Factors associated with insulin-induced weight gain in an Australian type 2 diabetes outpatient clinic.

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Novelty Statements

- Insulin-induced weight gain does not correlate with cardiovascular risk
- Short-acting insulin is associated with weight gain
- Weight gain was less common in people receiving oral agents in combination with insulin

Keywords: Insulin-induced weight gain, type 2 diabetes, obesity

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Abstract

Background

Insulin-induced weight gain is a key concern for people with type 2 diabetes (T2D) and their treatment team. This study aimed to document the prevalence of insulin-induced weight gain and its impact on cardiovascular risk factors in patients attending the Royal Melbourne Hospital diabetes clinic.

Method

Clinical and biochemical data were extracted from a prospective clinic database and from the hospital record. These variables were correlated to the percentage weight change one year after starting insulin and compared between groups with or without clinically significant weight gain, defined as more than 7% of the baseline body weight.

Results

The population comprised 340 patients (184 male), representing 36% of people with T2D who commenced insulin at our clinic. Their mean±SD age and duration of diabetes was 63±11 and 13±8 years respectively. The mean (95% CI) change in body weight at one year was 3.0 (2.5 to 3.5) kg, but this was not associated with deleterious changes in blood pressure or lipid profile. Weight gain was associated with higher insulin doses, the use of short-acting insulin and with lower baseline body weight. Clinically significant weight gain occurred in 87 patients and was associated with glucose-lowering regimens that included short-acting insulin or a thiazolidinedione, whereas regimens that incorporated other oral agents, particularly sulfonylureas, were associated with less weight gain.

Conclusions

In this Australian tertiary hospital population with T2D, insulin-induced weight gain was common but was not associated with deleterious changes in blood pressure or lipids. Treatment regimens that avoid short-acting insulin but include oral agents other than thiazolidinediones might prevent insulin-induced weight gain in T2D.

Study registered as ACTRN12615000462583

Introduction

Insulin therapy for type 2 diabetes (T2D) is associated with weight gain of between 2 and 7 kilograms during the first year (1-3). Fear of weight gain by both patients and their clinicians can delay initiation of insulin (4). This is despite the efficacy and safety of insulin in patients with suboptimal glucose control (3) and the observation that insulin-induced weight gain is not associated with increased risk of cardiovascular disease (5, 6). Prior studies report insulin-induced weight gain is associated with lower body mass index (1, 7, 8) and higher HbA1c (1, 7-9) and insulin dose (1, 9), and to be more common in people using short-acting (prandial) insulin (3). These risk factors differ between health care settings and patient populations, which may explain geographical differences in insulin-induced weight gain (1).

Studies describing factors associated with insulin-induced weight gain in Australians have not been reported. This study aimed to determine the extent of this problem in an Australian tertiary hospital diabetes clinic using 'real-life' data collected during the course of clinical care. Clinical characteristics associated with substantial weight gain were then determined to gain insight into its impact on cardiovascular risk, its potential causes and how it might be prevented.

Methods

Patients and data

We studied all patients who attended Royal Melbourne Hospital outpatient diabetes clinic between May 1998 and January 2015. Inclusion criteria were type 2 diabetes, first use of insulin after the first clinic visit, and weight measurements available for both the baseline (-180 to +30 days after starting insulin) and one-year (+335 to +548 days after starting insulin) time points. Insulin dosing data were not available for 2 participants included in the study.

Patient weight was measured using scales within each consulting room entered together with other clinical data by the attending endocrinologist. In-house pathology data were automatically downloaded from the hospital pathology service. The majority of the pathology tests were performed outside the hospital and their results, where available, were sourced from the hospital file. The study was approved by the Melbourne Health Human Research Ethics Committee and registered with the Australian New Zealand Clinical Trials Registry as study ACTRN12615000462583.

Data analyses

The averaged insulin dose per day was calculated as the area under the trapezoidal dose/time curve divided by time in days. Missing data for analyses of weight, HbA1c and insulin dose over time were imputed by averaging values either side of the missing time point.

Statistical analyses were performed using Prism 6 for Mac (v6.0g) software (GraphPad, CA). Categorical data were compared using Fisher's exact test. Although continuous data were generally not normally distributed according to Shapiro-wilk test, they were reported as mean±SD and compared using Student's *t* test. Supplemental Table 1 provides data presented as median [Q1, Q3] with p-values from a Wilcoxon matched-pairs signed rank test. The significance threshold for correlation analyses, performed using the method of Spearman, were corrected for multiple comparisons using the Bonferroni method. Multiple regression analysis was performed using R software

(*www.**r**-project.org*) and the *lm* function. A p-value of less than 0.05 was considered significant.

