of insulin therapy was 0.1 kg/month (0.055–0.143 kg/month) and that this weight gain was independent of the baseline body weight. As a result, body weight of the patient with mean baseline body weight increased from 90.5 kg (89.4–91.5 kg) at 9th month to 93.1 kg (91.6–94.7 kg) at 36 months after start of insulin therapy. In addition, the results of the mixed model

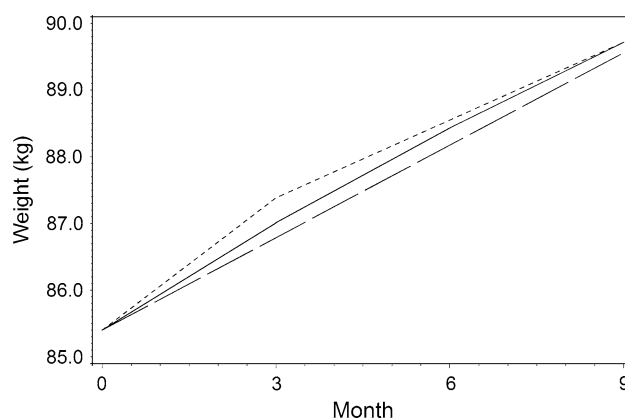


Fig. 4 The estimated mean weight-profile in the first 9 months after insulin therapy (baseline body weight of 85.3 kg) with various decreases in HbA1c. Solid line: decrease in HbA1c since baseline at 3rd, 6th and 9th month is 0.6, 1.1 and 1.6%, respectively. Short dashed line: decrease in HbA1c since baseline at 3rd, 6th and 9th month is 1.6, 1.6 and 1.6%, respectively, i.e. already the maximal decrease in HbA1c is reached at 3 months. Long dashed line: decrease in HbA1c since baseline at 3rd, 6th and 9th month is 0.0, 0.0 and 0.0%, respectively, i.e. no decrease in HbA1c

for the HbA1c profiles showed no statistical significant change during this time period ($-0.004 \pm 0.005\%$ per month). As a result, for every patient in the model, the increase in weight per month (i.e. slope) on the long-term

was similar. However, body weight at 9 months was dependent on baseline body weight and HbA1c. For example, a patient with a 1 kg higher baseline body weight will have a 0.95 kg (0.909–0.999 kg) higher body weight at 9 months. In addition, a patient with a 1% higher baseline HbA1c will have a 0.55 kg (0.060–1.036 kg) higher body weight at 9 months.

Discussion

In this study, we studied individual weight-profiles of patients with T2DM up to 36 months after initiation of insulin therapy. Mean body weight increased by more than 0.5 kg per month during the first 9 months after initiation of insulin therapy. Thereafter, the increase in body weight was more gradual, but still patients had a weight gain on average of 1.2 kg per year. This is well in line with other studies which investigate weight gain and insulin therapy [13, 14].

However, although glycaemic control improved considerably, only 12% of the monthly weight gain within the first 9 months could be attributed to the change in HbA1c. We also found that the effect of a decrease in HbA1c was most prominent during the first months after start of insulin therapy. After 9 months of insulin therapy, the change in HbA1c did no longer affect the change in body weight.

To our knowledge, this is the first study to show results of a longitudinal analysis of change in body weight after commencing insulin therapy and its relation to the change in HbA1c. Other studies showed that after short-term insulin therapy the level of improvement of glycaemic control correlated with the increase in body weight, with reported correlations between -0.21 and -0.47 [8, 10]. We believe our study adds valuable information by assessing to what extent the change in glycaemic control contributes to weight gain over time. To study the relationship between body weight and HbA1c over time, we performed an observational longitudinal analysis using a linear mixed model for repeated measures data. The strength of the model allowed different regression lines for different patients, both in intercept and regression. In this way, the contribution of (change in) HbA1c to (change in) body weight in time could be estimated more accurately.

Although the model analysed the crude data properly, these data were collected retrospectively. As a consequence, we were not (fully) informed about other factors that determined weight gain. We can only speculate about other potentially contributing factors, unrelated to glucose control [8]. For example, anabolic effects of insulin may directly induce weight gain. Anabolic effects of insulin on adipose and muscle tissue may lead to sodium and water retention [15, 16]. The anabolic effects of insulin might play a

dominant role inducing weight gain after short-term insulin therapy. Furthermore, it could be argued that the insulin dose itself and change of insulin dose determines weight gain [10]. Unfortunately, we were not informed about the insulin dose of each patient at every time point. Weight gain might also be determined by changes in caloric intake (whether or not due to initiation of insulin therapy), physical activity and basal metabolic rate [17, 18]. The use of insulin may also lead to defensive eating habits because of (fear of) hypoglycemia [19]. Consequently, individuals may increase caloric intake to proactively avoid such an event, resulting in weight gain [20]. All these factors might contribute to weight gain after start of insulin therapy. To investigate these other factors/predictors a prospective analysis and follow-up will be required.

In clinical practice, many physicians are reluctant to initiate insulin treatment in poorly controlled obese patients because of fear of insulin-associated weight gain. Biesenbach et al. [21] already reported that the risk of weight gain and increase in insulin requirement was similar in insulin-treated type 2 diabetic patients with normal and elevated BMI. We now show that obese patients are even less likely to gain weight after initiation of insulin therapy than leaner patients. However, we believe our data are more accurate since in the study of Biesenbach et al. patients were pooled and assigned to one of three BMI subgroups (<26 , $26\text{--}30$ and >30) and calculations were based on only two time-points, thus ignoring variations in weight between these time-points. We think that obesity per se should not preclude physicians to initiate insulin therapy in poorly controlled patients with type 2 diabetes.

After long-term insulin therapy, change in HbA1c was not a predictor of weight gain at all. Still, patients gained an average of 1.2 kg/year. We cannot determine whether (part of) this weight gain was due to the “natural” course of body weight associated with aging, since we lacked a control group of either matched non-diabetic subjects, or subjects with T2DM on oral medication. In the UK Prospective Diabetes Study (UKPDS) [22], it was shown that patients assigned to the intensive glucose control with glibenclamide gained an average of approximately of 4 kg over 12 years of treatment, whereas those on insulin gained an additional 3 kg. Most of this weight gain developed within the first year of treatment. After 1 year of treatment patients with glibenclamide gained an average of approximately of 0.5 kg/year and those on insulin gained similar up to 3 years of treatment. Thereafter, little change in weight occurred in the group of patients on glibenclamide, in contrast to patients using insulin who continued to gain weight. It was shown that glycaemic control continued to deteriorate in both groups.

In conclusion, this study shows that initiation of insulin in patients with T2DM was associated with substantial

increase in body weight. However, the contribution of change in HbA1c to insulin-associated weight gain was rather small in the short term and even had no effect in the longer term. Further studies are needed to identify alternative factors that contribute to (insulin-associated) weight gain, such as differential effects on body composition, caloric intake and physical activity/energy expenditure.

Conflict of interest None.

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