Weight gain and insulin treatment

E Larger

SUMMARY
This review presents recent data on weight gain when on insulin treatment in type 1 and type 2 diabetic patients. In both types of diabetes, the excess weight gain with intensified insulin therapy compared with conventional insulin or sulfonylurea remains modest: 2.6 kg over 7.5 years in the Stockholm study (type 1 diabetic patients) and 1.7 kg when compared to glibenclamide over 10 years in the UKPDS (type 2 diabetic patients). Patients who gain the most weight after insulin initiation are those who: 1) had the worst metabolic control before the intensification of treatment, 2) had the greater weight loss prior to insulin initiation, and 3) in the case of patients with type 1 diabetes, have a family history of type 2 diabetes. This suggests that most of the weight gain observed after the insulin initiation is a “catch-up” weight re-gain. There is no evidence that weight gain after insulin therapy initiation is associated with a deterioration in the lipid profile or arterial hypertension or an excess risk for cardiovascular events, contrary to common beliefs. All clinical studies performed to date with the insulin analogue detemir have shown that this analogue is associated with lesser weight gain than NPH insulin. There is no explanation yet for these intriguing results. If confirmed on the long-term, this favourable effect on weight might be an interesting feature of this new insulin analogue.

Key-words: Insulin detemir · Insulin treatment · Type 1 diabetes · Type 2 diabetes · Weight gain.

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RÉSUMÉ
Prise de poids et insulinothérapie
Cet article fait la revue des données récentes concernant la prise de poids sous traitement insulinique chez des diabétiques de type 1 comme de type 2. Dans les deux types de diabète, la prise de poids avec le traitement intensifié comparé au traitement insulinique conventionnel ou aux sulfamides reste modeste : 2,6 kg sur 7 années dans le Stockholm study (diabète de type 1) et 1,7 kg comparé au glibenclamide sur 10 années dans l’UKPDS (diabète de type 2). Les patients qui prennent le plus de poids après l’introduction de l’insuline sont : 1) ceux qui avaient précédemment le plus mauvais contrôle métabolique avant l’intensification du traitement, 2) ceux qui avaient le plus perdu de poids avant le début de l’insuline, 3) chez les diabétiques de type 1, ceux qui ont des antécédents familiaux de type 2. Ceci suggère que l’essentiel de la prise de poids observée correspond à un rattrapage pondéral. Aucune donnée n’indique que cette prise de poids s’accompagne d’une détérioration du profil lipidique, d’hypertension artérielle ou d’une augmentation du risque d’événements cardio-vasculaires, et ce, contrairement aux idées reçues. Toutes les études de recherche clinique réalisées avec l’analoge de l’insuline détémir ont montré que l’usage de ce nouvel analogue de l’insuline s’accompagne d’une prise de poids moindre qu’avec les insulines NPH. Il n’existe pas actuellement d’explications à ces résultats surprenants. S’ils sont confirmés à long terme, ceci pourrait constituer une caractéristique particulièrement intéressante de l’insuline détémir.

Mots-clés : Diabète de type 1 · Diabète de type 2 · Insuline détémir · Insulinothérapie · Prise de poids.

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Often presented as an obstacle to the initiation of insulin treatment in type 2 diabetic patients, weight gain, considered as a “problem” or as a “side-effect” of insulin, is worth thinking over, with regards to its causes and consequences. We believe one cannot write without a critical analysis: “For diabetic patients, gaining weight can be especially undesirable because of its psychological effect and as it is associated with poor cardiovascular outcomes and other morbidity, and leads to increasing insulin resistance” [1]. Weight gain observed when on insulin treatment does not justify to avoid or to delay implementation of insulin treatment when needed for glycaemic control. Since our last review of this topic in this journal in 2001 [2], important results have been presented that help us to understand the causes of weight gain, and new results, from clinical studies with the insulin analogue detemir, have added new questions and put new perspectives.

