# THE LONG-TERM INFLUENCE OF INSULIN THERAPY ON THE WEIGHT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

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## Abstract

**Background and aims.** Insulin therapy may determine a sometimes important weight increase in patients with type 2 diabetes mellitus. This side effect can hamper its prescription. The purpose of this work was to study, on long-term (5 years), the weight behavior of patients with type 2 diabetes, started on insulin, and to find out the factors that influence it (age, gender, education, nutritional status, insulin dose and therapeutic scheme). **Patients and methods.** The study group was composed by 81 patients with type 2 diabetes mellitus, 35 male (43.2%), mean age±SD 56.4±7.4 years (range 34-73 years), followed-up in Diabetes Center Timisoara, who were started on insulin due to poor glycemic control. The body weight was measured yearly for 5 years. The statistical methods used were paired and unpaired t test and linear regression. The threshold for statistical significance for p was considered 0.05. **Results.** After 5 years, the mean weight increased extremely significant, with 8.2±8 kg, from 77.8±12.5 kg to 86±13.8 kg ($p<0.0001$). Weight increase was maximal in the first year of insulin therapy (4.4±5.7 kg). According to the weight behavior, 4 subgroups of patients were obtained: a. constant weight or weight loss (n=11, 13.6%); b. increase <5% from baseline body weight (n=12, 14.8%); c. increase 5-10% (n=16, 19.8%); d. increase >10% (n=42, 51.8%). Between baseline weight and weight gain there was an indirect correlation, extremely significant ($r=-0.3666$, $p=0.0008$). The ponderal status (normal weight, overweight, obesity) significantly influenced the further evolution (increase of 19.6±12.7% vs. 11.2±9.5% vs. 7.2±10.4%, respectively, $p=0.002$). Insulin dose (IU/kg) influenced significantly the weight increase ($r=0.4408$, $p<0.0001$), but the therapeutic scheme didn't seem to have an impact on it. **Conclusions.** Weight behavior of patients with type 2 diabetes mellitus started on insulin is heterogeneous. The mean body weight increases significantly. The weight gain is the most important in the first year of therapy. It decreases thereafter and reaches a plateau in the 5$^{th}$ year. Weight increase is directly correlated with the dose of insulin and inversely with baseline weight. Consequently, exaggerated fear is not justified in the case of insulin prescription in obese patients with type 2 diabetes mellitus.

**KEY WORDS:** weight gain, type 2 diabetes mellitus, insulin therapy

## Introduction

Type 2 diabetes mellitus (T2DM) is by far the commonest form of diabetes, accounting for 85-95% of all cases worldwide, and its global prevalence is increasing rapidly as a consequence of the westernized lifestyle. Epidemiological data are controversial. It is estimated that about 194 million people worldwide, or 5.1%, in the age group 20-79 years, had diabetes mellitus in year 2003. The number is expected to increase to some 333 million, or 6.3% of the adult population, by 2025 (19).

T2DM is characterized by disorders of both insulin action and secretion, usually present at the time of diagnosis, and either may be the prominent feature (9). Perhaps because the metabolic disturbances are less dramatic than in type 1 diabetes, T2DM has been regarded for many years as a "mild" form of the disease. This view is dangerously naïve, because these patients are at high risk of developing both macrovascular and microvascular complications, that cause huge burdens of morbidity and ultimately shorten life expectancy by an average of one-quarter for patients diagnosed in middle age (1).

General treatment objectives for patients with T2DM aim to abolish symptoms and the risk of acute metabolic complications, reduce the risk of chronic complications, increase life expectancy to that of non-diabetic counterparts and restore the quality of life to normal. These aims translate into specific treatment targets, represented by almost normal fasting and postprandial blood glucose levels and glycated hemoglobin ($HbA_{1c}$) values of less than 6.5% (16). The UKPDS trial showed that T2DM is a progressive disease that is often difficult to treat effectively and may deteriorate to the point at which insulin replacement is the only option left for controlling hyperglycemia (17, 18).

Despite poor glycemic control in T2DM treated with oral drugs, insulin is used less than needed. There are several factors that prevent prescription of insulin, one of them being the increase in weight generated by this drug (3, 14, 15).

**The objectives** of this study were to assess, on long-term (5 years), the weight behavior of patients with T2DM, started on insulin, and to find out the factors that influence it (age, gender, education, nutritional status, insulin dose, therapeutic scheme).

## Material and Methods

**The study group** was represented by 81 T2DM patients, 35 men (43.2%), mean age±SD=56.4±7.4 years (range 34-73 years), started on insulin therapy due to poor glycemic control. The baseline characteristics of the study group are shown in table 1.

