

# Changes in patient weight and the impact of antidiabetic therapy during the first 5 years after diagnosis of diabetes mellitus

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## Abstract

**Aims/hypothesis** It is generally thought difficult for type 2 diabetic patients to lose weight. We monitored changes in patients' weight during the first 5 years after diabetes diagnosis in relation to initiation of antidiabetic treatment.

**Subjects and methods** Data from 711 newly diagnosed diabetic patients aged 40 or over were analysed with a random-effect linear-regression model. Patients were included consecutively from a well-defined patient list in general practice.

**Results** In 245 patients whose only treatment was advice on diet, an initial weight loss of 6 to 7 kg was largely

maintained over 5 years. Patients receiving metformin ( $n=86$ ) or sulfonylureas ( $n=330$ ) maintained an average weight loss of 2 to 4 kg that was dependent on age and sex. Patients' weight did not change on initiation of treatment with sulfonylureas or metformin. Over 5 years, median HbA<sub>1c</sub> increased from 7.0 to 7.8% (reference range 5.4–7.4%) in the diet-alone group. HbA<sub>1c</sub> was approximately 1 percentage point higher for most of the other treatment groups.

**Conclusions/interpretation** In newly diagnosed type 2 diabetic patients, long-term weight loss was common and weight loss was not affected by sulfonylurea treatment. The measurements in the study are taken from treatment results achieved in the general population of diabetic patients, who are rarely treated in secondary care and seldom the subject of research; the results thus indicate that weight reduction is a practicable treatment in diabetic patients.

**Electronic Supplementary Material** Supplementary material is available for this article at <http://dx.doi.org/10.1007/s00125-006-0328-y> and is accessible for authorised users.

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## Abbreviations

ESM Electronic supplementary material  
UKPDS UK Prospective Diabetes Study

## Introduction

Obesity is associated with insulin resistance and an increased risk of developing type 2 diabetes mellitus [1–3]. Lifestyle changes, including weight reduction, may result in a clinically important reduction of the incidence of diabetes [4, 5], coronary heart disease [6] and even mortality [7] in

non-diabetic persons at high risk or in diabetic patients. It is commonly observed that treatment of type 2 diabetic patients with sulfonylureas [8–10] or insulin [10–12] is associated with weight gain. This effect of sulfonylureas and insulin could possibly aggravate the insulin-resistance syndrome associated with type 2 diabetes [2, 13, 14] and thereby counteract the otherwise beneficial effects of these agents. In contrast to insulin and sulfonylureas, treatment with metformin seems to be associated with weight reduction [8, 15] or weight stabilisation [9, 16].

It is widely held that lasting weight loss is difficult to achieve [17]. In type 2 diabetic patients this view is chiefly founded on studies concerned with selected groups of patients and on intervention studies implementing step-up treatment with specific antidiabetic drugs. In the United Kingdom Prospective Diabetes Study (UKPDS) the initial weight loss was regained after 2 years of treatment in the insulin and sulfonylurea randomisation arms [18]. The perspective of such studies needs to be widened by results from studies using individualised treatment schemes allowing for doctors' and patients' influence on choice of treatment modality.

In a population-based sample of type 2 diabetic patients receiving structured individualised care by primary-care physicians [19], we examined the changes in weight during the first 5 years after diabetes diagnosis in relation to initiation of antidiabetic pharmacological treatment.

## Subjects and methods

### Study population

At the end of 1988, 474 general practitioners volunteered to take part in the Danish study, 'Diabetes Care in General Practice'. Before the study started, the general practitioners were randomised to an intervention and a comparison group [19]. Weight measurements over the whole period were collected in the intervention group only, so this study is confined to 711 patients in this group (Fig. 1). Of these, 19 patients started insulin treatment within 180 days of diagnosis. Insulin was discontinued for two of these patients during the observation period. Thus, 694 (97.6%) patients were considered to have type 2 diabetes.

### The intervention

Follow-up every 3 months and annual screening for diabetic complications were supported by sending a questionnaire to the general practitioner 1 month before the next expected consultation [19]. The general practitioner was also requested to define, together with the patient,

the best possible goals, within three predefined categories of good, acceptable and poor control, for blood glucose, HbA<sub>1c</sub> ( $\leq 7.0$ ,  $\leq 8.5$  and  $> 8.5\%$ ), diastolic blood pressure ( $\leq 90$ ,  $\leq 100$  and  $> 100$  mmHg), total cholesterol ( $\leq 6.0$ ,  $\leq 7.0$  and  $> 7.0$  mmol/l) and fasting total triglycerides ( $\leq 2.0$ ,  $\leq 5.0$  and  $> 5.0$  mmol/l). At each quarterly consultation, the general practitioner was asked to compare the achievements with the goal and consider changing either goal or treatment accordingly. In overweight patients, the general practitioner was prompted to get agreement on a small, realistic weight reduction, write this down and to follow up on this. However, a specific relative bodyweight was not striven for. In Denmark, routine care of patients with type 2 diabetes is usually given by general practitioners in ordinary consultations and not in disease management sessions run by nurses.

