INSULIN MANAGEMENT IN OVERWEIGHT OR OBESE TYPE 2 DIABETES PATIENTS: THE ROLE OF INSULIN GLARGINE

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ABSTRACT

Type 2 diabetes mellitus (T2DM) and obesity commonly co-exist. Improved clinical management of T2DM and improved glycaemic control with traditional therapies including insulin usually results in some weight gain – a frequently perceived barrier to the introduction of insulin by both patient and healthcare professionals. Weight gain of 2.5 kg per 1% change in haemoglobin A1c (HbA_{1c}) is common in many studies. Strategies to minimise weight gain, particularly in obese patients, are essential to help patients better manage their diabetes and improve quality of life. Insulin analogues, with lower risk of hypoglycaemia and better within-patient variability compared with human insulin may help facilitate reaching treatment goals. Moreover, weight gain can be minimised by earlier insulinisation and the use of basal insulin, such as insulin glargine, instead of premixed insulin. Data specific to the obese patient with T2DM are presented; they are currently limited but do indicate that insulin glargine therapy is associated with improved glycaemic control as well as less weight gain than other insulins, including, premixed insulin and prandial insulin regimens. Retrospective subanalyses of earlier trials and on-going studies would shed further light on the impact of insulin therapy in obese people with T2DM, in addition to determination of optimal therapeutic strategies.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a significant health problem, the prevalence of which is steadily increasing [1-3], and is associated with increased risk of vascular disease. However, it is well established that T2DM is also closely associated with obesity. It is predicted that up to 60% of cases of T2DM could potentially be avoided if the body mass index (BMI) of the population was maintained within the normal healthy range [4]. In addition, with greater understanding of the pathophysiology of diabetes, it appears that there are some differences in insulin secretion profiles between people with normal weight and obese people with T2DM, which partly relates to the degree of peripheral insulin resistance [5].

For many patients, insulin therapy used in conjunction with oral glucose lowering drugs, most commonly sulfonylurea and metformin, is essential to maintain good glycaemic control. However, such a therapeutic strategy is associated with weight gain, which is a common barrier amongst patients and providers alike [6]. Understandably, therefore, there is some reluctance to use insulin in obese patients with T2DM as there is a perception that they may be more likely to gain relatively more weight, potentially worsening insulin resistance, thus, weight gain remains a significant barrier to insulin initiation [7-9]. Newer analogues, such as insulin glargine and insulin detemir offer a simple approach for the introduction of insulin, with once-daily dosing for insulin glargine and some insulin detemir patients, improved within-patient variability and lower risk of hypoglycaemia vs neutral protamine Hagedorn (NPH) insulin [10,11]. The aim of this review is to discuss the role of insulin therapy in obese patients with T2DM and strategies to minimise insulin-induced weight gain.

Obesity in Type 2 diabetes

The global prevalence of obesity is steadily increasing, particularly in highly industrialised regions, such as Europe [2] and North America [1,12]. Developing nations, and some ethnic groups, are also showing trends towards increasing prevalence of obesity and T2DM [13,14]. Obese individuals, typically defined as having a BMI $>30 \text{ kg/m}^2$, (although this threshold is lower in some ethnic groups; for example, the threshold for obesity is 27.5 kg/m^2 for South Asian populations [15]), are at greater risk of developing impaired fasting glucose and impaired glucose tolerance, which often progress to overt T2DM, as a result of progressive dysfunction in β -cell function [16]. In addition, obese individuals also show abnormal liver, muscle and adipose tissue lipid handling, which has also been implicated in the development of insulin resistance and T2DM [17]. This is of significant concern, given the trends towards increasing prevalence of obesity and T2DM [18] particularly over the next 25 years [3], in addition to the strong association between these risk factors and microvascular [19-21] and macrovascular disease [22-24].

