

Insulin-associated weight gain in diabetes – causes, effects and coping strategies

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Insulin therapy or intensification of insulin therapy commonly results in weight gain in both type 1 and type 2 diabetes. 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, or the ‘unphysiological’ pharmacokinetic and metabolic profiles that follow subcutaneous administration. There is, however, scope 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 such as pramlintide or metformin. Insulin replacement regimens that attempt to mimic physiological norms should also enable insulin to be dosed with maximum efficiency. The novel acylated analogue, insulin detemir, appears to lack the usual propensity for causing weight gain. Elucidation of the pharmacological mechanisms underlying this property might help clarify the mechanisms linking insulin with weight regulation.

Keywords: insulin analogues, insulin-associated weight gain, type 1 diabetes, type 2 diabetes

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Weight Gain and Insulin Therapy in Diabetes: How Large is the Problem?

The problem of weight gain in type 2 diabetes is widely recognized. More than 80% of individuals with type 2 diabetes are overweight, many at the time of diagnosis. Consequently, iatrogenic weight gain is not only unwelcome, but represents an important clinical issue that can become a barrier to the successful management of glycaemic control. Yet, most blood glucose-lowering pharmacotherapies exacerbate weight gain. In the United Kingdom Prospective Diabetes Study (UKPDS), increased weight gain was associated with improved glycaemic control

and intensification of therapy; on average, patients in the intensive intervention cohort gained in excess of 5 kg (about 3 kg more than conventionally treated patients) during the 10-year follow-up period, with most of this gain occurring in the first 12 months [1]. Weight gain was seen with all pharmacotherapies used for intensive intervention, with the exception of metformin, but was greatest in insulin-treated patients who gained a mean of 6.5 kg [1]. Weight gain was higher still in a subgroup of patients who were already more than 120% of their ideal body weight (figure 1a) [2]. However, UKPDS was a landmark study confirming that aggressive treatment of hyperglycaemia will significantly improve at least

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microvascular prognosis, there being no supraphysiological level of haemoglobin A_{1c} (HbA_{1c}) below which further benefit cannot be gained [3]. This finding has increased the onus for earlier and more intensive use of insulin in type 2 diabetes. It also inspired a longitudinal study of 14 outpatients with type 2 diabetes (mean weight, 93.5 ± 5.8 kg) that tested the feasibility of achieving major improvement in glycaemic control with multiple insulin injection therapy [4]. The treatment algorithm used succeeded in 'tolerably', lowering mean plasma glucose levels from 17.5 to 7.7 mmol/l ($p < 0.001$), but in just 6 months, mean weight gain was nearly 9 kg. Weight gain correlated directly with mean serum insulin level ($r = 0.67$, $p < 0.01$) and with the total exogenous insulin dose ($r = 0.62$, $p < 0.02$). Thus, in type 2 diabetes, it seems clear that insulin therapy can be used to bring about dramatic improvements in glycaemic control, but with the penalty of significant, dose-related weight gain.

In type 1 diabetes, weight gain is often perceived as desirable. At diagnosis, patients may be underweight following a period of glucosuria, osmotic diuresis and frank catabolism due to lack of insulin. Weight gain on commencing insulin is therefore often viewed as normalization. However, this popular view of type 1 diabetes might be of more historical than current relevance. Betts *et al.* [5] have recently linked the increasing incidence of type 1 diabetes in children, with the observation that children recently diagnosed with the disease tend to have preonset and postonset body mass index (BMI) values well in excess of population means, despite normal birth weight. In an analysis of anthropometric data recorded from birth in 168 young people, diagnosed between 1980 and 2002, BMI values were inversely correlated with age at onset ($r = -0.30$, $p < 0.001$), and waist circumference standard deviation scores were substantially greater than population norms [5]. This study suggests that children with type 1 diabetes (like other normal children) have become progressively heavier at diagnosis during the past 20 years, and suggests that heavier children are prone to earlier onset of disease. Data from the Diabetes Control and Complications Trial (DCCT) also suggest that weight gain in type 1 diabetes is not merely a case of patients being returned to population means [6,7]. As in the UKPDS, insulin-associated weight gain was greater in patients receiving intensified intervention than that of conventional intervention (5.1 vs. 3.7 kg, $p < 0.0001$ during the first 12 months of therapy), but the mean weight of both groups increased to values beyond ideal. Hence, these patients were not merely normalizing their weight, and after 12 months, the intensively treated cohort had a

body weight that was, on average, 10% above ideal (figure 1b) [8]. During the following 8 years, body weight continued to drift upwards in every year in both groups – more so in the intensively treated cohort. After an average 6 years of follow up, people in the intensively treated group had gained a mean of nearly 5 kg more than their conventionally treated counterparts ($p < 0.0001$). Some individual patients experienced considerable weight gain, with BMI increasing by more than 5 kg/m², this being most common in women (figure 2). It is also significant to note that weight gain in the DCCT (and in the UKPDS) occurred in the face of quite strenuous efforts with dietary and behavioural interventions specifically aiming to limit this problem in overweight patients. This implies that the study data might underestimate weight gain in the everyday clinical setting [9].

