

WEIGHT GAIN WITH INSULIN THERAPY IN TYPE 2 DIABETES PATIENTS FAILING ORAL ANTIDIABETIC DRUGS

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Abstract

Type 2 diabetes mellitus is a disease with progressive beta-cell decline and most patients will require insulin therapy to control their glycemic homeostasis. The aims of this study is to estimate the weight gain associated with insulin therapy in type 2 diabetes patients failing oral antidiabetic drugs. We retrospectively evaluated 58 patients, 36 women (62.06%) and 22 men (37.93%), with type 2 diabetes who required insulin for poor metabolic control, despite dietary measures and maximal-dose oral agents. The subjects were between 47 and 71 years. 25 patients required analog insulin and 33 patients biosynthetic human insulin. The insulin regimes were conventional treatment (basal insulin, premixed insulin-11 patients in treatment with analog insulin, and 15 patients with biosynthetic human insulin) or intensive-treatment (basal/bolus insulin-14 patients in treatment with analog insulin and 18 patients with biosynthetic human insulin). The following parameters were determined at the beginning of the study, and were monitored over 5 years of insulinotherapy: weight, glycosylated hemoglobin (HbA1c), insulin requirement and types of insulin. Mean age at the diagnosis of diabetes was 50.16 ± 5.39 years (range 38-62 years) and mean age at insulin introduction was 55.80 ± 6.16 years (range 42-71 years). Mean weight at insulin introduction was 71.00 ± 9.50 kg (range 58-101 kg), after 1 year 73.92 ± 9.47 kg (range 63-105 kg) and after 5 years 76.71 ± 9.71 kg (range 67-107 kg). The mean baseline levels of HbA1c was $9.61 \pm 0.80\%$ and after 5 years of insulin therapy $8.02 \pm 0.44\%$. The mean weight gain in the study group after 1 year from started insulin was 2.86 ± 0.86 kg and after 5 years 6.08 ± 1.59 kg. The weight gain was directly correlated with the insulin dose. Weight gain was significantly greater in the intensive-treatment group compared with the conventional-treatment group.

key words: type 2 diabetes mellitus, insulin therapy, weight gain.

Introduction

Type 2 diabetes mellitus is characterized by insulin resistance, progressive beta-cell function decline and increased of gluconeogenesis in the liver. At the time of clinical diagnosis, patients with type 2 diabetes mellitus have lost, 50% of their beta-cell function and beta-cell function tends to decline over time [1]. United Kingdom Prospective Diabetes Study (UKPDS), reveal that patients with type 2 diabetes mellitus lost about 4% of their beta-cell function per year [2]. Type 2 diabetes mellitus is a disease with progressive beta-cell decline and most patients will require insulin therapy to control their glycemic homeostasis. According to the consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes, patients experiencing poor glycaemic control with lifestyle interventions and oral antidiabetic drugs should intensify their treatment with the addition of insulin [3]. Insulin is effective in lowering hyperglycaemia; its disadvantage remains its potential to induce weight gain and hypoglycaemia. There are several proposed theories for weight gain associated with insulin therapy: decreased glycosuria due to improved glycemic control, the anabolic effects of insulin, decreased metabolic rate, treatment of hypoglycemia, or eating to prevent hypoglycemia or deal with the fear of hypoglycemia [4].

Strategies to limit insulin-mediated weight gain include: life style changes, the use of combination therapy-continuation of metformin after adding insulin reduce dose of insulin needed to achieve glycemic goal, the use of analog insulin [5, 6, 7].

The aims of this study is to estimate the weight gain associated with insulin therapy in type 2 diabetes patients failing oral antidiabetic drugs.

Material and Methods

We retrospectively evaluated 58 patients, 36 women (62.06%) and 22 men (37.93%), with type 2 diabetes who required insulin for poor metabolic control, despite dietary measures and maximal-dose oral agents. The subjects were aged between 47 and 71 years. 25 patients required analog insulin and 33 patients biosynthetic human insulin.

The insulin regimes were conventional-treatment (basal insulin, premixed insulin-11 patients in treatment with analog insulin and 15 patients with biosynthetic human insulin) or intensive-treatment (basal/bolus insulin-14 patients in treatment with analog insulin and 18 patients with biosynthetic human insulin). The following parameters were determined at the beginning of the study, and were monitored over 5 years of insulinotherapy: weight, glycosylated hemoglobin (HbA1c), insulin requirement and types of insulin.