Indeed, in people with T2DM and who are obese, the level of insulin resistance is typically greater than that in lean people with T2DM, as was demonstrated in a study by Røder et al [5] who reported that in lean (mean BMI $23.5 \pm \text{kg/m}^2$) and obese (BMI $30.1 \pm 0.4 \text{ kg/m}^2$) patients with T2DM (matched for fasting glucose [10.2 ± 0.6 vs $10.3 \pm 0.4 \text{ mmol/L}$ (184 ± 11 vs $186 \pm 7 \text{ mg/dL}$), respectively], and with similar diabetes duration [5.1 ± 1.4 vs 5.5 ± 1.2 years, respectively]), there were clinically relevant differences in β -cell peptides in the fasting state and after glucagon stimulation. In particular, levels of intact proinsulin (6.6 ± 1.0 vs $7.7 \pm 2.0 \text{ pmol/L}$, respectively; $p < 0.01$) and C-peptide (598 ± 32 vs $893 \pm 112 \text{ pmol/L}$, respectively; $p < 0.05$) were significantly different in both groups, while insulin tended (although not statistically significant) to be higher in the obese group compared with the lean group (32.5 ± 4.9 vs $63.9 \pm 20.4 \text{ pmol/L}$, respectively), which likely reflects increased insulin resistance in the obese patients [25,26].

Treatment of T2DM and improved metabolic control is associated with weight gain, particularly when insulin, thiazolidinediones (TZDs) or sulfonylureas are used [27]. In ADOPT (A Diabetes Outcome Progression Trial), weight gain over 5 years was 4.8 kg with rosiglitazone and 1.6 kg with glyburide [27]. This compares with a weight loss of 1.6 kg in the metformin group in that study [27]. However, for many patients, weight gain is unacceptable and commonly results in poor adherence to therapy or refusal to accept more intensive therapy, particularly the addition of insulin, despite its proven efficacy [9]. Therefore, it is important to understand why weight gain is common with insulin therapy and then consider potential strategies to minimise the impact of weight gain.

Type 2 diabetes, weight gain and therapeutic strategies to minimise weight gain

Management of T2DM typically involves the intensive use of a number of therapeutic agents, which should be optimally titrated according to the patient's needs and glycaemic status. However, a common feature is that most commonly used therapeutic agents are associated with some weight gain, except metformin, which is largely weight neutral [28]. Weight gain is a barrier to the introduction of insulin therapy. However, the natural progression of T2DM means that insulin therapy is often essential [29]. Therefore, it is important to consider how best to use insulin therapy to minimise weight gain, which is particularly true for the obese patients. Indeed, it has been suggested that for each 1% absolute reduction in HbA_{1c}, an increase in body weight of 2.5 kg can be expected [30], which is supported by data showing a strong, inverse association between improvements in fasting glucose and changes in body weight (Figure 1). However, before strategies to minimise weight gain can be discussed, it is important to understand why insulin therapy is associated with weight gain.

[Insert Figure 1 near here]

Mechanisms of weight gain in insulin-treated Type 2 diabetes – pharmacodynamic studies of insulin

A number of pharmacodynamic studies have determined potential mechanisms that would conceptually lead to weight gain with long-term insulin therapy. Key factors included hypoglycaemia-associated snacking, reduced glucose excretion (glycosuria) and reduced metabolic rates.

Hypoglycaemia and snacking

A common unwanted effect of insulin therapy is that of hypoglycaemia, and patients may respond to symptomatic hypoglycaemia, in particular, by increased snacking, to maintain stable blood glucose levels [31], although patients on insulin therapy should be aware of the risks of hypoglycaemia. The modern insulin analogues are associated with lower risk of hypoglycaemia [10], lower within-patient variability [32] and lower fluctuation [33] in action compared with the human equivalent. Thus, the need for snacking to avoid hypoglycaemia should be reduced. Thus one might anticipate that reduced hypoglycaemia-related snacking with newer insulin analogues would allow for less weight gain. In studies with insulin glargine, the reduced weight gain versus NPH insulin was evident in the studies by Rosenstock et al [34] and by Yki-Jarvinen et al [35], while reduced weight gain is consistent in studies with insulin detemir versus NPH insulin [36], although the underlying mechanism for this is still not fully understood.

Glycosuria

In people with poorly controlled T2DM, excess glucose is usually excreted in urine (glycosuria). In one study of six obese patients with T2DM, baseline urinary glucose excretion was 48 ± 19 g/day. After switching to glyburide treatment, glucose excretion fell to 20 ± 9 g/day and further declined to 2 ± 1 g/day with insulin therapy [37]. This reversal of glycosuria will inevitably lead to weight gain unless diet or exercise levels are changed, as demonstrated in Figure 2.

[Figure 2 near here]

Basal metabolic rate

The basal metabolic rate is also influenced by insulin therapy and is largely decreased by insulin, with reduced resting energy expenditure, which may reflect increased efficiency in

fuel selection as a result of better glycaemic control [30]. Therefore, weight gain will ensue unless diet or activity levels are adjusted accordingly.