The patients were admitted in Diabetes Clinic Timisoara during year 2002, where they were fully evaluated and received adequate education regarding lifestyle changes, insulin administration and problems that may occur during insulin therapy, with focus on hypoglycemic events. In all cases, oral drugs were discontinued and insulin started. The therapeutic scheme was labeled as simple (1 or 2 shots) or complex (3 or 4 shots). All the subjects received a glucometer and performed self blood glucose monitoring.

**Table 1. Baseline characteristics of the study group**

| Parameter | Value |
|---|---|
| *Patients** | 81 (100) |
| *Gender*:* | |
| - male | 35 (43.2%) |
| - female | 46 (56.8%) |
| *Mean age (years)*** | 56.4±7.4 (34-73) |
| *Body weight (kg)*** | 77.8±12.5 (43-105) |
| *Body mass index (kg/m$^2$)*** | 28.9±4.2 (17-41) |
| *Nutritional status*:* | |
| - normal weight / underweight | 9 (11.1) |
| | 40 (49.4) |
| - overweight | 32 (39.5) |
| - obese | 8.5±6.5 (1-28) |
| *Duration of diabetes (years)*** | 33 (40.7) |
| *Education*:* | 43 (53.1) |
| - elementary school | 5 (6.2) |
| - high-school | |
| - college | |

**Legend:** *=number (%); **=mean±SD (range).

The glucose strips were partly supported by the Romanian National Diabetes Programme. Some patients bought additional tests. After discharge, the patients were followed-up in the Diabetes Center Timisoara (visits every three months) for a period of 5 years. Body mass was measured every year.

**The statistical methods** used were paired and unpaired t test and linear regression. The threshold for statistical significance for p was considered 0.05. The statistic programme used was GraphPad Instat 3.

## Results

The mean weight increased extremely significant over a 5 years period ($p<0.0001$), with 8.2±8 kg, from 77.8±12.5 kg (range 43-105 kg) to 86±13.8 kg (range 57-135 kg). Every year an increase in mean body weight was recorded, the maximum increment (4.4±5.7 kg) being noted in the first year of insulin therapy (fig. 1). The weight seemed to reach a plateau in the fifth year of follow-up, when the gain was almost zero.

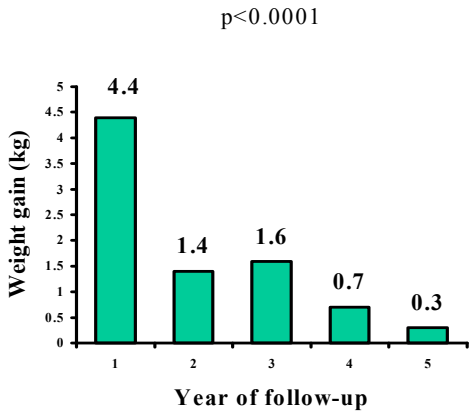


**Figure 1. Yearly increase in body weight in T2DM patients, started on insulin.**

According to the evolution of their body weight, the patients were divided into 4 subgroups: a. patients who maintained their body mass or even lost weight (n=11, 13.6%); b. patients who increased less than 5% of their initial weight (n=12, 14.8%); c. patients who increased between 5 and 10% of the baseline value (n=16, 19.8%); d. patients who gained more than 10% of their initial weight (n=42, 51.8%). The distribution of the patients, according to this criterion, is shown in fig. 2.