Results

Cohort selection is shown in Figure 1. Of 4335 patients treated for type 2 diabetes, 957 initiated insulin treatment after their first visit to the clinic. Of these, 340 (184 males, 156 females) had weight data at insulin initiation and one year afterwards. Their mean±SD age and duration of diabetes when started on insulin therapy was 63±11 and 13±8 years respectively and they visited clinic 4.3±2.3 times over the year after starting insulin. Around half the cohort (75 out of 165 with available data) had baseline albuminuria. Eighty-nine patients (26%) used insulin alone without additional glucose-lowering drugs. Of the remaining 251, 242 (71% of the study cohort) used metformin and/or a sulphonylurea drug. The regimens of 19, 11, 3 and 1 patients included a thiazolidinedione, acarbose, DPP4 antagonist and exenatide respectively. The insulin regimen comprised premixed insulin, long-acting insulin alone or the combination of long- and short-acting (basal-bolus) insulin in 210 (62%), 105 (31%) and 25 (7%) patients respectively. No patients were recorded as receiving anti-psychotic medication and none commenced oral glucocorticoid during the year after they started insulin.

The mean weight gain at one year of 3kg was associated with a decrease in mean HbA1c from 9.4 to 8.1% (79 to 65mmol/mol). Blood pressure and lipid values did not change significantly over the year whereas serum creatinine concentration increased by 5µmol/l (Table 1). The distribution of weight gain is presented in Figure 2. One hundred and thirty-four (39%) participants gained more than 5% body weight, of whom 42 (12%) gained more than 10% of their baseline body weight.

Correlation analyses were performed between percent weight gain at one year and all available clinical and biochemical variables. Percent weight gain correlated significantly with initial and averaged insulin dose/kg ($R=0.35$; $p<0.0001$ and $R=0.30$; $p<0.0001$ respectively), baseline weight and body mass index ($R= -0.22$; $p<0.0001$ and $R= -0.19$; $p=0.0038$ respectively), and with treatment regimens that included short-acting insulin (ie pre-mixed or basal-bolus regimens; $R=0.17$; $p=0.0019$). Weight gain also correlated

inversely with the insulin start date, albeit at borderline statistical significance (R=-0.12; p=0.0318). Weight gain did not correlate with baseline HbA1c or any of the other variables. Multiple regression analysis using initial insulin dose/kg, initial weight, insulin regimen and insulin start date as inputs confirmed all but insulin start date were independently associated with weight gain at one year, although together they explained only 10% of its variance.

We then compared the characteristics of 87 patients who experienced clinically significant weight gain of more than 7% of the baseline value. The 7% threshold was chosen based on our clinical experience and on a prior study of weight gain and type 2 diabetes in patients treated with anti-psychotic medication (10). Figure 2 shows the mean weight, HbA1c and insulin doses over time for people gained more than 7% body weight (so-called 'Gainers') alongside the corresponding values from 253 'Non-gainers'. Weight gain was progressive and linear in Gainer group whereas the Non-gainers showed minimal weight change from a higher baseline value. The initial insulin dose was lower and it increased more over the first six months in Non-gainers compared to Gainers (mean±SD change 0.14±0.22 v 0.07±0.26 units/kg respectively; p=0.0138). The profiles of mean HbA1c of both groups were similar, decreasing abruptly in the first six month and then plateauing. Although the baseline HbA1c and the overall reduction in mean HbA1c over 12 months was greater in Gainers compared to Non-gainers, these differences were not statistically significant. When compared to Non-gainers, a higher proportion of Gainers were treated with short-acting insulin (80 v 60%, p=0.0074), thiazolidinediones (10% v 4%, p=0.0323) and insulin alone without additional oral agents other than thiazolidinediones (38% v 24%, p=0.0197). Non-gainers were more likely than Gainers to use a sulphonylurea in combination with insulin (45% v 30%, p=0.0165) but the proportion of patients using metformin was similar in each group (61% v 52%, p=0.1306). These differences between Gainers and Non-gainers were also observed when a 5% weight gain threshold was used (data not shown). Blood pressure and lipid measures did not change significantly in the Gainer group whereas Non-gainers experienced a significant mean reduction in systolic blood pressure of 3mmHg (Supplemental Table 2).