Statistical analyses

Data are presented as mean $\pm$ SD. Clinical characteristics were compared using the t Student Test. Pearson's moment-product correlation coefficients were calculated to evaluate relationships between variables. Significance was defined at the 0.05 level of confidence. All calculations were performed using the Statistical Package for Social Sciences (SPSS) version 15.

Results

The subjects were between 47 and 71 years, mean age $\pm$ SD 60.80 ± 6.16 years. Mean age at diagnosis of diabetes was 50.16 ± 5.39 years (range 38-62 years) and mean age at insulin introduction was 55.80 ± 6.16 years (range 42-71 years). Mean weight at insulin introduction was 71.00 ± 9.50 kg (range 58-101 kg), after 1 year 73.92 ± 9.47 kg (range

63-105 kg) and after 5 years 76.71 ± 9.71 kg (range 67-107 kg). The mean baseline levels of HbA_{1c} was $9.61 \pm 0.80\%$ and after 5 years of insulin therapy $8.02 \pm 0.44\%$.

There were statistically significant differences in the recorded parameters in patients in treatment with analog insulin compared with patients in treatment with biosynthetic human insulin. The differences of the study group are show in Table 1.

Table 1. Characteristics of patients in treatment with analog insulin compared with patients in treatment with human insulin.

	Characteristics of patients in treatment with analog insulin	Characteristics of patients in treatment with biosynthetic human insulin	P
Mean age (years)	58.48 ± 5.68	62.50 ± 6.01	0.005
Mean age at diagnosis of diabetes (years)	48.96 ± 5.44	51.82 ± 5.10	0.022
Mean age at insulin initiation (years)	53.48 ± 5.68	55.50 ± 6.02	0.006
Mean weight at insulin initiation (kg)	75.68 ± 11.41	67.56 ± 5.92	0.001
Mean weight after 1 year of insulin initiation (kg)	78.76 ± 11.24	70.35 ± 5.90	0.0008
Mean weight after 5 year of insulin initiation (kg)	81.04 ± 11.07	73.53 ± 7.21	0.002
Baseline levels of HbA _{1c} (%)	9.95 ± 0.80	9.37 ± 0.71	0.003
Levels of HbA _{1c} after 5 year of insulin initiation (%)	8.03 ± 0.55	8.01 ± 0.35	NS
Dose of insulin	37.12 ± 14.80	37.68 ± 17.05	NS

Table 2. Characteristics of patients in treatment with analog insulin

	Characteristics of patients in conventional treatment with analog insulin	Characteristics of patients in intensive treatment with analog insulin.	P
Mean age (years)	57.64 ± 6.86	59.14 ± 4.72	NS
Mean age at diagnosis of diabetes (years)	47.00 ± 6.13	50.50 ± 4.45	NS
Mean age at insulin initiation (years)	52.64 ± 6.86	54.14 ± 4.72	NS
Mean weight at insulin initiation (kg)	83.09 ± 11.32	69.86 ± 7.66	0.002
Mean weight after 1 year of insulin initiation (kg)	85.09 ± 11.60	73.43 ± 7.76	0.004
Mean weight after 5 year of insulin initiation (kg)	87.36 ± 11.72	76.07 ± 7.75	0.006
Baseline levels of HbA _{1c} (%)	10.02 ± 0.86	9.89 ± 0.78	NS
Levels of HbA _{1c} after 5 year of insulin initiation (%)	8.29 ± 0.52	7.83 ± 0.49	0.017
Dose of insulin	23.45 ± 6.07	47.86 ± 9.69	0.0001

11 patients in treatment with analog insulin followed conventional-therapy (basal insulin, premixed insulin) and 14 intensive-treatment (basal/bolus). The characteristics of the patients in conventional treatment with analog insulin compared with patients in intensive-treatment with analog insulin are shown in Table 2.

33 patients received therapy with human insulin: 15 patients conventional-treatment (basal insulin, premixed insulin) and 18 intensive-treatment (basal/bolus). The characteristics of patients in treatment with human insulin were are show in Table 3.