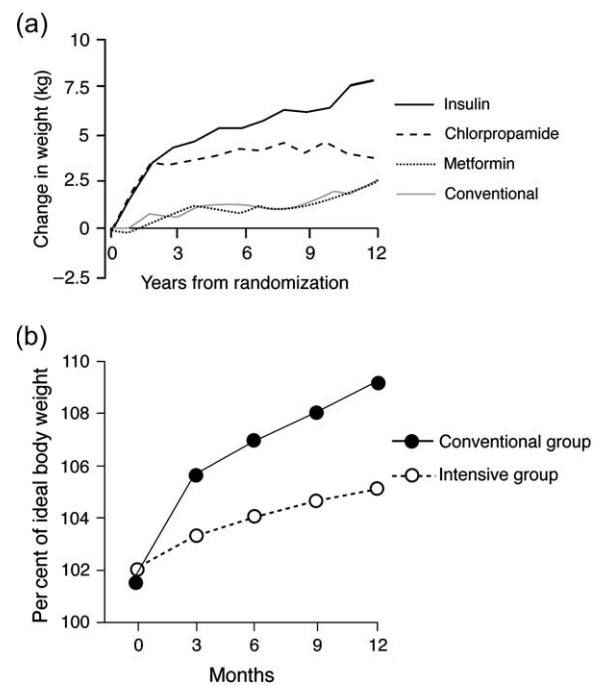
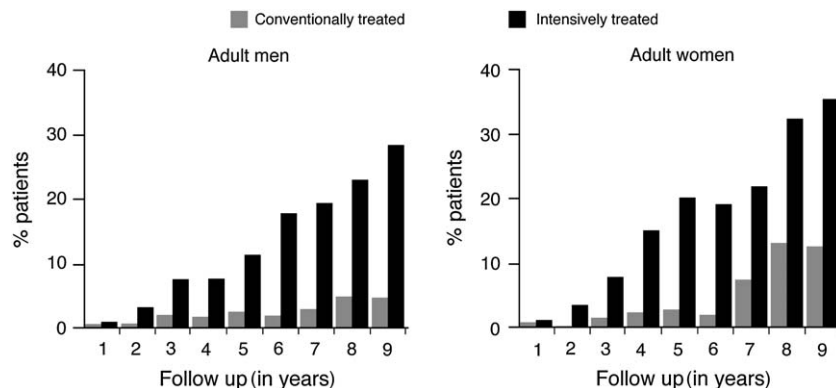


Fig. 1 Insulin-associated weight change in type 2 and type 1 diabetes. (a) Weight change by treatment in overweight patients with type 2 diabetes in UKPDS assigned to intensive intervention with insulin, chlorpropamide or metformin, or conventional treatment. Reproduced from UK Prospective Diabetes Study Group [2], Copyright © 1998, with permission from Elsevier. (b) Changes in body weight at quarterly measurement in patients with type 1 diabetes in Diabetes Control and Complications Trial, compared with 1983 life insurance norms for ideal body weight. Copyright © 1988 American Diabetes Association from DCCT Research Group [8]. Reproduced with permission from The American Diabetes Association.

Fig. 2 Proportion of adult patients with major weight gain (>5 kg/m² increase in body mass index) occurring during the Diabetes Control and Complications Trial. Copyright © 2001 American Diabetes Association from DCCT Research Group [7]. Reproduced with permission from The American Diabetes Association.



Insulin-associated Weight Gain: Does It Really Matter?

Counting the Cost of Kilograms, Control and Compliance

Given that improved glycaemic control improved outcome in both UKPDS and DCCT, it can be argued that the 'price' paid for lower blood glucose levels in terms of weight gain is a fair one [10,11]. However, this rather simplistic argument makes two assumptions. First, that patients will accept weight gain with insulin and actually achieve beneficial glycaemic targets, and second, that the improvement in prognosis gained by lowering blood glucose will not be compromised by weight gain.

One way in which weight gain matters, even if it is only a cosmetic concern, is if it becomes a barrier to compliance and affects diabetic control. The possibility of weight gain is now widely recognized as a psychological barrier (for both patients and physicians) to the initiation of insulin in type 2 diabetes [12,13]. As a consequence, initiation of insulin is often delayed well beyond the point where oral antidiabetic agents fail to control glycaemia. But even if insulin is initiated in a timely fashion, the emotional effects of weight gain may contribute to the avoidance or neglect of self-management [13].

In type 1 diabetes, initiation of insulin is not at issue, but adherence to prescribed regimens may be compromised by a desire to avoid weight gain. A study in the United States, of 341 women (aged 13–60 years) with type 1 diabetes, reported that 31% intentionally omitted insulin, with this habit being frequent for 8.8% [14]. Approximately half cited weight control as the primary reason for insulin omission, and these women were characterized by poorer glycaemic control, more diabetes-related hospitalizations and microvascular complications and greater psychological distress than insulin-adherent

women and women not pre-occupied with weight gain. The authors concluded that 'patients pre-occupied with eating and weight concerns may also become emotionally overwhelmed by diabetes and/or fearful of normoglycaemia (and the associated weight-related consequences), thus reinforcing the desire to omit insulin and maintain elevated blood glucose levels'.