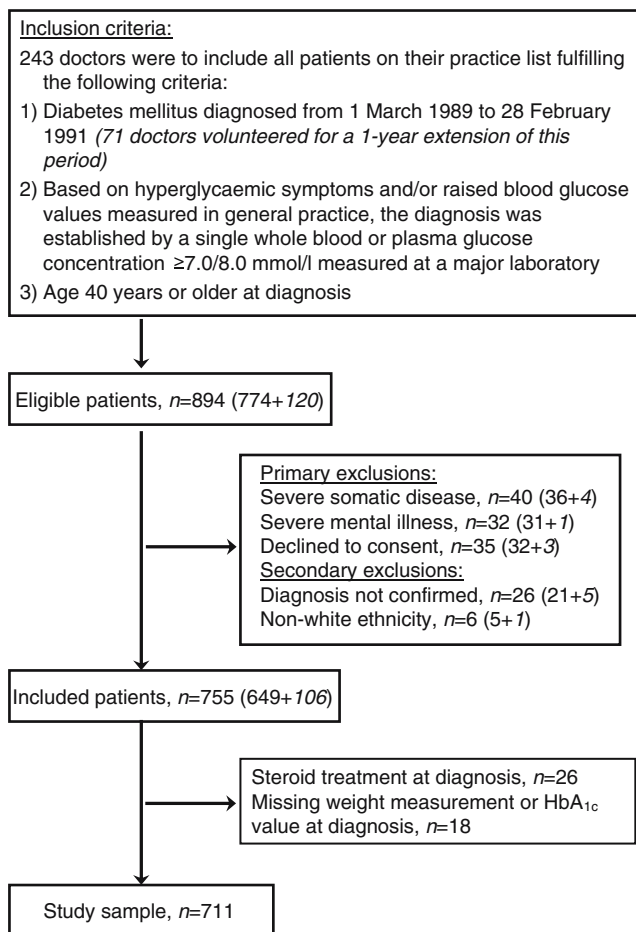
The general practitioners were introduced to possible solutions to therapeutic problems through six annual half-day seminars, annual descriptive feedback reports on individual patients, and folders and leaflets for doctors and patients. Generally, the importance of diet was stressed and doctors were recommended to postpone, if possible, the start of antidiabetic drugs until at least 3 months after diagnosis to observe the effect of a possible weight loss. It was suggested that the general practitioners recommend increased physical exercise and simple diet rules: increase complex carbohydrate to at least 50% of the diet, and in particular increase water-soluble fibre, reduce fat content to a maximum of 30%, reduce alcohol intake, and eat five or six meals a day. At study start the intervention doctors described their access to a dietician: private dietician (3%), only through referral to a diabetes clinic (42%) and no access at all (55%). In cases of persistent hyperglycaemia, metformin was recommended for patients who were overweight by clinical judgement, and glipizide or glibenclamide was suggested for patients with normal weight. In patients  $\geq 70$  years, tolbutamide was given preference. If the goal for blood glucose was not met, a combination of metformin and a sulfonylurea was recommended as the last step before starting insulin.

On 26 September 1995, the protocol-based final follow-up examinations were initiated in both groups and the intervention was terminated.

The protocol was approved by the ethics committee for Copenhagen and Frederiksberg, and informed consent was obtained from all patients.

### Measurements

Patients were weighed without shoes and outer garments by the general practitioner on the scales in his/her practice at diagnosis and at 98.7% of the annual examinations and 95.5% of the 3-monthly consultations.



**Fig. 1** Flow of participants through the study. The numbers of patients included during the 1-year extension of the 2-year inclusion period for

Fasting blood samples were drawn at diagnosis and at annual examinations. Fraction of HbA<sub>1c</sub> was determined at Odense University Hospital by ion exchange HPLC (reference interval 5.4–7.4%).

The general practitioner reported on the 3-monthly questionnaires whether treatment with oral antidiabetic agents or insulin had been initiated or changed. The exact type and dosage of the medication were reported on the annual questionnaires.

#### Statistical analyses

Because of observed sex differences (Table 1), we did separate analyses for men and women. The course of HbA<sub>1c</sub> relative to the first pharmacological treatment was described by connecting the median values of the first-measured HbA<sub>1c</sub> for each patient in each of the 1-year intervals after diabetes diagnosis.