Discussion

This analysis of 'real life' data from an Australian hospital diabetes clinic accords with prior studies showing insulin-induced weight gain in patients with type 2 diabetes occurs frequently and is more common in those with a relatively low body weight who have a higher HbA1c and receive higher doses of insulin (1, 7-9). Our finding that weight gain is more common with regimens that include short-acting insulin is consistent with the findings of the *Treat to Target* randomised trial of different insulin regimens in type 2 diabetes (3) but was not observed in other observational studies (1, 7). The association between weight gain and concurrent thiazolidinedione therapy is an expected finding (11-13) and the protective effect of combined treatment with insulin and sulfonylurea compared to insulin alone has been described previously (8, 14).

In the overall group, the rate of weight gain was constant over the year and clearly higher in those who gained the most weight. This pattern of weight gain raises the possibility that it might continue beyond a year, although this seems unlikely given the 3-year outcomes of the *Treat to Target* trial, which reported minimal weight gain beyond the first year (15).

Although at times substantial, weight gain after a year of insulin therapy was not associated with adverse changes in blood pressure or lipid measures. This accords with the prevailing view, based on the UKPDS trial (6), that insulin-induced weight gain carries no increased risk of cardiovascular disease. It also raises the possibility that the weight gain over the first year of insulin therapy is due to restoration of fluid and electrolyte deficits caused by hyperglycaemia rather than accretion of visceral fat due to the anabolic effects of insulin. This possibility is suggested by an Israeli longitudinal study of type 2 diabetes outpatients, who were noted to lose weight in the period leading up to insulin therapy and then regain this weight after starting insulin (8). However, studies of changes in body composition before and after insulin therapy for type 2 diabetes suggest increases in both lean body mass and fat mass contribute to weight gain (16, 17). The introduction of body composition measures into our clinic could help clarify this issue.

How might we better predict insulin-induced weight gain in patients with type 2 diabetes? Our finding that baseline insulin dose, body weight and insulin regimen only accounted for 10% of the weight gain variance indicates that these variables alone are unsuitable prognostic markers. Diabetes distress, measured by questionnaire, is another potential risk factor that was recently shown to correlate with insulin-induced weight gain (9). However, again, the strength of this correlation was weak, arguing against the utility of diabetes distress as a prognostic marker. The identification of robust predictors of insulin-induced weight gain is likely to require prospective research of larger cohorts in which change in body weight is the primary outcome.

Our analysis of treatment regimens suggest insulin-induced weight gain might be prevented by more liberal use of oral agents other than thiazolidinediones in combination with insulin, and less frequent use of short-acting insulin. In addition, the patterns of insulin dosing and HbA1c reductions in Gainers and Non-gainers, which show that Gainers received higher initial doses of insulin and, as in a prior Dutch study (9), achieved greater reductions in HbA1c at 1 year, suggest weight gain might be averted by lower initial insulin doses and a dose-escalation strategy that incorporates more gradual reduction in HbA1c. Other prevention strategies worth considering given outcomes of recent randomised trials include dietary counselling (18), SGLT2 inhibitors (19) and GLP-1 analogues (20, 21). The recent addition of dapaglifozin to the Australian Pharmaceuticals Benefits Scheme will provide an opportunity to assess the impact of SGLT2 inhibitors on insulin-induced weight gain in our clinic population.

Our study has several limitations borne of the fact that it is based on ‘real life’ data capture by busy clinicians. The large number of patients with missing weight data dramatically decreased the sample size, reducing our ability to detect factors associated with weight gain. Furthermore, if other missing measures such as waist circumference, dietary therapy, frequency of hypoglycaemia and liver tests were available, we may have identified additional factors associated with weight gain. In addition, the absence of reliable data on antihypertensive drug treatment qualifies our conclusion that insulin-

induced weight gain did not affect blood pressure, and the relatively long period of 3 months between reviews at our clinic may have increased the risk of insulin-induced weight gain. Finally, because these data were collated at a time when very few insulin-sparing therapies such as GLP-1 analogues and SGLT2 inhibitors were available, we cannot assume similar degrees of weight gain will be observed in more contemporary cohorts.