Table 3. Characteristics of patients in treatment with human insulin

	Characteristics of patients in conventional treatment with human insulin	Characteristics of patients in intensive treatment with human insulin.	P
Mean age (years)	62.53 ± 7.82	62.47 ± 4.33	NS
Mean age at diagnosis of diabetes (years)	52.73 ± 6.68	51.11 ± 3.43	NS
Mean age at insulin initiation (years)	57.53 ± 7.82	57.47 ± 4.34	NS
Mean weight at insulin initiation (kg)	68.00 ± 6.36	67.21 ± 5.70	NS
Mean weight after 1 year of insulin initiation (kg)	70.67 ± 6.33	70.11 ± 5.70	NS
Mean weight after 5 year of insulin initiation (kg)	71.93 ± 8.56	74.79 ± 5.86	0.0001
Baseline levels of HbA _{1c} (%)	9.26 ± 0.74	9.45 ± 0.69	NS
Levels of HbA _{1c} after 5 year of insulin initiation (%)	8.03 ± 0.39	7.98 ± 0.33	NS
Dose of insulin	20.53 ± 3.66	51.21 ± 9.19	0.0001

Discussion

The mean weight gain in study group after 1 year of started insulin was 2.86 ± 0.86 kg and after 5 years 6.08 ± 1.59 kg. The weight gain was directly correlated with the insulin dose: $r = 0.528$, $p < 0.0001$ for weight gain correlation with insulin dose after 1 year of treatment, $r = 0.802$, $p < 0.0001$ for weight gain correlation with insulin dose after 5 years of treatment. Weight gain was significantly greater after 5 years in the human insulin treatment group compared with the analog insulin treatment group (6.59 ± 1.40 kg versus 5.40 ± 1.60 kg, $p = 0.002$) but not after 1 years. Weight gain was significantly greater in the

intensive-treatment group compared with the conventional-treatment group. The mean weight gain in patients with intensive-treatment with analog insulin after 1 year was 3.43 ± 1.09 kg and in patients with conventional treatment with analog insulin after 1 year was 2.45 ± 0.93 kg ($p = 0.012$). After 5 years the mean weight gain in patients with intensive-treatment was 6.21 ± 1.58 kg and in patients with conventional treatment was 4.36 ± 0.92 kg ($p = 0.0001$). In patients in treatment with human insulin the mean weight gain after 1 year from started insulin was similar in intensive-treatment group compared with the conventional-treatment group (2.84 ± 0.50 kg versus 2.67 ± 0.75 kg) but statistically

significant greater after 5 years (7.58 ± 0.69 kg versus 5.33 ± 0.98 kg, $p = 0.0001$).

The mean weight increase over a 5 years period, but the maximum increment (2.68 ± 0.86 kg) being noted in the first year of insulin therapy. In another studies, patients gained the most weight in the shortest period of time [2, 8].

Our results are consistent with several, large, prospective studies that have reported the association between the insulin therapy and weight gain [2, 5, 6, 7]. In the United Kingdom Prospective Diabetes Study (UKPDS), the patients gained weight over the study; weight gain was significantly greater in the intensive-treatment group compared with the conventional-treatment group. Patients in the intensive-treatment group gained, on average, 3.1 kg more than patients in the conventional-treatment group [2].

The majority of patients with type 2 diabetes are overweight and the weight gain associated with insulin therapy may delay insulin initiation. In addition, weight gain may have metabolic and cardiovascular consequences. Weight gain may also increase low-density lipoprotein (LDL) cholesterol, hypertension, and lower high-density lipoprotein (HDL) cholesterol, which are risk factors for cardiovascular diseases [9, 10].

We observed no relation between weight gain and age at diagnosis of diabetes, age at insulin introduction, weight at insulin introduction or baseline levels of HbA_{1c}.

The interventions that minimize the weight gain associated with insulin therapy are recommended. Lifestyle interventions are an integral part of any diabetes treatment and several studies have convinced that lifestyle interventions are extremely effective [11, 12]. Diet has an important role in the management of glycemia in diabetic patients [14]. The use of combination therapy with metformin should be considered, because metformin is an insulin sensitizer and treatment or continuation of metformin after adding insulin may reduce the dose of insulin needed to achieve glycemic goal [15, 16, 17].

Conclusion

Our data show that the weight gain was directly correlated with the insulin dose. Weight gain was significantly greater after 5 years in the human insulin treatment group compared with the analog insulin treatment group. Weight gain was significantly greater in the intensive-treatment group compared with the conventional-treatment group.

The mean weight increase over a 5 years period but the maximum increment being noted in the first year of insulin therapy.

We observed no relation between weight gain and age at diagnosis of diabetes, age at insulin introduction, weight at insulin introduction or baseline levels of HbA_{1c}.

The interventions that minimize the weight gain associated with insulin therapy are recommended.

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