The course of bodyweight and the effect of initiation of antidiabetic pharmacological treatment on this course was analysed in a random-effect model [20–22]. The data show

that many patients experience a weight loss after diagnosis until the second or third quarterly consultation, after which weight seems to stabilise or increase slightly. Utilising this information, the course of bodyweight for an individual was modelled as piecewise linear, consisting of an intercept at diagnosis, a linear weight loss within the first year after diagnosis, and a linear weight regain tendency thereafter. We investigated models with a variety of breakpoints in the first year after diagnosis. A model with a breakpoint at 5 months was selected, as the residual plot for this model was the most favourable. On initiation of antidiabetic pharmacological treatment a change in weight regain tendency was allowed for in the model. The longitudinal information on bodyweight was subsequently censored at the end of follow-up, at death, exclusion or last study examination, or when a second antidiabetic pharmacological treatment was initiated. The weight at diagnosis, the drop thereafter, and the following weight regain tendency are different for each patient. These individual characteristics, however, are not the topic of analysis and regarded as normally distributed random variables in the mixed model. Furthermore, all components of the piecewise linear curve were allowed to depend linearly on age and HbA<sub>1c</sub> at diagnosis and the first pharmacological treatment; only the possible change in weight regain tendency at initiation of pharmacological treatment did not depend on HbA<sub>1c</sub> at diagnosis. The above implies a modelling of the average individual course of bodyweight relative to age, sex, HbA<sub>1c</sub> at diagnosis and first antidiabetic treatment. The modelled average courses of individual bodyweight for selected values of covariates are represented graphically (Figs. 2 and 3). The number of men/women who contributed to the model with weight measurements in the period after 1, 2, 3, 4 and 5 years after diabetes diagnosis is 344/313, 308/289, 264/251, 200/209 and 126/146. *p* values are from *F*-tests assessing a significant difference for different values of the covariate for that specific weight course component. A detailed description of the model is contained in the Electronic supplementary material (ESM).

#### Results

Patient characteristics are shown in Table 1. The male:female ratio was 1.16 (382/329), and there are important sex differences. The median diagnostic plasma glucose was 13.6 mmol/l. The median length of the follow-up period was 1,843 days (range 4–2,757 days). On 26 September 1995, 155 patients had died and 12 had been excluded. Of the remaining 544 patients, 501 were re-examined at the final follow-up examination (Table 2). A considerable weight loss was maintained among those treated with metformin, sulfonylureas and diet alone at 5-year follow-

**Table 1** Characteristics of study population and treatment according to antidiabetic treatment

Antidiabetic treatment	Number of patients			Age at diabetes diagnosis (years)			BMI at diabetes diagnosis (kg/m <sup>2</sup> )		
	Males	Females	Total	Males	Females	<i>p</i>	Males	Females	<i>p</i>
First pharmacological treatment									
Metformin	41	45	86	58.1 (51.7–64.0)	62.3 (54.6–68.4)	0.037	31.5 (29.4–33.6)	33.7 (30.7–37.9)	0.012
Sulfonylureas	174	156	330	65.0 (54.6–72.9)	69.6 (58.5–76.4)	0.003	28.5 (25.9–30.7)	28.8 (25.7–32.9)	0.25
Metformin+sulfonylureas	16	9	25	56.4 (50.8–63.7)	68.1 (66.3–71.9)	0.12	30.8 (26.8–35.5)	33.6 (30.9–35.9)	0.24
Insulin	12	13	25	70.2 (65.4–77.3)	53.0 (46.8–72.5)	0.11	29.6 (23.4–30.4)	22.3 (20.0–27.2)	0.034
Diet alone <sup>a</sup>	139	106	245	63.8 (54.6–72.1)	69.0 (59.6–75.9)	0.003	29.8 (26.6–33.0)	29.3 (25.6–33.1)	0.40
All patients	382	329	711	63.5 (54.0–71.5)	67.8 (57.6–75.7)	<0.0001	29.3 (26.3–32.1)	29.7 (26.1–33.6)	0.29
Antidiabetic treatment									
	HbA <sub>1c</sub> at diabetes diagnosis (%) <sup>b</sup>			Time from diagnosis until initiation of first antidiabetic pharmacological treatment (years)			Duration of first antidiabetic pharmacological treatment (years)		
	Males	Females	<i>p</i>	Males	Females	<i>p</i>	Males	Females	<i>p</i>
First pharmacological treatment									
Metformin	10.0 (8.6–11.2)	9.8 (8.8–11.6)	0.83	1.4 (0.3–2.6)	0.9 (0.3–2.9)	0.64	2.0 (1.0–3.3)	2.2 (1.2–3.6)	0.52
Sulfonylureas	10.4 (8.9–11.8)	9.9 (8.4–11.6)	0.067	1.0 (0.3–2.2)	1.2 (0.3–2.4)	0.34	2.5 (1.2–3.9)	2.9 (1.4–4.2)	0.18
Metformin+sulfonylureas	10.6 (8.6–12.7)	10.0 (9.2–12.8)	0.98	0.7 (0.4–2.6)	0.3 (0.1–0.3)	0.066	2.1 (1.1–3.2)	2.7 (1.8–5.3)	0.16
Insulin	8.2 (7.5–10.6)	9.5 (8.3–11.7)	0.38	0.02 (0–1.0)	0.3 (0.0–0.3)	0.81	4.0 (1.7–5.7)	5.0 (4.2–5.6)	0.38
Diet alone <sup>a</sup>	8.7 (7.5–10.8)	8.8 (7.5–10.2)	0.99	–	–	–	–	–	–
All patients	9.9 (8.2–11.4)	9.4 (8.1–11.5)	0.47	1.0 (0.3–2.2)	1.0 (0.3–2.3)	0.90	2.4 (1.1–3.8)	2.9 (1.4–4.4)	0.033