In summary, we found that the majority of patients with type 2 diabetes in our hospital outpatient clinic experienced weight gain after they commenced insulin but that this was not associated with deterioration of blood pressure or lipid measures. The association of weight gain with insulin monotherapy, with regimens that include short-acting insulin and with relatively abrupt lowering of HbA1c suggests weight gain might be prevented by a combination of oral agents with long-acting insulin that is titrated to achieve a more gradual reduction in HbA1c.

Author Contributions

The study was conceived by JMW. Data were collated by RYY, PGC, SF and JMW and analysed by RYY and JMW. JMW drafted the manuscript and RYY, PGC and SF reviewed and edited it.

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Table 1: Weight, blood pressure and lipid parameters at baseline and one year after starting insulin therapy

	N	Baseline	One year	Difference (95% CI)	P
Weight (kg)	340	81.9±18.3	84.9±18.4	3.0 (2.5 to 3.5)	<0.0001
Body mass index (kg/m^2)	226	30.7±6.4	31.8±6.4	1.1 (0.9 to 1.3)	<0.0001
HbA1c (%)	238	9.3±1.5	8.1±1.3	-1.2 (-1.5 to -1.0)	<0.0001
HbA1c (mmol/mol)	233	79±17	65±16	-13 (-16 to -11)	<0.0001
Systolic blood pressure (mmHg)	329	138±19	136±18	-2 (-4 to 0)	0.0614
Diastolic Blood pressure (mmHg)	329	77±10	76±9	-1 (-3 to 0)	0.0342
Total cholesterol (mmol/l)	170	4.6±1.2	4.5±1.2	-0.1 (-0.2 to 0.1)	0.3189
HDL cholesterol (mmol/l)	170	1.12±0.36	1.12±0.31	0.00 (-0.04 to 0.04)	0.9953
Calculated LDL cholesterol (mmol/l)	165	2.4±1.0	2.4±1.0	0.0 (-0.1 to 0.1)	0.8387
Triglycerides (mmol/l)	170	2.5±2.1	2.2±1.4	-0.27 (-0.54 to 0.01)	0.0568
Creatinine (µmol/l)*	188	93.3±29.4	98.2±33.5	4.9 (2.5 to 7.4)	0.0001
eGFR (%)	188	74±26	71±27	-3 (-5 to -1)	0.0076

The number (N) of participants with paired data for each variable is indicated

Data are mean±SD and mean of differences (95% CI)

* excluding 5 patients with end-stage renal failure

Supplemental Table 1: Weight, blood pressure and lipid parameters at baseline and one year after starting insulin therapy expressed as median [Q1,Q3]

	N	Baseline	One year	P
Weight (kg)	340	79 [69, 93]	83 [71, 95]	<0.0001
Body mass index (kg/m^2)	226	29.7 [26.7, 33.4]	30.7 [27.6, 35.0]	<0.0001
HbA1c (%)	238	9.0 [8.3, 10.1]	7.9 [7.2, 8.7]	<0.0001
Systolic blood pressure (mmHg)	329	140 [128, 150]	130 [123, 149]	0.1581
Diastolic Blood pressure (mmHg)	329	80 [70, 80]	80 [70, 80]	0.0061
Total cholesterol (mmol/l)	170	4.4 [3.9, 5.2]	4.3 [3.6, 5.1]	0.5791
HDL cholesterol (mmol/l)	170	1.08 [0.88, 1.25]	1.06 [0.90, 1.30]	0.3025
Calculated LDL cholesterol (mmol/l)	165	2.3 [1.7, 3.0]	2.2 [1.7, 2.8]	0.9161
Triglycerides (mmol/l)	170	1.9 [1.4, 2.9]	1.8 [1.2, 2,8]	0.0671
Creatinine (mmol/l)*	188	90 [70, 110]	90 [72, 120]	0.0001
eGFR (%)	188	70 [56, 87]	68 [52, 85]	0.0019

The number (N) of participants with paired data for each variable is indicated

P-value was determined using the Mann-Whitney *U* test

Supplemental Table 2: Clinical characteristics at baseline and one year according to weight gain status