The problem of insulin omission was confirmed in a UK study of 65 young subjects with type 1 diabetes, who were followed during the transition from adolescence to young adulthood [15]. Here, 30% of the women admitted to having under-dosed insulin to manipulate their weight, while 45% of women who developed microvascular complications had intentionally misused insulin to prevent weight gain. One woman had omitted insulin for periods of up to 2 weeks; another had taken no more than two injections per week for 7 years. Despite this misuse, average weight and BMI increased during the 10-year study; women were overweight, both as adolescents and adults, while men became overweight as young adults. Concern about body weight and form increased significantly with time for both sexes, resulting in increased dietary restraint.

Suboptimal glycaemic control arising from weight-related insulin misuse has ominous prognostic implications. An adolescent cohort that had participated in the DCCT ($n = 175$) was followed up as part of the Epidemiology of Diabetes Interventions and Complications (EDIC) study [16]. Four years after termination of DCCT, the level of glycaemic control between individuals originally assigned to conventional and intensified intervention had converged (HbA_{1c} approximately 8.4%). However, the prevalence of worsening in retinopathy was reduced by some 75% in individuals formerly assigned to intensive therapy. This implies that periods of suboptimal control in earlier life can result in enduring morbidity that cannot be reversed even if

glycaemic control is regained later. In summary, the cost paid by individuals with diabetes who attempt to control their weight by under using insulin is a high one, but many individuals seem willing to bear the consequences.

Increased Kilograms, Increased Risk?

The association of weight gain and the incidence of type 2 diabetes is well documented [17–20], as is the correlation between body weight and cardiovascular risk [20]. It therefore seems logical that weight gained in people with diabetes, a disease with a high incidence of cardiovascular events, would be predictive of macrovascular complications. In fact, there is little direct evidence to support this. Hard cardiovascular endpoints recorded by large-scale studies, such as UKPDS and DCCT, do not appear to have been stratified by weight or weight gain, so it is not easy to give a definitive answer to the question: 'is outcome adversely affected by weight gain for any given level of glycaemic control?' This 'omission' may relate to the fact that the correlations between macrovascular endpoints and glycaemic control were not statistically significant in these studies, and there being no theoretical reason to link weight gain to microvascular outcomes. Indeed, data from UKPDS suggest that the greater microvascular benefits of insulin vs. oral agents are achieved without an increase in cardiovascular mortality [10].

Nevertheless, there is compelling indirect evidence that weight gain does adversely affect cardiovascular risk. Purnell *et al.* did stratify data from the intensively treated DCCT cohort by quartiles of weight gain [6]. Comparing the first quartile (where BMI remained stable) with the fourth (where BMI increased by some 7 kg/m²), the baseline values for mean BMI were 24 kg/m² in both groups, with HbA_{1c} being 8.7 and 9.2% ($p < 0.01$) respectively. After a mean follow-up of 6.1 years, HbA_{1c} was identical at 7.3% in both groups, implying a greater improvement in glycaemia in the quartile that gained the most weight. However, while the first quartile showed improvements in all parameters of cardiovascular risk, the fourth was associated with significant negative changes in all of these parameters (Table 1). Hence, improved glycaemic control did not result in secondary improvements in the cardiovascular risk profile for the patients who gained weight, and those who gained the most weight were not necessarily those with the worst baseline cardiovascular profile. Of course, a causal relationship between weight gain and adverse cardiovascular outcomes cannot be assumed, but other studies have shown that people with diabetes who actively lose

Table 1 Diabetes Control and Complications Trial data for parameters of cardiovascular risk by quartile of weight gain in intensively treated patients

	Quartiles of weight gain			
	1	2	3	4
HbA _{1c}	7.3	7.2	7.1	7.3
BMI	24	25	27	31
Systolic BP (mmHg)	113	117	115	120*
TG (mmol/l)	0.79	0.82	0.91	0.99*
LDL cholesterol (mmol/l)	2.74	2.79	2.92	3.15*
HDL cholesterol (mmol/l)	1.40	1.34	1.29	1.27*

HbA_{1c}, haemoglobin A_{1c}; BMI, body mass index; BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride.

Adapted from Purnell *et al.* [6].

* $p < 0.001$

weight improve not only their risk profile [20–22] but also their longevity [23,24]. A retrospective analysis calculated that for the average patient with type 2 diabetes who lost weight, each 1 kg weight loss was associated with 3–4 months of prolonged survival [23]. A prospective analysis with a 12-year mortality follow up of nearly 5000 overweight individuals with diabetes (aged 40–64 years), also showed a survival benefit for weight loss [24]. Here, intentional weight loss was reported by 34% of the cohort and after adjustment for initial BMI and other factors, this was found to be associated with a 25% reduction in total mortality (Relative Risk = 0.75; 95% CI 0.67–0.84), and a 28% reduction in cardiovascular and diabetes mortality (RR = 0.72; 95% CI 0.63–0.82).