Data are numbers or medians (interquartile range). *p* values are from Wilcoxon tests

<sup>a</sup>The diet-alone group included all patients treated with diet alone throughout the study

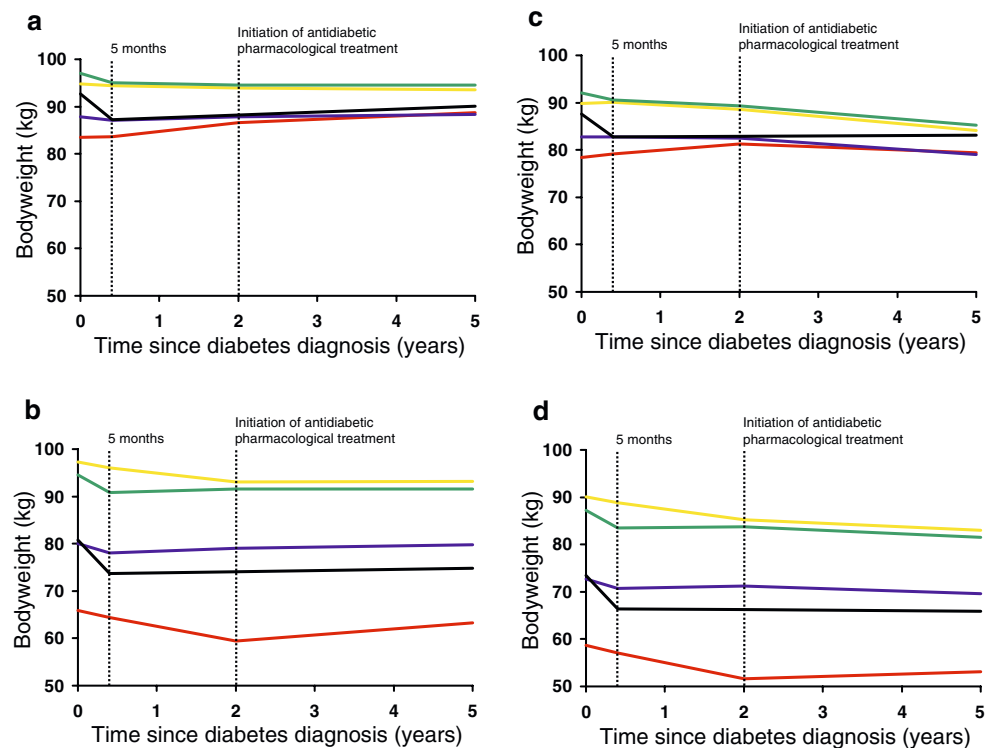
<sup>b</sup>Reference range 5.4–7.4%

up. Patients with glucosuria at 5-year follow-up had smaller average weight loss than patients without glucosuria (Table 2). Only glucosuric patients treated with a combination of metformin and sulfonylureas had a relatively larger weight loss (data not shown). In a linear-regression analysis the weight at 5-year follow-up was predicted by weight at diagnosis ( $p<0.0001$ ), age ( $p<0.0001$ ), sex ( $p=0.044$ ) and treatment at 5-year follow-up ( $p<0.0001$ ), but not by glucosuria at 5-year follow-up ( $p=0.28$ ). Compared with patients receiving sulfonylureas the diet and insulin group attained a weight loss ( $p=0.001$ ) and a weight gain ( $p=0.006$ ), respectively. Patients receiving metformin ( $p=0.83$ ) or metformin and sulfonylurea ( $p=0.35$ ) did not experience a weight change different from the sulfonylurea group.