**Weight gain associated with insulin treatment in patients with type 1 diabetes**

In the DCCT, the patients randomised to the “intensive” treatment group gained more weight than those randomised to the “conventional” treatment group [3, 4]. These results confirmed those observed in the “Stockholm Intervention Study” [5]. In the DCCT, weight increased during the whole study in both treatment groups. The excess weight gain in the intensive treatment group was mostly observed during the first years of the study [4]. In this study the excess weight gain was 2.1 kg during the first year, 4.6 kg at 5 years and 4.7 kg at the end of the study [3, 6]. In the Stockholm study, the excess weight gain of the patients in the “intensive” treatment group was 2.6 kg over a 7.5 years’ period. In the “intensive” treatment group of the Stockholm study, glycaemic control was similar to that observed in the intensive group of the DCCT (mean HbA1c level: 7.1%), but glycaemic control was better in the conventional group of the Stockholm study than in the conventional group of the DCCT (mean HbA1c level were 8.5% in the Stockholm study and 9.1% in the DCCT). This suggests that in the DCCT, the poor metabolic control of the “conventional” treatment group prevented weight gain in this group. Indeed, even in the “conventional” treatment group of the DCCT, the mean HbA1c level was significantly higher in the first quartile of weight gain than in the fourth one (Figure 1) [7], and the weight gain in the fourth quartile of weight gain of the conventional treatment group was greater to that of the first and second quartiles of weight gain of the intensive group, similar to that of the third quartile and only surpassed by the fourth quartile of the intensive treatment group (Figure 1).

The data on the body weight composition analysis in the DCCT have been recently published [6]. In women, the excess weight gain in the intensive group compared to the conventional group was for one-third due to an increase in the fat-free mass, and among patients without major weight gain, intensive therapy was associated with greater fat-free mass but without difference in adiposity [6, 8].

What are the causes for this excess weight gain in intensively treated patients? At the end of the trial, the insulin dose was similar in both treatment groups in the Stockholm study (0.67 ± 0.21 U • kg⁻¹ • day⁻¹). In the DCCT, patients in the conventional treatment group received 0.62 ± 0.17 vs 0.69 ± 0.21 U • kg⁻¹ • day⁻¹ in the intensive treatment group, and both in the conventional and in the intensive treatment group, the insulin dose of the fourth quartile of weight gain was higher than that of the first quartile [7]. This does not imply that insulin dose was the cause of weight gain, this can also be interpreted as an association of weight gain and greater insulin resistance.

It has been suggested that hypoglycaemic episodes, three times more frequent in the DCCT in the intensive than in the conventional group, were major causes of weight gain. A recent analysis of the DCCT contradicts the previous results reported from this trial, but obtained from a smaller sample of patients followed-up over a shorter period of time: the incidence of hypoglycaemic episodes is not related to changes in BMI. This recent analysis estimates that hypoglycaemic episodes account for only 2% of the weight gain that occurred over the whole duration of the study [9].

The data on the weight gain in the DCCT have been further analysed in a recently published article [9]. It appears that type 1 diabetic patients with a family history of type 2 diabetes mellitus gained more weight than those without

**Figure 1**

Body mass index (BMI, kg/m², boxes) and mean HbA1c (%) levels (circles) in patients in the DCCT. Patients were divided by quartiles (Q) of weight gain during the trial. Black boxes, open circles: conventional treatment group. White boxes, black circles: intensive treatment group [data from ref. 7].
such history ($\Delta$BMI $3.9 \pm 2.8$ vs $2.9 \pm 3.2$ kg/m$^2$). At the end of the study, the prevalence of obesity in the intensive group was close to that reported for the general population. Finally, other components of the metabolic syndrome were more likely to be observed in patients with a family history of type 2 diabetes than in those without history, with significant differences for triglycerides, HDL- and LDL-cholesterol, increased waist-to-hip ratio [WHR] (but neither systolic nor diastolic pressure differences), and the insulin doses were higher in these patients.

The first conclusions of the weight and lipid parameters analysis of the DCCT were negative: “The changes in lipid levels and cholesterol content in the lipoprotein fractions that occur with excessive weight gain (...), along with the findings of higher blood pressures, increased WHR, may over a long follow-up period contribute to an increased risk of macrovascular disease” [7]. These conclusions are now balanced by the recent analysis of the full data, and thus their authors concluded: “These findings supports the hypothesis that intensive therapy permits expression of several components of the central obesity syndrome phenotype in a subset of individuals with a family history of type 2 diabetes” [9]. In agreement with this line of evidence, one has to remember that this is a classic fact that patients with type 1 diabetes may remain leaner than nondiabetic control subjects.