	Non-gainer (<7% weight gain at 1yr)					Gainer (>7% weight gain at 1yr)				
	N	**Baseline**	**One year**	**Difference (95% CI)**	**P**	**N**	**Baseline**	**One year**	**Difference (95% CI)**	**P**
Weight (kg)	253	83.3±18.2	84.5±17.9	1.1 (0.7 to 1.5)	<0.0001	87	77.8±18.2	86.4±19.7	8.6 (7.8 to 9.3)	<0.0001
Body mass index (kg/m2)	170	31.1±6.5	31.5±6.4	0.4 (0.2 to 0.6)	<0.0001	56	29.3±5.9	32.5±6.4	3.2 (2.9 to 3.5)	<0.0001
HbA1c (%)	174	9.3±1.4	8.2±1.5	-1.1 (-1.4 to -0.8)	<0.0001	59	9.6±2.0	7.9±1.3	-1.6 (-2.2 to -1.1)	<0.0001
Systolic blood pressure (mmHg)	246	139±19	135±18	-3 (-6 to -1)	0.0097	83	134±19	136±16	2 (-3 to 6)	0.4619
Diastolic Blood pressure (mmHg)	246	77±10	75±10	-2 (-3 to 0)	0.0445	83	77±8	77±8	-1 (-3 to 1)	0.4823
Total cholesterol (mmol/l)	120	4.5±1.2	4.4±1.2	0.0 (-0.2 to 0.1)	0.5887	50	4.7±1.2	4.6±1.2	-0.1 (-0.4 to 0.1)	0.2746
HDL cholesterol (mmol/l)	120	1.06±0.27	1.08±0.26	0.02 (-0.02 to 0.05)	0.3210	50	1.26±0.49	1.21±0.38	-0.04 (-0.15 to 0.06)	0.3955
Calculated LDL cholesterol (mmol/l)	114	2.3±0.9	2.4±1.0	0.0 (-0.1 to 0.1)	0.9287	50	2.5±1.1	2.5±0.9	-0.1 (-0.3 to 0.2)	0.6093
Triglycerides (mmol/l)	120	2.6±2.3	2.3±1.4	-0.3 (-0.7 to 0.0)	0.0781	50	2.2±1.4	2.1±1.3	-0.1 (-0.5 to 0.2)	0.4764
Creatinine (mmol/l)	137	93±29	97±33	4 (1 to 7)	0.0076	51	94±29	102±36	7 (3 to 12)	0.0026
eGFR	137	74±25	72±26	-2 (-4 to 0)	0.1059	51	74±31	69±29	-5 (-9 to -1)	0.0152

The number (N) of participants with paired data for each variable is indicated

Data are mean±SD and mean difference (95% CI)