For the remaining analyses, data from all patients were included from the day of diagnosis until the last follow-up examination done while they were on the first antidiabetic treatment, which was either antidiabetic drugs or diet for those patients on diet alone throughout the study. The median time spent on first pharmacological antidiabetic treatment was not less than 2 years for any treatment (Table 1). First antidiabetic treatment was not associated with sex ( $\chi^2$ -test,  $p=0.45$ ), but for both sexes first treatment varied with age at diagnosis (Wilcoxon test,  $p=0.001$  for men;  $p=0.009$  for women) and BMI at diagnosis ( $p=0.0002$  and  $0.0001$ , respectively) (Table 1).

We modelled changes in weight after diabetes diagnosis according to first antidiabetic treatment. The model is summarised in Table 3, which shows that the intercept of

**Fig. 2** Examples of the course of bodyweight developments as described by the model according to age, sex and first antidiabetic pharmacological treatment, sulfonylureas (*blue*), metformin (*green*), metformin and sulfonylurea (*yellow*), insulin (*red*), or diet alone (*black*). **a** Males, 40–64 years. **b** Females, 40–64 years. **c** Males, 65+ years. **d** Females, 65+ years. HbA<sub>1c</sub> was set at 10.0% in all panels. The *first and second vertical lines* indicate changes in weight course 5 months after diabetes diagnosis and any change at initiation of antidiabetic pharmacological treatment if this occurs 2 years after diabetes diagnosis, respectively

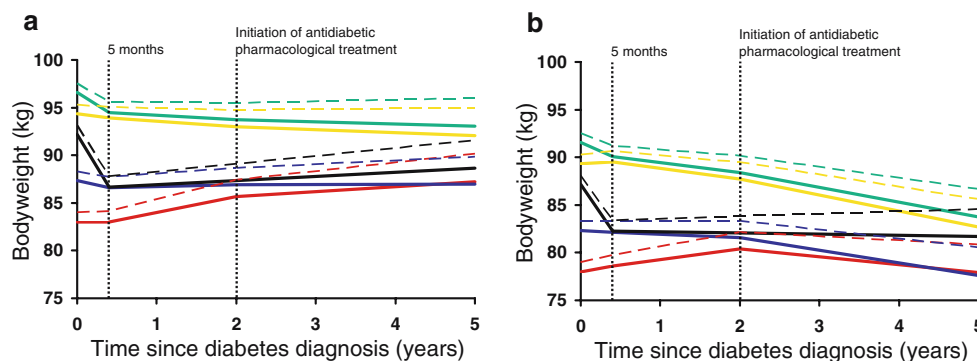


the expected weight course, i.e. the weight at diagnosis, varies with age and first treatment. Similarly, the average weight loss tendency during the first 5 months after diagnosis depends on first antidiabetic treatment and for men also on HbA<sub>1c</sub>, and the average weight regain tendency from 5 months after diagnosis depends on age and first antidiabetic treatment. Figure 2 displays the age- and sex-related features of the model including statistically non-significant effects. Initiation of first pharmacological antidiabetic treatment is assumed to occur 2 years after diabetes diagnosis in this visualisation of the model. The initial and long-term average weight loss is most pro-

nounced in the diet group, in accord with Table 2. Both weight variability and achieved weight loss seem to be greater for women than for men (Table 3, Fig. 2).

The effect of HbA<sub>1c</sub> is small and statistically non-significant for females, so this effect is illustrated in Fig. 3 for males only. For all treatment modalities, weight curves for patients with relatively high HbA<sub>1c</sub> values lie above and have a more ascending slope than weight curves for patients with relatively low HbA<sub>1c</sub> measurements (Fig. 3, Table 3).

The model in Table 3 includes terms for a change in weight regain tendency at the time of initiation of first drug



**Fig. 3** Examples of the course of bodyweight developments (males only) as described by the model according to HbA<sub>1c</sub>, age and first antidiabetic pharmacological treatment, sulfonylureas (*blue*), metformin (*green*), metformin and sulfonylurea (*yellow*), insulin (*red*), or diet alone (*black*). **a** 40–64 years. **b** 65+ years. HbA<sub>1c</sub>=8.0% (*solid lines*). HbA<sub>1c</sub>=12.0%

(*broken lines*). Reference range of HbA<sub>1c</sub>: 5.4–7.4%. The *first and second vertical lines* indicate changes in weight course 5 months after diabetes diagnosis and any change at initiation of antidiabetic pharmacological treatment if this occurs 2 years after diabetes diagnosis, respectively

**Table 2** Bodyweight at diabetes diagnosis and 5-year follow-up according to treatment modality or glucosuria at 5-year follow-up