Furthermore, there is clear evidence that excess adiposity in type 2 diabetes is associated with insulin resistance [25,26], which not only contributes to dyslipidaemia [27,28] but can also fuel a vicious circle of beta-cell dysfunction, increasing insulin resistance, increasing requirement for insulin and further weight gain [29,30]. Purnell *et al.* [6] likened the natural history of the patients who gained the most weight in the intensively treated DCCT cohort to the 'insulin resistance syndrome', implying that this metabolic derangement can also occur in type 1 diabetes. Interestingly, a predictor of weight gain in these individuals was a family history of type 2 diabetes [31]. The recently articulated 'accelerator hypothesis' of diabetes regards the distinction between type 1 and type 2 diabetes as blurred with weight gain as a central trigger [5,32]. In short, as well as potentially undermining the cardiovascular benefits of improved blood glucose control, weight gain could accelerate the disease processes underlying diabetes. In this context, weight gain has to be viewed as an undesirable side effect of insulin therapy.

Weight Gain with Insulin Therapy – What are the Mechanisms?

Conservation of Calories?

A number of mechanisms have been described to explain weight gain with insulin therapy, and one of the most familiar concerns the conservation of ingested calories as improved glycaemic control returns patients to glycaemic levels that are below the renal threshold. This effect was very well illustrated in a study of six patients with poorly controlled type 1 diabetes who were switched to an intensified insulin regimen, while maintaining a constant calorie intake [33]. After 2 months, the patients' mean daily blood glucose concentration had been reduced from 14.8 to 7.7 mmol, with HbA_{1c} reduced from 12.9 to 9.6% (both $p < 0.01$). This improved control resulted in an almost complete elimination of glycosuria from 428 to 39 mmol/day ($p < 0.05$), with body weight increasing by 2.6 kg ($p < 0.05$), of which 2.4 kg was accounted for by fat mass. Daily energy expenditure decreased by 5% (118 kcal/day, $p < 0.05$). In this study, 70% of the weight gain was calculated to be accounted for by improved conservation of ingested calories, the remaining 30% by the decrease in energy expenditure. However, the patients in this study were in very poor control at baseline – well above the renal threshold – so this study may not be representative of the mechanisms of insulin-induced weight gain generally.

Change in Metabolism?

Insulin is a very anabolic hormone. In addition to its main physiological role of regulating (by inhibition) hepatic glucose output and stimulating peripheral glucose uptake (PGU), insulin has profound and equally important roles on free fatty acid metabolism (inhibiting lipolysis and promoting lipogenesis) and protein metabolism. Unlike animal models, the main anabolic action of insulin on protein metabolism is one of inhibiting protein catabolism [34,35]. Indeed, insulin is abused by athletes to enhance performance and muscle building. Insulin has also been shown to improve survival in highly catabolic patients in intensive care units [36]. Thus, weight gain may simply result from slight overreplacement of insulin, producing a general anabolic effect.

Compensation for Hypoglycaemia?

Another well-cited explanation for insulin-associated weight gain is that patients increase their carbohydrate

and hence, total calorie intake in response to the perceived threat or experience of hypoglycaemia. Although widely accepted, this mechanism is difficult to prove; if patients are successful in eliminating hypoglycaemia through increased eating, then a correlation between hypoglycaemic risk and weight gain cannot be expected. Effectively, weight gain might become a surrogate for the perceived risk of hypoglycaemia [37]. There is, however, some evidence that this mechanism is operative in insulin-associated weight gain. During the first year of the DCCT, 29 patients experienced severe hypoglycaemia, and gained a mean 6.8 kg, which was 2.2 kg more ($p < 0.05$) than the weight gained by those who did not experience severe hypoglycaemic episodes [8].

Some possible indirect evidence for fear of hypoglycaemia as a cause of weight gain came from a longitudinal study of 100 patients switched from twice-daily insulin to basal-bolus therapy [38]. Here, there was no gain in weight in the year before therapy change, yet median weight increased (by approximately 1–1.5 kg) in each of the subsequent 4 years, in contrast to a matched control group of 30 patients. Weight gain did not correlate with glycaemic control, which did not alter after the switch to multiple injection therapy. The mean total insulin dose did not increase after switching to multiple injection therapy either. It is therefore difficult to attribute the weight gain to anything other than increased calorie intake. Speculatively, this could relate to patients perceiving an increased risk of hypoglycaemia from their more frequent injection regimen, although the authors suggested that patients perceived greater dietary freedom. Of course, increased calorie intake resulting from an increased frequency of neuroglucopenia need not be a conscious behavioural change; increased appetite is an early, involuntary and adaptive response to low blood glucose level [9].

Central Effect on Appetite and Weight Regulation?