Figure 1: Patient flow diagram

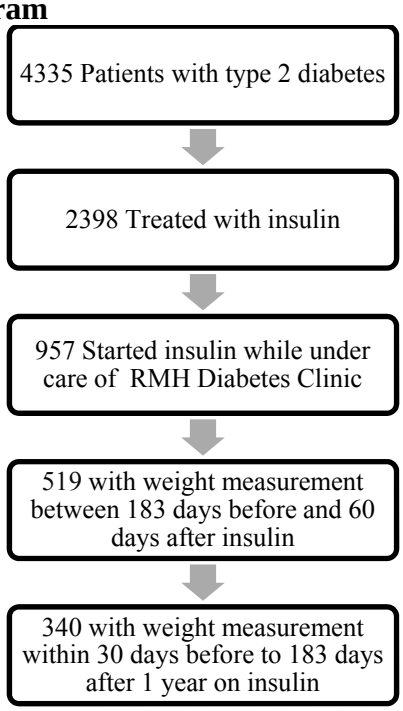


Figure 2: Distribution of weight change one year after starting insulin

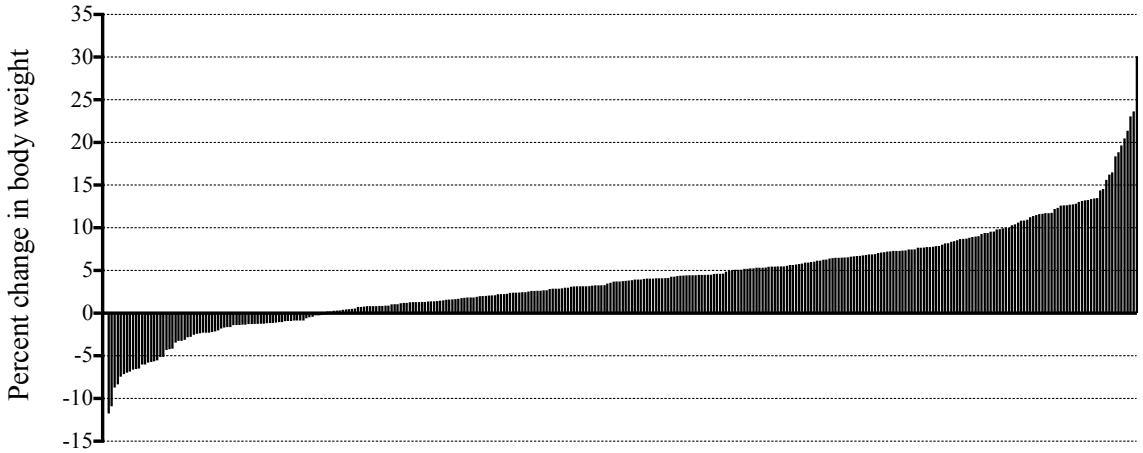
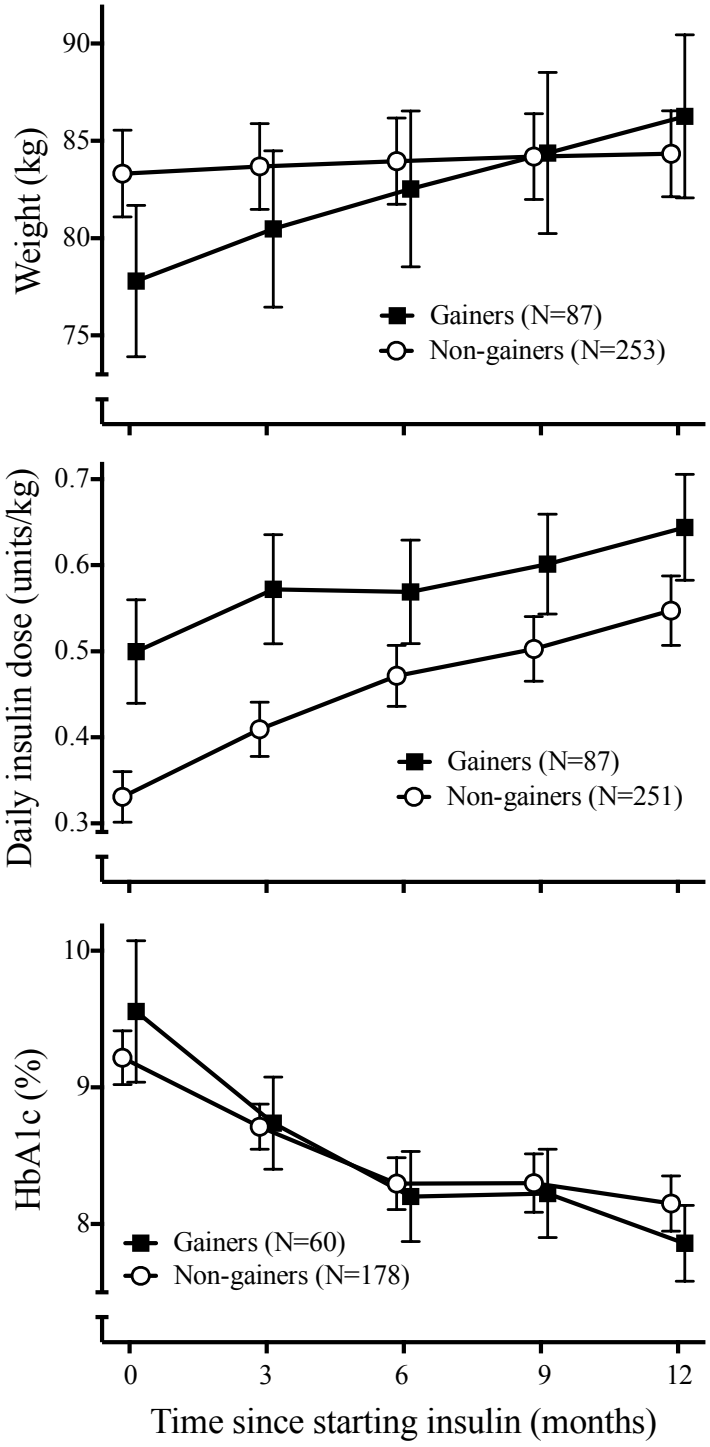


Figure 3: Progressive weight, insulin dose and HbA1c during the first year of insulin therapy

Data are mean±95%CI



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