Antidiabetic treatment or presence of glucosuria at 5-year follow-up	Number of patients	Bodyweight at diabetes diagnosis (kg)	Bodyweight at 5-year follow-up (kg)	Weight change since diabetes diagnosis (kg)	<i>p</i>
Antidiabetic treatment					
Metformin	43	92.5	88.2	-4.3 (-6.3; -2.3)	<0.0001
Sulfonylureas	180	81.8	78.9	-2.9 (-3.9; -1.9)	<0.0001
Metformin+sulfonylureas	70	88.8	86.8	-2.0 (-3.7; -0.4)	0.014
Insulin	56	79.4	80.0	0.5 (-1.0; 2.1)	0.48
Diet alone	152	84.1	78.7	-5.4 (-6.5; -4.2)	<0.0001
All patients	501	84.1	80.9	-3.3 (-3.9; -2.6)	<0.0001
All patients with glucosuria <sup>a</sup>	107	88.3	86.5	-1.8 (-3.0; -0.5) <sup>b</sup>	0.005
All patients without glucosuria <sup>a</sup>	381	82.9	79.4	-3.5 (-4.2; -2.8) <sup>b</sup>	<0.0001

Data are numbers or means (95% CIs). *p* values are from a *t*-test for  $H_0$ : mean=zero

<sup>a</sup>In 13 patients information about glucosuria at 5-year follow-up was missing

<sup>b</sup>*p*=0.022, *t*-test of whether the weight change is the same for patients with and without glucosuria

treatment and these terms were not significant in the reduced model either (see the **ESM**). Consequently we do not expect any change in average regain at the time of initiation of first drug treatment, and the bending of the curves in Figs. 2 and 3 at initiation of first antidiabetic pharmacological treatment is not statistically significant.

The median daily doses of the first pharmacological treatment agents were (range in parenthesis): metformin: 1,000 (500–2,000) mg, glibenclamide: 3.5 (0.875–21) mg, glipizide: 5 (2.5–25) mg, tolbutamide: 750 (250–2,000) mg, insulin: 27 (10–48) IE. Only 19 patients received sulfonylureas other than those mentioned above. During the period of first treatment the median doses increased only for tolbutamide (to 1,000 mg) and glipizide (to 7.5 mg).

Plots of the changes in HbA<sub>1c</sub> after diabetes diagnosis show relatively favourable glucose status in the diet group and relatively high glucose levels in the few men treated with insulin (Fig. 4). The comparatively low initial HbA<sub>1c</sub> values in the insulin group are because many of these patients had been hospitalised when insulin treatment started and were enrolled in the study at a relatively late stage.

## Discussion

We found that a sustained weight loss is common in type 2 diabetic patients up to 5 years after diabetes diagnosis, and that initiation of treatment with sulfonylurea was not followed by a change in average weight-regain tendency.

In type 2 diabetes the interrelationships between the metabolic state, antidiabetic treatment and changes in weight are complex. On the one hand, obesity is a strong risk factor for the development of type 2 diabetes [1, 3], but in newly diagnosed diabetic patients a high level of blood

glucose is associated with glucosuria and thereby loss of energy and weight. On the other hand, improving glycaemic control, e.g. through antidiabetic pharmacological treatment, may reverse a weight loss [23], but weight loss is in itself associated with reduced insulin resistance and improved glucose metabolism [14]. Caught in this delicate causal web we can only suggest various possible interpretations of our findings.

### Weight loss due to calorie loss in glucosuria

The sustained weight loss observed in the present study may possibly be due to undertreatment, relatively poor glycaemic control and consequent energy loss in glucosuria. We found, however, that patients with relatively high HbA<sub>1c</sub> measurements at diagnosis actually had weight trajectories that were above those of patients with relatively low HbA<sub>1c</sub> values (Fig. 3). Furthermore, patients with glucosuria at 5-year follow-up had smaller average weight loss than patients without glucosuria (Table 2). These findings are more in line with the explanation that weight loss is followed by improved glycaemic control. Even small weight losses are associated with a pronounced improvement of glucose tolerance [24, 25]. Weight loss and improved glycaemia are also more readily achieved in subjects with diabetes of relatively short duration [26, 27].