Insulin in normal physiology has effects in the central nervous system (CNS), and most of those that have been elucidated seem to concern suppression of appetite [39–42]. As insulin is secreted in response to nutrient intake, it effectively functions in the brain as a signal that the organism is replete with nutrients. In concert with leptin, which is secreted in proportion to stored fat, insulin therefore appears to act as a satiety signal [43,44]. In this context, a possible explanation for weight gain derives from the 'neurocentric' model of 'diabesity', recently articulated by Schwartz, Niswender, Porte, Baskin and others [43–45]. According to this model, the primary lesion causing weight gain and progression to type 2

diabetes might involve a reduction in signalling of satiety to the arcuate nucleus of the hypothalamus. As both intact insulin and leptin signalling are believed to be required to produce an anorectic response, any single defect involving these signals could effectively cause 'central insulin resistance'. This would result in the anabolic actions of circulating insulin no longer being opposed by the catabolic and anorectic neuronal responses that insulin would normally stimulate via the hypothalamus. In turn, this could trigger a vicious circle of chronic nutrient overload, weight gain and insulin resistance. In this model, specific neuronal insulin resistance or reduced transport of insulin across the blood-brain barrier would mean that insulin was having an unphysiological pattern of action. Of course, exogenously administered insulin would be no worse than endogenous insulin in this respect, but the addition of large doses of exogenous insulin to drive down blood glucose could accelerate weight gain in such a system.

Unphysiological Insulin Replacement?

In health, body weight remains relatively stable in adult individuals who remain physically fit and/or achieve a good balance between calorie intake and exercise. Therefore, the rapid weight gain seen in association with insulin therapy of diabetes implies that insulin replacement is not being given in ways that accurately recreate the healthy physiological balance. Certainly, this is true when the time-action profiles of exogenously administered insulins are considered; the mean pharmacokinetic insulin profiles produced by basal-bolus therapy are not perfect recreations of normal physiological secretion profiles [46] and variability in the absorption, and hence pharmacodynamic profiles of subcutaneously injected insulin means that the intended profile is seldom recreated by any given injection [47-49]. Thus, there is always likely to be a prevailing and unpredictable imbalance between insulin supply and physiological need, with periods of both over and under supply during each day. Intervals of oversupply will potentially result in episodes of hypoglycaemia. Imperfect mean pharmacodynamic profiles and variability are particularly problematic with traditional basal insulins [47-49] and as these are generally dosed in the evening, hypoglycaemia often occurs at night. This becomes another limiting factor for adherence with insulin doses, and may compound weight gain through defensive snacking, as previously discussed.

Another way in which the provision of exogenous insulin therapy is inherently unphysiological concerns the route of administration [50]. In normal physiology, insulin is secreted into the portal vein and arrives at the liver

first. Here, it suppresses endogenous glucose production (EGP) and up to 60% is cleared via receptor interaction. Only the surviving 40-50% continues into the systemic circulation to act on peripheral muscle and fat tissue to increase PGU and suppress lipolysis. When insulin is given subcutaneously, the situation is very different. Here, the absorbed insulin first circulates systemically, so it has a disproportional influence on muscle and adipose tissue [51]. In effect, the liver is 'under-insulinized' and the periphery 'over-insulinized', so perhaps an unphysiological distribution partly explains the disproportionate increase in fat mass typically reported with insulin therapy [10]. There is also strong evidence that this unphysiological under-insulinization of the liver due to systemic (subcutaneous) insulin delivery has other effects, particularly on the growth hormone/insulin-like growth factor (IGF)-I system. This system is known to play a central role in the maintenance of body composition and the balance of anabolism and catabolism [51,52]. The lack of portal insulin reduces hepatic IGF production with knock on effects on pituitary growth hormone secretion [52,53]. In this respect, continuous intraperitoneal insulin infusion (CPII), where insulin is delivered into the portal vein, offers a theoretical advantage [54].

Limiting Insulin-associated Weight Gain

Increasing Insulin Sensitivity

Two broad strategies can be expected to limit weight gain with insulin therapy: limiting the insulin dose requirement and administering insulin in ways that more accurately reflect the dynamic physiological needs.

One strategy for limiting insulin-associated weight gain that has long been recognized is to limit the required insulin dose by increasing the patient's insulin sensitivity. In type 2 diabetes, insulin sensitivity is known to be inversely related to adiposity, so programmes of exercise and dieting can help to break into the vicious circle of high insulin requirement and increasing weight. The great potential of this strategy was shown in a study of 15 patients older than 65 years who had poorly controlled, insulin-treated type 2 diabetes and obesity [55]. A weight loss programme was successfully completed by 12 patients, and the average loss of 9 kg enabled their mean dose of 52 ± 5 U of insulin per day to be discontinued altogether. A more recent study randomized patients with poorly controlled, but insulin-naive, type 2 diabetes to one of three groups: an intensive diet plus exercise programme; the same programme with insulin initiation, or insulin initiation alone [56]. During 12 months, HbA_{1c} decreased by 1.2, 1.0 and 1.5%, respectively (ns),

with respective weight changes being -3.0 , $+3.5$ and $+4.9$ kg. This study therefore showed the potential of effective lifestyle intervention to delay the need for insulin or to limit insulin-associated weight gain. However, patients assigned to the lifestyle programme regained weight and had deteriorating glycaemic control after the study. Indeed, a failure to maintain the initial weight loss achieved through calorie restriction or exercise in the long term is documented in many trials [57].