We believe that all the data we summarised here, indicate that as long as they are poorly controlled, patients with type 1 diabetes remain below “their” weight (i.e. the weight they would have in the absence of diabetes). Intensive insulin therapy allows them to reach “their” weight. Those who would have been obese without diabetes will become obese with insulin therapy, and may express the full phenotype of the insulin resistance syndrome if they possess the genetic potential for it. The data obtained from the EDIC study, a follow-up study of the DCCT, indicate that as far as macroangiopathy is concerned, the benefits of a good glycaemic control outweigh the risk of obesity and dyslipidemia and their consequences [10]. Only further follow-up of the DCCT cohort will definitively answer this question. Even a meta-analysis of the currently available data was unconvincing, but the number of cardiovascular events collected in this meta-analysis, apart from those of the DCCT, were only 4/150 patients on intensive treatment and 10/140 patients on conventional treatment [11].

**Weight gain associated with insulin treatment in patients with type 2 diabetes**

Insulin therapy induces weight gain in patients with type 2 diabetes, but, unlike the observations in patients with type 1 diabetes, intensification of insulin treatment does not seem to induce further weight gain [2]. One of the most intriguing fact is that most of the excess weight gain occurs within the first two years following the initiation of insulin treatment, suggesting that most of the weight gain is a “catch-up” re-gain, allowing patients to return to “their” weight (again, “their” refers to the weight patients would have in the absence of diabetes-induced weight loss), as we discussed above for patients with type 1 diabetes.

We have conducted a retrospective study of 58 patients with type 2 diabetes, for whom clinical records stated clearly the maximal weight they reached in the past, before insulin initiation [12]. Table I presents the clinical characteristics of the patients. In these patients, in whom oral antidiabetic agents failed to maintain an optimal glycaemic control more than 10 years after diabetes diagnosis, weight loss had begun before the diagnosis of diabetes, and remained so during all the years on oral antidiabetic treatment. These patients gained $8.0 \pm 5.3$ kg during the first 2 years after insulin introduction, and then their weight stabilised during the third year (gain $0.15 \pm 3.1$ kg). When we plotted the maximal weight reached after initiation of insulin treatment against the maximal weight ever reached before insulin therapy initiation, a highly significant correlation appeared and these two weights were linked by the following equation: weight after insulin $= 0.96 \times$ weight before (adjusted R$^2$: 99.2%) (Fig. 2) [12]. Weight gain correlated weakly with insulin dose (adjusted R$^2$: 6.6%, Fig. 3), but not with metabolic control in terms of the minimal HbA1c level (adjusted R$^2$: 4.4%; figure 3).

Thus, we believe our results indicate that the weight gain observed in insulin-treated patients with type 2 diabetes is mostly a “catch-up” weight re-gain. This explains why most studies have shown that most weight gain after insulin initiation occurs over a limited period of time.

A major argument often been put forward against insulin treatment in patients with type 2 diabetes is that the excess weight gain observed with insulin should worsen lipid disorders associated with diabetes. Curiously, this point has seldom been studied in the long term. Multiple studies have shown that, on the short term, improvement of glycaemic control with insulin, as well as with others therapies, is associated with lipid profile improvements [13]. Of note, the greater improvement in glycaemic control with oral antidiabetics and insulin combination regimen compared to insulin alone, observed in 11 out of 14 studies reviewed by Yki-Jarvinen [13], has not been consistently (4 of 11 studies) associated with

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<td>Characteristics of 58 patients with type 2 diabetes requiring insulin for glycaemic control (expressed as mean ± SD when appropriate) [personal data and from ref. 12].</td>
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Figure 2
Relation between the maximal body weight ever reached during life and the maximal body weight reached within 3 years after insulin initiation in patients with type 2 diabetes [data from ref. 12].

Figure 3
Relation between maximum insulin daily dose (in U/kg⁻¹) and weight gain (in kg), and between minimal HbA₁c level (in %) and weight gain (in kg) in patients with type 2 diabetes [data from ref. 12].
a greater decrease in serum triglycerides. To our best knowledge, the only long-term (> 1 year) study to have studied this point is the one by Lindström et al. [14]. In this small study, although patients gained about 8 kg during the 3 years on insulin treatment, triglycerides levels remained lower (1.8 ± 0.3 vs 2.8 ± 0.6 mmol/l) at 3 years than before insulin initiation, and total-, HDL- and LDL-cholesterol remain unchanged. UKPDS results on lipid profiles in the long-term have not been reported yet.