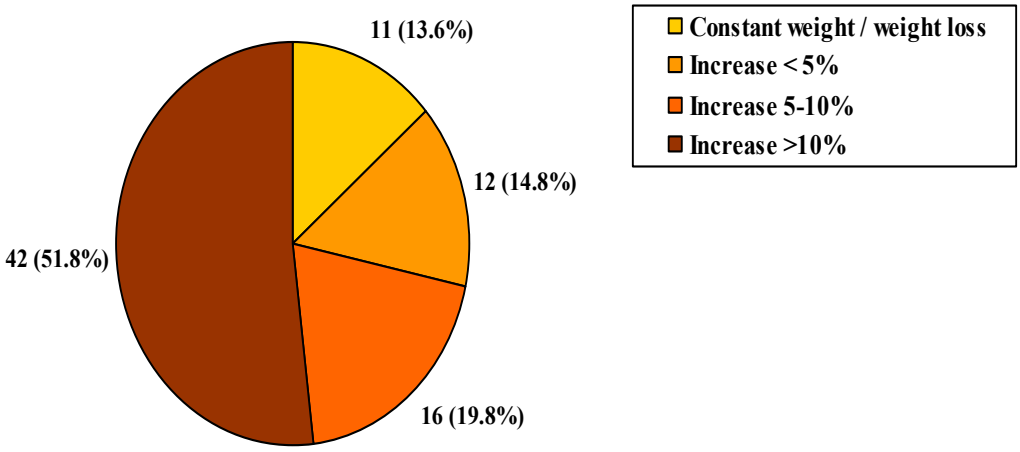


**Figure 2. Weight behavior of T2DM patients, started on insulin**

We tried to establish the existence of a relationship between the weight of the patient, or ponderal status, on one side, and the magnitude of weight increase. We found an extremely significant inverse correlation (p=0.0008) between the initial body weight and its increment, having a correlation coefficient r = –0.3666 (fig. 3).

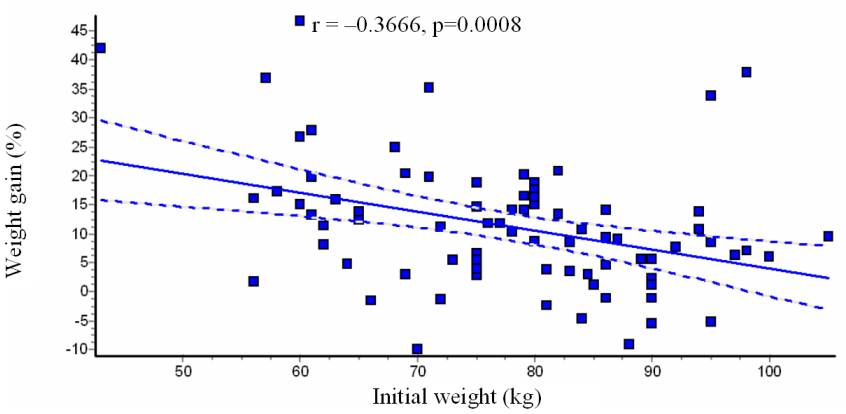


**Figure 3. Correlation between initial weight and weight gain**

By comparing the patients with normal weight, overweight, and obesity, in terms of weight gain, we found the maximum increment in the subgroup with normal weight and the smallest one in obese subjects (fig. 4). The differences were extremely significant (p=0.002).

The increase of body mass was directly correlated (r=0.4408, p<0.0001) with the insulin dose administered (fig. 5). On contrast, the complexity of the insulin scheme seemed not to influence the importance of weight gain (table 2).