Strategies to reduce weight gain

As described above, weight gain is largely an expected effect of insulin therapy, but is, nevertheless, unwanted by the majority of people treated with insulin. However, there are strategies to minimise the extent of weight gain associated with improved glycaemic control in patients on insulin.

Insulin versus alternative oral agents

Typically, insulin is added as a third agent, after metformin and sulfonylurea doses have reached the maximum tolerated, although the joint American Diabetes Association and European Association for the Study of Diabetes consensus statement advocates the earlier use of basal insulin [29]. For the third agent, there is a choice between adding a TZD or adding insulin. This was evaluated in a study comparing triple therapy of insulin glargine vs rosiglitazone (both added to sulfonylurea plus metformin) [38]. In that study, insulin glargine was associated with significantly less weight gain (1.6 vs 3.0 kg, respectively; $p=0.02$) over 24 weeks. Furthermore, it appears that weight gain with insulin therapy can be further minimised, depending on the stage of the treatment pathway at which insulin is started, such as initial therapy in combination with metformin, or later in the treatment pathway, when a combination of maximally tolerated doses of sulfonylurea plus metformin provides inadequate glycaemic control.

Ordinarily, insulin therapy would be expected to increase weight by 2.5 kg for every 1% reduction in HbA_{1c}. Indeed, in a study by Mäkimattila et al [30], which assessed the impact of insulin therapy alone or insulin plus metformin therapy on weight gain in T2DM patients, improvements in HbA_{1c} were similar in both groups, but the insulin plus metformin group required 47% less insulin and experienced less weight gain than the insulin alone group (3.8 vs 7.5 kg, respectively; $p<0.05$). Thus, unless contra-indicated, metformin should continue when insulin is initiated in T2DM.

Insulin analogues, human insulin or premixed insulin?

Moreover, the choice of insulin may limit the weight gain observed. Indeed, the LANMET study showed that, when adding insulin glargine or NPH insulin to metformin, weight gain was lower with insulin glargine (+2.6 vs 3.5 kg, respectively; Table 1) [35]. Similarly, the LAPTOP (LANTUS + Amaryl + metformin vs Premixed insulin in T2DM patients after failing Oral treatment Pathways) [39] and INITIATE (INITiation of Insulin to reach A1c TargEt) [40]

studies demonstrated that the use of once-daily insulin glargine is associated with less weight gain than either twice-daily human insulin (+1.4 vs +2.1 kg, respectively; $p=0.0805$) or twice-daily biphasic insulin aspart (+3.5 vs +5.4 kg, respectively) (Table 1), when added to existing oral agents.

However, in these studies, although the study populations comprised a majority of obese people (mean BMI was $\sim 30 \text{ kg/m}^2$), it was not reported whether there was differential effects in normal weight, overweight or obese patients. Insulin glargine may offer benefits to these people, with lower risk of hypoglycaemia and potentially a decreased need for snacking or other preventative measures. Some studies have ascertained the effects of insulin glargine therapy in obese patients with T2DM.

Weight management with insulin glargine in randomized controlled trials and observational studies

In randomized controlled trials comparing insulin glargine with NPH insulin, when added to existing oral antidiabetic drugs (OADs), weight gain was seen with both insulins, but was broadly similar across the trials (Table 1). In contrast, in the two studies that compared insulin glargine therapy with premixed insulin, insulin glargine was associated with less weight gain, which was significant in one trial and of borderline significance in the other (Table 1).

[Table 1 near here]

In the AT.LANTUS study, which compared a physician-managed algorithm (Algorithm 1; mean BMI at baseline: $29.0 \pm 4.7 \text{ kg/m}^2$) with a patient-managed algorithm (Algorithm 2; mean BMI at baseline: $29.0 \pm 4.7 \text{ kg/m}^2$) for the initiation of insulin glargine, baseline to endpoint increases in body weight were relatively modest in both algorithms (Algorithm 1: 79.8 ± 15.8 to $80.8 \pm 16.0 \text{ kg}$; Algorithm 2: 79.8 ± 16.2 to $81.1 \pm 16.5 \text{ kg}$) and similar to that expected for the magnitude of HbA_{1c} reduction (-0.9 and -1.1% , respectively) achieved [30].