Another strategy has been to use pharmacological interventions to increase insulin sensitivity. Some insulin-sensitizing agents with peroxisomal proliferator-activated receptor agonist properties (notably thiazolidinediones) actually promote weight gain by stimulating adipocyte proliferation [58], although it is possible that fat is redistributed 'favourably' from visceral to subcutaneous depots [59,60]. Nevertheless, the long-term consequences of this mechanism are unknown. A recently reported study measured total body water using deuterated water, and body composition using dual-energy X-ray absorptiometry and computed tomography after 12 weeks of treatment with either pioglitazone or glipizide [60]. This study found that about 75% of the 3.1 kg mean weight gain seen with pioglitazone was due to fluid retention. There were also potentially beneficial reductions in diastolic blood pressure and systemic vascular resistance associated with pioglitazone in this short-term study.

Metformin has been associated with weight loss in type 2 diabetes, and with insulin-sparing and cardioprotective properties [61,62]. In one retrospective study, addition of metformin to the regimen of 71 insulin-treated obese patients with type 2 diabetes reduced HbA_{1c} and BMI, while enabling the mean insulin dose to be decreased from 46.4 U per day to just 6.1 U, with 83% of patients able to discontinue insulin completely [63]. Metformin can also be used to limit weight gain in patients beginning insulin therapy. In a recent study of 183 patients with type 2 diabetes referred for insulin initiation [64], the continuation of metformin was associated with less weight gain than placebo (6.1 vs. 7.6 kg, $p = 0.02$), a greater reduction in HbA_{1c} (adjusted difference, 0.5%, $p = 0.02$) and a lower insulin requirement (62 vs. 86 U, $p < 0.001$), albeit at the cost of increased hypoglycaemia (RR 1.24).

The mechanism underlying the weight-sparing properties of metformin may relate to appetite suppression rather than a direct effect on insulin use. A study of 12 diet-treated women with obesity and type 2 diabetes randomized the participants to two dose levels of metformin or placebo for 3 consecutive days [65]. Metformin resulted in a dose-related reduction in calorie intake in a subsequent meal test. A supplementary placebo-controlled

experiment was performed, involving 48 diet-treated women with obesity and type 2 diabetes who had previously failed to lose weight. Addition of metformin enabled a mean weight loss that was 8 kg greater than that of the placebo group, suggesting that the drug had facilitated adherence to the diet. Pharmacological evidence suggests that the satiety effect of metformin might be mediated by increasing the production of the anorectic incretin glucagon-like peptide (GLP)-1 [66,67], or by inhibiting its metabolizing enzyme, dipeptidyl peptidase IV [68].

Indeed, recently developed analogues or mimetics of anorectic hormones, including the GLP-1 analogue liraglutide [69–71], the GLP-1 mimetic exenatide [72,73] and the amylin analogue pramlintide [74–76] show great potential as antidiabetic therapies with weight-reducing properties. They could therefore one day be used as insulin- and weight-sparing adjunctive therapies, notwithstanding the need for additional injections that this tactic would impose. Pramlintide has already been studied in this role. In an analysis of overweight patients with type 2 diabetes, the addition of pramlintide to insulin decreased HbA_{1c} by approximately 0.4% and weight by 1.8 kg relative to placebo (both, $p < 0.0001$), during 6 months [75]. The greatest reductions in weight were observed in patients with BMI >40 kg/m², and in those concomitantly treated with metformin (-3.2 and -2.5 kg, respectively, both $p < 0.001$).

The concept of using insulin-sparing adjunctive therapies has recently been extended to type 1 diabetes. In a placebo-controlled 3-month study of 27 adolescents taking more than 1 U insulin/kg/day, addition of metformin enabled a 0.12 U/kg dose reduction in comparison with placebo ($p < 0.05$), achieved with a relative HbA_{1c} reduction of 0.6% [77]. BMI remained unchanged in this short-term study, but longer duration studies are planned to quantify the potential benefits of adjunct insulin-sparing therapy and to determine whether specific subgroups stand to gain particular benefit. Other studies have examined the addition of pramlintide to insulin therapy in type 1 diabetes [76,78]. A pooled analysis of three studies showed pramlintide to be associated with reductions in both HbA_{1c} (by 0.3%, $p < 0.001$) and body weight (by 1.8 kg, $p < 0.001$) during 6 months, with these benefits achieved without an increase in severe hypoglycaemia [78].

Other drugs that act primarily as antiobesity agents are also being studied in diabetes. These include the appetite suppressant, sibutramine, and the gastrointestinal lipase inhibitor, orlistat [79]. The selective serotonin reuptake inhibitors might also have a role to play in increasing insulin sensitivity and reducing weight gain in diabetes [80,81]. In addition, the drug rimonabant, the first of

a new class of selective cannabinoid type 1 receptor antagonists, has shown promise in producing significant weight reductions, as well as improvement in parameters of cardiovascular risk in overweight people with or without diabetes [82,83]. Combined with a low-calorie diet, a daily dose of 20 mg reduced weight by a mean 6.6 kg during 1 year (compared with a 1.8 kg weight loss with placebo, $p < 0.001$) [82]. The role of each of these agents in mitigating the weight gain associated with insulin therapy, however, awaits clarification.