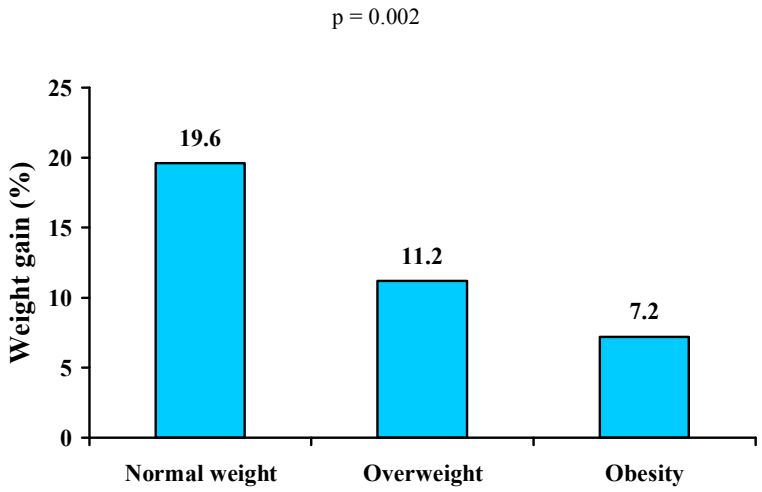


**Figure 4. Influence of ponderal status on weight increase**

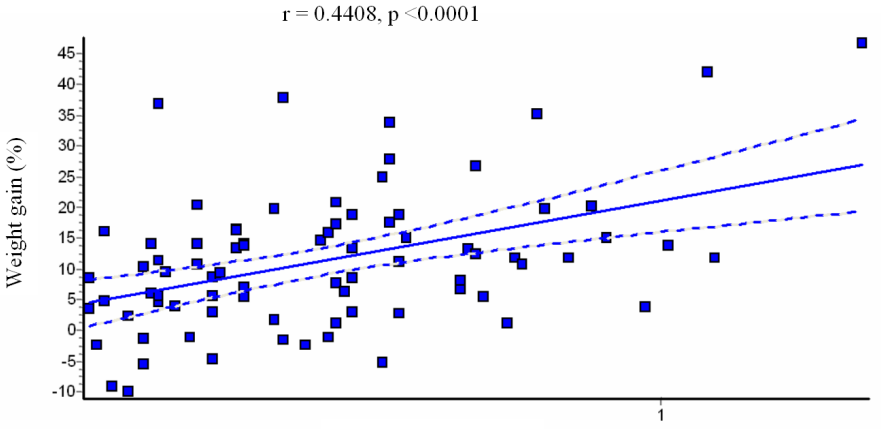


**Figure 5. Influence of insulin dose on weight gain**

**Table 2. Parameters that did not influence weight gain**

| Parameter | Value |
|---|---|
| Insulin scheme (simple v. complex) | 10.5±10.5% v. 12.2±11.9%, p=0.52 |
| Age | r=0.048, p=0.67 |
| Education (0-8 classes v. >8 classes) | 12.1±11.2% v. 11.3±11.1%, p=0.72 |
| Gender (male v. female) | 7.1±6.9% v. 9.1±8.7%, p=0.27 |

Weight gain (expressed as a percentage from initial weight) was more important, without reaching the threshold of significance, in women compared to men (9.1±8.7% vs.

7.1±6.9%, p=0.27) and in persons with educational level of maximum 8 classes (12.1±11.2% vs. 11.3±11.1%, p=0.72). The age influenced directly, not significant, the degree of weight increase (r=0.048, p=0.67) (table 2).

## Discussions

Insulin therapy or intensification of insulin therapy commonly results in weight gain in T2DM. This weight gain can be excessive, adversely affecting cardiovascular risk profile. The spectre of weight gain can increase diabetic morbidity and mortality when it acts as a psychological barrier to the initiation or intensification of insulin, or affects adherence with prescribed regimens. Insulin-associated weight gain may result from a reduction of blood glucose to levels below the renal threshold without a compensatory reduction in calorie intake, a defensive or unconscious increase in calorie intake caused by the fear or experience of hypoglycaemia, decreased caloric expenditure, sedentary lifestyles, anabolic effects of insulin or the "unphysiological" pharmacokinetic and metabolic profiles that follow subcutaneous administration (4, 5, 7, 13). Peripheral hyperinsulinism induced by the use of long-acting insulin may be the key to explain this adverse effect (3, 6). There are, however, possibilities for limiting insulin-associated weight gain. Strategies include limiting dose by increasing insulin sensitivity through diet and exercise or by using adjunctive anorectic or insulin-sparing pharmacotherapies. The most prescribed drug that limits weight increase induced by insulin therapy is metformin (8, 12, 20), but some authors doubt its effects in this direction (2). Registered dietitians must be involved before and after initiation of insulin therapy to help patients avoid or minimize weight gain, maximize adherence and glycemic control, and avoid the long-term complications of diabetes (4, 5, 7, 13).

Our study showed a continuous increase of body weight after starting insulin, with the highest effect in the first year of therapy and a plateau reached in the fifth. Similar data were reported by Larger et al. (10), who evidenced an important increase of weight in the first 6 months and the stop of progression 2 years later.

The patients showed a heterogeneous behavior regarding the evolution of their weight, most of them (71.6%) having an important weight gain. There was a proportion of the subjects (28.4%) who presented only a minor weight increase after 5 years, or even preserved their initial body mass. This heterogeneity suggests that other factors, except insulin therapy, may be involved in the weight gain (11).

We found a more important weight increase in patients with lower initial body mass index, in contrast with Biesenbach et al. (2) who reported a constant weight gain irrespective of the ponderal status.

The weight gain was directly correlated with the insulin dose, showing the role of the hormone in generating this side effect.

Other factors did not influence the evolution of the body weight after the patients were started on insulin. An explanation for the lack of influence of the education level on weight behavior can be a diminished interest for diabetes care or lack of time for lifestyle changes, shown by these subjects.

## Conclusions

The conclusion drawn from this paper are:

1. Weight behavior of patients with T2DM started on insulin is heterogeneous.
2. The mean body weight increases significantly.
3. The weight gain is the most important in the first year of insulin therapy; it decreases thereafter and reaches a plateau in the fifth year.
4. Weight increase is directly correlated with the dose of insulin and inversely with baseline weight and body mass index. Consequently, exaggerated fear is not justified in the case of insulin prescription in obese patients with T2DM.
5. Other factors don't seem to influence the weight gain.

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