Meanwhile, in an observational study of everyday clinical practice, which evaluated the switch from premixed insulin to insulin glargine plus OADs in 5045 patients (mean diabetes duration: 8.7 years) for 12 weeks, mean weight change was $-1.5 \pm 3.2 \text{ kg}$, while HbA_{1c} decreased by 1.1% and fasting blood glucose (FBG) decreased by 2.0 mmol/L (36 mg/dL) [41].

Insulin glargine therapy in overweight or obese individuals with Type 2 diabetes

In a subanalysis of overweight patients (BMI >28 kg/m²) in a 1-year, randomised multicentre study, comparing insulin glargine with NPH insulin, insulin glargine was associated with significantly greater improvements in HbA_{1c} (−0.42 vs −0.11%, respectively; p=0.0237) and a trend towards greater improvements in FBG (−2.62 vs −2.29 mmol/L [47 vs 41 mg/dL], respectively). Insulin glargine was also associated with a significantly lower prevalence of nocturnal hypoglycaemia (22.2 vs 9.5%, respectively; p=0.0006), but with similar change in weight (+1.95 vs +1.88 kg, respectively) [42].

A recent, 32-month, open-label, uncontrolled, multicentre, observational study (which had previously demonstrated improvements in HbA_{1c} at 3, 9 and 20 months), assessed the efficacy and safety of initiating insulin glargine in addition to existing OADs [43,44]. In this study, the greatest reductions in HbA_{1c} (−1.8 ± 1.8%) were in patients who were obese (≥30 kg/m²) at the start of observation. Furthermore, some weight loss was also seen in these patients (−4.4 ± 10.7 kg) (Figure 3).

[Figure 3 near here]

These results are promising for obese patients, suggesting that improvements in glycaemic control and weight loss can be achieved and importantly, maintained, over 32 months of treatment with insulin glargine.

In the majority of trials of insulin glargine, many of the patients are obese, as is common in T2DM. Several of these studies, including AT.LANTUS [45], GOT (Glycaemia Optimisation Trial) [46] and GOAL A1c (**G**lycemic **O**ptimization with **A**lgorithms and **L**abs **A**t po1nt of **C**are) [47] involved in excess of 3000 patients each. The size of these studies will provide an opportunity to evaluate through retrospective subanalyses the efficacy of insulin glargine therapy across the cut-points for obesity.

DISCUSSION

Good blood glucose control reduces the risk of long-term diabetes complications. However, tight metabolic control can be particularly difficult in obese patients. Hypoglycaemia resulting from insulin therapy is a common fear for many patients with T2DM, and it can be a possible influence on health providers' and patients' treatment policies alike. This fear can be a major barrier to achieving good glycaemic control.

Insulin glargine provides at least equivalent glycaemic control when compared with NPH insulin regimes, and hypoglycaemic episodes are less common, as reported in a meta-regression of six studies of insulin glargine versus NPH insulin [10]. This provides the opportunity for patients with diabetes to titrate to optimal doses and thereby increases the potential for further glycaemic control.

Weight gain is a commonly cited barrier to insulin therapy [7-9] and results of many studies indicate that weight gain is largely unavoidable, which may be a result of improved tissue glucose uptake, reduced glycosuria, snacking and reduced resting energy expenditure. However, studies in clinical practice, suggest that weight gain can be minimised with insulin therapy [41,44], and this does not appear to compromise the improvements in glycaemic control seen in these studies.

A number of large, randomised, controlled trials have been performed to evaluate the efficacy and safety of insulin glargine in T2DM. In particular, the AT.LANTUS [45], GOT [46] and GOAL A1c [47] studies each recruited a large number of patients across a range of BMI values. Subanalyses of these studies, by stratifying the patients according to BMI, are in progress, and should provide informative comparisons between normal weight and obese patients.

Such data would allow for a greater understanding of the impact of insulin therapy, not only on glycaemic control and risk of hypoglycaemia, but also weight management, in these patients. Indeed, this seems essential owing to differences in pathophysiology of T2DM in lean and obese patients, as well as optimum insulin titration regimens and dosing algorithms, owing to the differential insulin secretory capability and insulin resistance in these patients [5]. Although both insulin glargine and insulin detemir are associated with less weight gain than other insulin preparations, particularly premixed insulin or regular human/NPH insulin, this does not preclude the continuation of lifestyle factors, such as diet and exercise, to help prevent excessive weight gain.

Finally, while weight gain may be an undesired factor and excessive adiposity is a risk factor for cardiovascular disease, the improvements in glycaemic control would be expected to outweigh these risks, as indicated by the United Kingdom Prospective Diabetes Study [48] and Kumamoto [49] studies. These studies demonstrated that the improvements in glycaemic control were associated with significantly reduced risk for cardiovascular endpoints, despite weight gain.