Towards More Physiological Insulin Replacement

Insulin secretion in health is characterized by a low and constant basal output, best seen in the overnight profile, supplemented by rapidly arising increases in response to prandial stimuli [84]. Modern basal-bolus injection and continuous subcutaneous infusion (CSII) regimens attempt to recreate this profile by using insulin preparations with appropriate absorption properties. By providing insulin *when needed*, it is logical to assume that diabetic control should be improved and the risks of adverse effects minimized. Also, the appropriate timing of insulin availability might enable greater dose-efficiency, and this too should help avoid weight gain. The importance of increasing early postprandial insulin availability in this respect has been demonstrated in a number of studies involving patients with type 2 diabetes [85–87]. These have shown that a given dose of insulin has a significantly greater overall blood glucose-lowering effect when administered as a bolus early in the prandial setting than when delayed or protracted. The mechanism appears to be that a rapid increase in plasma insulin concentration acts as a hepatic signal to suppress EGP ahead of the absorption of ingested carbohydrate [88]. The implication is that effective postprandial glucose control should enable dose-sparing insulin regimens, at least in type 2 diabetes. Hence, supplementation of the prandial insulin response might be a more insulin-efficient strategy than supplementation of basal insulin. If the blood glucose-lowering effects of given insulin doses vary according to the timing of their delivery, then weight gain might indicate inefficient insulin replacement.

Notwithstanding the potential clinical importance of effective postprandial glucose control, multiple injection or CSII regimens probably do make efficient use of the total insulin doses [89,90]. Evidence for this is provided by a recent study in Bosnia where patients with type 1 diabetes on 'conventional' twice-daily insulin regimens were found to have a higher mean BMI, compared with those on multiple injection insulin treatment (23.2 vs.

21.2 kg/m², $p < 0.01$), with the proportion overweight also being higher (27.3 vs. 0%, $p = 0.012$) [91]. Insulin doses were higher in the conventionally treated patients (0.84 vs. 0.77 iu/kg, $p < 0.05$), but glycaemic control was poorer. However, in clinical practice, the main concern has been to use the more sophisticated regimens to gain improvements in overall glycaemic control, and, as previously noted, improvement in glycaemia has in itself been associated with weight gain [8,90], albeit that the efficacy : tolerability balance is probably shifted in a favourable direction when basal-bolus therapy is compared with cruder regimens such as twice-daily NPH insulin. The potential of a more physiological route of administration to limit weight gain in this context was showed in a 1-year study of CII vs. multiple injection therapy in type 2 diabetes [92]. Here, patients receiving CII achieved an HbA_{1c} of 7.5% with modest weight loss (−1.0 kg), while patients receiving subcutaneous insulin had modest weight gain (0.4 kg).

In clinical practice, most patients treated with insulin rely on subcutaneous administration, however, but the development of insulin analogues has offered the opportunity to match the timing of insulin replacement to physiological need more closely. The rapidly absorbed analogues (insulin aspart; insulin lispro and insulin glulisine) have pharmacokinetic profiles that more closely match the physiological prandial insulin response than soluble human insulin, and are well suited to CSII. Clinically, these analogues improve postprandial glycaemic control significantly, compared with exogenous soluble human insulin and also reduce hypoglycaemic risk concomitant with minor improvements in HbA_{1c}, but their short duration of action often obliges an increase in the dose of basal insulins when used in basal-bolus therapy [46]. Insulin glargine has been developed as a basal insulin analogue to produce a flatter and more protracted time-action profile than traditional zinc- or protamine-retarded basal insulins. This analogue has been shown clinically to improve the balance between glycaemic control and hypoglycaemic risk in comparison with NPH insulin [46]. For each of these analogues, however, the benefits have not extended to a clear indication that weight gain can be limited commensurate with the improved glycaemic control. For example, in a 24-week algorithm-driven treat-to-target study in which insulin glargine or NPH insulin were added to oral agents in overweight individuals with type 2 diabetes, HbA_{1c} improved from about 8.6–7.0% in both groups, but with a clear relative reduction in hypoglycaemic risk with the analogue [93]. However, a mean weight gain of 3.0 and 2.8 kg (ns) was reported for insulin glargine and NPH respectively. Thus, the 'class' effects

of insulin with regard to weight gain holds true for the insulin analogues. There is, however, one exception:

The Enigma of Insulin Detemir with Regard to Weight Gain

One recently introduced insulin analogue is worthy of special consideration in this review because it has consistently been associated with a reduced propensity for weight gain in comparative studies. Insulin detemir [LysB29(N-tetradecanoyl)des(B30) human insulin] is a novel insulin–fatty acid hybrid, in which myristic acid has been acylated to the terminus of the B chain, enabling reversible albumin binding. Insulin detemir was engineered to achieve a smooth and protracted absorption profile, with low variability in pharmacodynamic response from injection to injection, and it is believed that albumin binding contributes to these properties [49,94]. It was anticipated that, clinically, these properties would reduce the risk of nocturnal hypoglycaemia and allow more aggressive targeting of fasting glycaemia. Indeed, when used as the basal component of basal–bolus therapy, insulin detemir has consistently resulted in a lower relative risk for nocturnal hypoglycaemia than NPH insulin at equivalent or superior glycaemic control [37,95–100]. But an unexpected finding that has reached statistical significance in every phase 3 trial reported has been a relative reduction in weight gain in comparison with NPH insulin. Used as the basal component of basal–bolus therapy for patients with type 1 diabetes, insulin detemir was associated with weight neutrality or even small non-significant reductions in weight during periods of up to 12 months, whereas NPH insulin was associated with weight gain of 0.7–0.8 kg during 6 months [94–96,98,100] and 1.2–1.4 kg during 12 months [37,101]. In a 6-month study of basal–bolus therapy in individuals with type 2 diabetes, insulin detemir was associated with a gain in weight of 0.4 kg, whereas patients receiving NPH insulin gained 1.3 kg ($p = 0.017$) [102]. In a 24-week comparison with NPH insulin as add-on therapy to oral agents in type 2 diabetes, with aggressive titration to an HbA_{1c} of approximately 6.5%, insulin detemir was associated with a mean weight gain of 1.2 kg, compared with 2.8 kg with NPH insulin ($p < 0.001$) [98]. Interestingly, when weight change data from this study were stratified by baseline BMI, the treatment disparity was seen to increase with BMI (i.e. the more overweight the patients were, the less weight they gained with insulin detemir) despite mean unit dose increasing with BMI [103].

The mechanism underlying this apparent advantage has not been defined, although ideas have been suggested. The mechanism, once elucidated, may have therapeutic

potential in other areas and serve to advance our understanding of normal physiology. It is therefore of the utmost scientific interest.

One suggestion concerns the observation that insulin detemir was associated with a reduced risk of nocturnal hypoglycaemia in most of these studies. This might imply that patients are avoiding weight gain by reducing their defensive snacking, although this reasoning should also apply to the other analogues where a weight advantage has not been shown. Another putative mechanism concerns the blood glucose–lowering action of insulin detemir. An assessment of EGP and PGU during pharmacological clamp studies has indicated that insulin detemir may have a more pronounced effect on EGP and a lesser effect on PGU, compared with NPH [104,105]. This has led to the intriguing suggestion [104] that because insulin detemir is 98% albumin bound in the circulation [106,107], its access to peripheral compartments is physically limited, whereas it retains full access to hepatocytes via hepatic sinusoids. Thus, its relative effects on EGP and PGU may be more ‘physiological’ than other subcutaneously delivered insulins.

A third speculative theory is that the lipophilic fatty acid side chain of insulin detemir or the relatively low albumin content of cerebrospinal fluid permits a relatively increased access to CNS receptors [108]. There is, in fact, some evidence from animal studies that insulin detemir does have a relatively increased penetration into the CNS [108], in which case it might have some potential to reverse defects implied in the neurocentric model of diabetes elaborated above.

Elucidation of the mechanism(s) at play in the weight-sparing effect of insulin detemir could provide valuable insights into the ways in which insulin modifies metabolism to influence weight in health and in diabetes. Such knowledge might also enable the future development of insulin analogues with even greater metabolic advantages. Certainly, data from the insulin detemir studies (and an understanding of normal physiology) tell us that weight gain need not be regarded as an inevitable consequence of insulin replacement therapy for diabetes mellitus.

Summary

Exogenous insulin replacement therapy remains the most effective treatment for hyperglycaemia in type 1 and advanced type 2 diabetes, but in both cases, it regularly results in excessive weight gain that might adversely affect prognosis. The risk of weight gain is well known to doctors and patients, and often results in a delay in the initiation or intensification of insulin, or in its misuse by

patients, with serious prognostic implications. The underlying causes of insulin-associated weight gain include conservation of glucose calories previously renally excreted, and perhaps also increased calorie intake as a defence against hypoglycaemia. It is possible to limit insulin doses and insulin-associated weight gain, however, by increasing patients' insulin sensitivity. This can be done with diet, exercise, and insulin-sensitizing drugs such as metformin. In addition, the novel analogue, insulin detemir, is less prone to causing weight gain than conventional basal insulin preparations so offers scope for addressing the problem.

Ultimately, the subcutaneous administration of insulin is inherently unphysiological in terms of both distribution and time-action profile, and it is likely that these factors also have an impact on weight gain. As advances are made in our understanding of weight regulatory mechanisms and in our technical abilities to manipulate and administer insulin therapies, it should be possible to refine insulin replacement therapy to reduce associated adverse events. Given that weight gain is not inevitable in normal physiology, it should not be regarded as inevitable with insulin replacement therapy.

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