The quality of the glycaemic control in our study may seem relatively poor when viewed in the context of present day intentions, but it is on a level with that of UKPDS; in the UKPDS intervention group the average HbA<sub>1c</sub> dropped to normal during the first year, but then began to rise to reach approximately 7.2% after 6 years [10]. In our study the average HbA<sub>1c</sub> after 6 years was 8.5% [19]. The reference range of HbA<sub>1c</sub> was 4.5–6.2% in UKPDS and 5.4–7.4% in our study. The development of glycaemic control in our

**Table 3** Estimation of fixed effects in the mixed model for course of bodyweight after diabetes diagnosis

Explanatory variable	Males		Females	
	Estimate	<i>p</i> <sup>a</sup>	Estimate	<i>p</i> <sup>a</sup>
Weight at diagnosis	85.20		73.98	
Age		0.0016		0.0001
40–64 years	5.03		7.26	
65+ years	0		0	
HbA <sub>1c</sub>	24.08	0.48	–4.78	0.89
First antidiabetic treatment		0.0008		0.0001
Sulfonylureas	–4.82		–0.74	
Metformin	4.41		13.74	
Metformin+sulfonylurea	2.18		16.56	
Insulin	–9.15		–14.88	
Diet alone	0		0	
Slope of weight curve ( <i>s</i> )	–12.96	0.0006	–17.83	0.0001
<i>s</i> ×Age		0.30		0.95
40–64 years	–1.52		–0.10	
65+ years	0		0	
<i>s</i> ×HbA <sub>1c</sub>	9.73	0.040	1.68	0.76
<i>s</i> ×First antidiabetic treatment		0.0001		0.0001
Sulfonylureas	11.80		12.45	
Metformin	8.46		8.38	
Metformin+sulfonylurea	12.64		14.46	
Insulin	13.70		13.90	
Diet alone	0		0	
Change in slope after 5 months ( <i>c</i> <sub>5</sub> )	12.05	0.003	17.54	0.0001
<i>c</i> <sub>5</sub> ×Age		0.18		0.87
40–64 years	2.08		0.26	
65+ years	0		0	
<i>c</i> <sub>5</sub> ×First antidiabetic treatment		0.0001		0.0001
Sulfonylureas	–12.02		–12.00	
Metformin	–9.36		–8.13	
Metformin+sulfonylurea	–13.64		–16.59	
Insulin	–12.45		–17.23	
Diet alone	0		0	
Change in slope at initiation of first antidiabetic pharmacological treatment ( <i>c</i> <sub>A</sub> )	–0.98	0.36	–0.84	0.17
<i>c</i> <sub>A</sub> ×Age		0.22		0.48
40–64 years	0.78		0.37	
65+ years	0		0	
<i>c</i> <sub>A</sub> ×First antidiabetic treatment		0.91		0.16
Sulfonylureas	0		0	
Metformin	0.46		–0.02	
Metformin+sulfonylurea	0.45		2.38	
Insulin	–0.95		4.81	
Diet alone	0		0	

Data are explanatory variables for the mean in the full model. Age and HbA<sub>1c</sub> are as measured at diabetes diagnosis

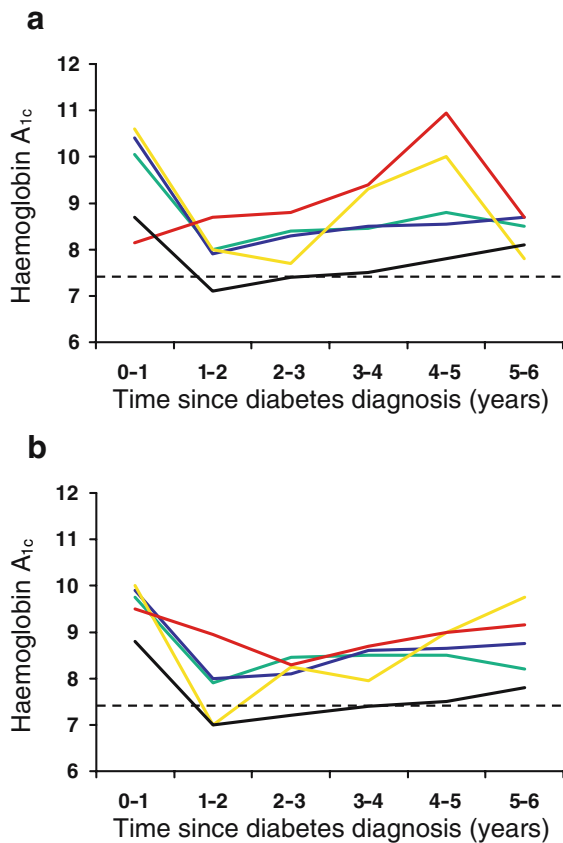
<sup>a</sup>Wald test based on restricted maximum likelihood estimation

study thus seems comparable with that of the intervention arm of UKPDS, even though the median plasma glucose concentration at presentation in our study was 13.8 mmol/l [19] compared with 11.3 mmol/l in UKPDS [28].