With regards to blood pressure, several theoretical arguments suggest that blood pressure should increase with weight gain. Again, long-term data are lacking, and in the Lindström's study, despite a weight gain of about 8 kg, blood pressure did not change during insulin treatment [14]. We only found indirect evidence against significant effects of insulin or weight gain in the UKPDS: despite greater weight gain in the “intensive” treatment group, means costs of anti-hypertensive drugs were similar to those of the “conventional” treatment group [15]. Finally some have argued that the relative hyperinsulinaemia observed with insulin treatment compared to sulphonylureas should be detrimental with regards to cardiovascular diseases. A recent meta-analysis concluded that hyperinsulinaemia is, at best, only a weak predictor of the occurrence of cardiovascular events [16].

To summarise, although insulin treatment increases more the body weight than sulphonylureas do (there are no long-term data yet to compare insulin and thiazolidinediones on this point), the excess weight gain observed for a comparable improvement in glycemic control remains generally modest: 1.7 kg over 15 years by comparison to glibenclamide in the UKPDS [17], and there is no clear evidence that this modest excess weight gain is associated with deleterious effects on lipid profile or blood pressure. Indeed, some patients will experience major weight gain when on insulin treatment, but results of our retrospective study have shown it is likely these patients were those with the greater weight loss prior to being prescribed insulin [12].

**Weight gain and insulin detemir**

Against this background, it has been extremely surprising that all studies conducted with the insulin analogue detemir, either in patients with type 1 or in patients with type 2 diabetes, have shown significantly less weight gain in comparison to NPH insulin, over the 4 to 12 months study-periods [1, 18] (Table II). The reason for this difference remains unknown. The ratio of affinity for insulin receptor/IGF-1 receptor of detemir is similar to that of insulin and the ratio of metabolic potency/mitogenic potency is favourable when compared to insulin [19] [European Medicine Agencies, public assessment report, www.emea.eu.int/humandocs/Humans/levemir/levemir.htm, last accessed 31/01/2005]. Although the longest trials lasted 12 months only, it is unlikely this lesser weight gain is a sign of serious side effects. However, the number of deaths was higher among patients currently or recently treated with insulin detemir than among those treated with NPH insulin (13 deaths for 1248 subject-years of exposure vs 2 in patients treated with NPH), but apparently it seems unlikely the deaths were connected to the insulin treatment [European Medicine Agencies, public assessment report, www.emea.eu.int/humandocs/Humans/levemir/levemir.htm, last accessed 31/01/2005]. Only post-marketing safety data will clarify this point. It has been hypothesised that acylation might favour the passage of insulin detemir through the blood-brain barrier, but there is no direct evidence for this. No further clarifications on the mechanisms of this effect.

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<td><strong>Published studies reporting weight evolution in patients with type 1 or type 2 diabetes treated with the insulin analogue detemir.</strong> All studies were randomized study comparing insulin detemir to insulin NPH, none was double blind. Different pre-meal insulins have been used in these studies: either human soluble insulin (Hum Sol) or insulin aspart. HbA1c vs NPH refers to differences in the HbA1c level at the end of the study between the studied groups; NS: difference not statistically significant; Yes: p &lt; 0.05.</td>
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have been requested by the experts of the European Medicine Agencies [public assessment report, www.emea.eu.int/humandocs/Humans/levemir/levemir.htm, last accessed 31/01/2005].

Conclusion

Data obtained in the recent years have confirmed the idea that most of the weight gain observed when HbA1c is significantly reduced with insulin, both in type 1 and type 2 diabetic patients, is a “catch-up” weight re-gain. The patients who are prone to gain the more weight are those who have lost the more weight or who possess genetic or behavioural components of the metabolic syndrome. In all cases, the excess weight increases observed with intensified insulin treatment, compared with conventional insulin or sulphonylurea remains modest. Furthermore, it has not been demonstrated that this weight gain is associated with an increased in cardiovascular risk or in risk factors. The significantly lesser weight gain observed with the insulin analogue detemir by comparison to NPH insulin is potentially of interest, but remains intriguing and has to be confirmed during longer follow-up studies.

References