In summary, insulin therapy with insulin glargine is associated with clinically important improvements in glycaemic control. Retrospective analysis of earlier trials and new studies would help elucidate the impact of insulin therapy in normal weight to obese patients with T2DM. Such data are of interest to help the clinician (and patient) determine the optimal treatment algorithms.

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TABLES AND FIGURES

Table 1. Weight management in randomised controlled trials with insulin glargine versus NPH insulin, premixed insulin or insulin lispro

	BMI at baseline (kg/m ²)		HbA _{1c} change (%)			Weight change (kg)		
	glargine	comparator	glargine	comparator	p-value	glargine	comparator	p-value
Insulin glargine versus NPH insulin								
Yki-Jarvinen H et al, 2000 [50]	29.3 ± 0.3	28.5 ± 0.3	−0.83	−0.77	n/s	+2.6	+2.3	n/d
Rosenstock J et al, 2001 [34]	30.7 ± 5.0	30.4 ± 5.1	−0.41	−0.59	n/s	+0.4	+1.4	0.0007
Fritsche A et al, 2003 (bedtime) [51]	28.7 ± 3.9	28.9 ± 3.9	−0.96	−0.84	n/s	+3.7	+2.9	n/s
Massi Benedetti et al, 2003 [42]	29.3 ± 4.3	28.8 ± 4.3	−0.46	−0.38	n/s	+2.0	+1.9	n/s
Riddle MC et al, 2003 [32]	32.5 ± 4.6	32.2 ± 4.8	−1.65	−1.59	n/s	+3.0	+2.8	n/s
Chang Yu Pan et al, 2006 [52]	24.8 ± 3.1	25.1 ± 3.3	−1.1	−0.92	0.0319*	+1.4 kg/m ² †	+1.3 kg/m ² †	n/d
Yki-Jarvinen J et al, 2006 [35]	31.3 ± 0.7	32.0 ± 0.8	−1.99	−2.10	n/s	+2.6	+3.5	n/s
Insulin glargine versus premixed insulin								
Janka HU et al, 2005 [39]	29.5 ± 3.6	29.6 ± 3.6	−1.64	−1.31	0.0003	+1.4	+2.1	0.0805
Raskin P et al, 2005 [40]	31.4 ± 5.3	31.5 ± 5.5	−2.60	−2.79	<0.01	+3.5	+5.4	<0.05
Insulin glargine versus insulin lispro								
Bretzel et al, 2006 [53]	29.2 ± 3.7	29.4 ± 3.5	−1.72	−1.83	n/s	+3.1	+3.5	n/s

*Based on superiority analysis; †actual weight change (kg) was not reported; BMI=body mass index; HbA_{1c}=haemoglobin A1c; n/d=not determined; n/s=not significant

FIGURE LEGENDS

Figure 1

The association between changes in fasting glucose levels and changes in body weight over 12 months of insulin therapy [30]. From *Diabetologia*, 42(4), 1999, 406-12, Causes of weight gain during insulin therapy with and without metformin in patients with Type II diabetes mellitus, Yki-Jarvinen H, Nikkila K, Makimattila S, Figure 3b. With kind permission from Springer Science and Business Media.

Figure 2

Energy balance in patients treated with insulin. This figure shows the relationship between changes in glucosuria, energy intake and basal metabolic rate on energy balance in patients treated with insulin (with or without metformin) for 12 months. Glucosuria decreased by 0.83 ± 0.27 MJ/day and energy intake decreased by 0.48 ± 0.34 MJ/day. $\Delta\text{BMR} - \text{Observed}$ denotes the measured change in BMR. $\Delta\text{BMR} - \text{Predicted}$ denotes the predicted change in BMR based on observed changes in body weight and fasting plasma glucose [30]. BMR=basal metabolic rate. From *Diabetologia*, 42(4), 2006, 406-12, Causes of weight gain during insulin therapy with and without metformin in patients with Type II diabetes mellitus, Yki-Jarvinen H, Nikkila K, Makimattila S, Figure 2. With kind permission from Springer Science and Business Media.

Figure 3

Change in body weight over 32 months in patients treated with insulin glargine plus oral glucose lowering agents in everyday clinical practice according to BMI at the start of observation [43]. BMI=body mass index.