#### Weight loss due to successful treatment

Promoting long-term weight loss in type 2 diabetic patients is difficult [29, 30]. Even in successful intensive behaviour-

modification programmes a pattern of weight regain is the predominant outcome [31, 32], and diabetic patients demonstrate even poorer weight loss maintenance than their non-diabetic peers [33]. However, one early study of diet counselling to newly diagnosed diabetic patients showed that a weight loss of 9 kg was maintained over 6 years [34]. Although it is tempting to ascribe the benign weight course in our study to the treatment model, there is no evidence to suggest that primary-care practitioners in general have



**Fig. 4** The course of HbA<sub>1c</sub> from the time of diagnosis according to sex and first antidiabetic pharmacological treatment, sulfonylureas (blue), metformin (green), metformin and sulfonylurea (yellow), insulin (red), or diet alone (black). **a** Males. **b** Females. Values are medians. The upper limit of the reference range of HbA<sub>1c</sub> (5.4–7.4%) is indicated by the horizontal dotted line

special competence in obtaining weight loss among their patients [35, 36]. But general practitioners may be more likely to give weight-control advice to their diabetic patients than to patients who are obese but without risk factors [37].

In the present study, doctors largely followed the recommendations given to them, supplying metformin to the most obese patients and sulfonylureas to patients with lower bodyweight (Fig. 2). In contrast to other experimental studies [9, 10, 16], we observed no change in the course of weight after initiation of sulfonylurea treatment (Table 3). Weight loss is a common concomitant of the onset of metformin treatment [9, 10, 16], a finding which we cannot confirm either (Table 3). These results were possibly affected by the doctors' considerations about who would benefit from which drug treatment in our individualised treatment model. Our study shows the average weight development for patients selected in daily practice to be treated with diet alone, oral agents or insulin. The factors influencing this treatment choice, besides age, sex and HbA<sub>1c</sub>, are unclarified in our analyses. At the yearly seminars the intervention doctors were repeatedly encour-

aged to increase the dose of oral agents to the maximum if needed. Nevertheless the observed doses were low compared with other studies. It is possible that the general practitioners in our study unwittingly found a better balance between the dosage of sulfonylurea and its side-effects, e.g. weight gain. A more aggressive high-dose treatment would probably have resulted in a steeper increase in bodyweight, as was observed in UKPDS. Whether such a treatment model would have given better glycaemic control than our individualised model is an open question.

#### Weight loss and the natural history of type 2 diabetes

The well-defined background population in each general practice, the unchanged inclusion activity during the inclusion period and the small number of exclusions all suggest that our patients are representative of the general population of newly diagnosed diabetic patients in this age group in Denmark. Furthermore, 6 years after diagnosis, only 17% of the surviving patients had ever been treated at a diabetes clinic [19]. The high average age in the present study in comparison with UKPDS may primarily be ascribed to differences in inclusion criteria for age (25–65 years inclusive in UKPDS and 40 years or over in the present study).

In contrast to the belief that few individuals succeed in maintaining long-term weight loss, a relatively large proportion of the general population experience weight losses and maintain these for at least 1 year [38]. Although it is unclear whether the prevalence and maintenance of successful weight loss are higher in the general community than in the research clinic [20], we wish to propose that our study reflects treatment results obtained in the general population of type 2 diabetic patients rarely treated in secondary care and rarely participants in clinical trials.

#### Further study limitations

We make full use of the longitudinal structure of data, and our statistical model provides a visualisation of the changes in weight (Fig. 2), which confirms and extends our cross-sectional analysis of surviving patients from the 5-year follow-up examination (Table 2). We did not, however, include HbA<sub>1c</sub> measurements from the follow-up period as such a model would be difficult to interpret because of the unclarified causal relationships mentioned above.

In the present study, data come from the intervention group of a randomised trial, but it is unlikely that the observed weight changes are a result of the specific intervention tested in this study. Firstly, the comparison group had experienced the same average weight loss as the intervention group at the final 6-year follow-up examination [19]. Secondly, treatment with diet alone was equally



common in the intervention and comparison groups, and metformin was the only drug used more frequently in the intervention group (24 vs 15%) [19]. The median value of HbA<sub>1c</sub> at 6-year follow-up, however, was lower for intervention patients than for comparison patients (8.0 vs 8.5%).

### Conclusions and implications

We had two major findings in this group of diabetic patients observed for 5 years after diabetes diagnosis: (1) a sustained weight loss was common and patients with a pronounced weight loss were often treated with metformin or diet alone, and (2) there was no evidence of a change in course of weight on initiation of treatment with any antidiabetic medication, including sulfonylureas, even though acceptable glycaemic control was achieved. The study was conducted in a clinical setting allowing doctors to select patients for specific antidiabetic treatments according to the development of the disease, the recommendations of clinical guidelines, and patient preferences. However, specific reasons for the weight loss cannot be deduced from our observational study. The important message for doctors and patients is that weight reduction is a practicable treatment in newly diagnosed diabetic patients even when patients are given sulfonylureas.

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