REVIEW ARTICLE

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Bodyweight Changes Associated with Antihyperglycaemic Agents in Type 2 Diabetes Mellitus

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Contents

Abstract

The majority of patients with type 2 diabetes mellitus are overweight or obese at the time of diagnosis, and obesity is a recognised risk factor for type 2 diabetes and coronary heart disease (CHD). Conversely, weight loss has been shown to improve glycaemic control in patients with type 2 diabetes, as well as to lower the risk of CHD. The traditional pharmacotherapies for type 2 diabetes can further increase weight and this may undermine the benefits of improved glycaemic control. Furthermore, patients' desire to avoid weight gain may jeopardise compliance with treatment, thereby limiting treatment success and indirectly increasing the risk of long-term complications. This review evaluates the influences of established and emerging therapies on bodyweight in type 2 diabetes.

Improvement in glycaemic control with insulin secretagogues has been associated with weight gain. On the other hand, biguanides such as metformin have been consistently shown to have a beneficial effect on weight; metformin appears to modestly reduce weight when used as a monotherapy. α-Glucosidase inhibitors are considered weight neutral; in fact, the results of some studies show that they cause reductions in weight.

Thiazolidinediones (TZDs) are typically associated with weight gain and increased risk of oedema, while the impact of some TZDs, such as pioglitazone, on lipid homeostasis could be beneficial. Insulin, the most effective therapy when oral agents are ineffective, has always been linked to significant weight gain.

Newly developed insulin analogues can lower the risk of hypoglycaemia compared with human insulin, but most have no advantage in terms of weight gain. The basal analogue insulin detemir, however, has been demonstrated to cause weight gain to a lesser extent than human insulin. The emerging treatments, such as glucagon-like peptide-1 agonists and the amylin analogue, pramlintide, seem able to decrease weight in patients with type 2 diabetes, whereas dipeptidyl peptidase-4 inhibitors seem to be weight neutral.

In summary, while reduction of hyperglycaemia remains the foremost goal in the treatment of patients with type 2 diabetes, the avoidance of weight gain may be a clinically important secondary goal. This is already possible with careful selection of available therapies, while several emerging therapies promise to further extend the options available.

1. Bodyweight and Diabetes Mellitus

Obesity is a major risk factor for developing type 2 diabetes mellitus, and an estimated 60–90% of patients are overweight or obese prior to diagnosis.[1,2] Being overweight increases the risk for coronary heart disease (CHD) in healthy individuals, and this association may be even more important in people with diabetes, as CHD is responsible for >75% of deaths in these individuals.[3] A recent cross-sectional study of 44 000 patients with type 2 diabetes reported that 80% were overweight, with 37% of these obese.[4] Such excessive weight is associated with insulin resistance, impaired glucose homeostasis and other cardiovascular risk factors seen in patients with type 2 diabetes, including hypertension and dyslipidaemia.[5] Importantly, the localisation of fat in the body has a significant effect on health; fat, especially in the visceral area, liver, muscle and in pancreatic β cells, can cause a worsening of glucose tolerance in patients with type 2 diabetes. It has been estimated that a weight gain of 5kg could increase the risk of CHD by 30%, and that the changes in blood pressure and lipids associated with this weight gain[6] could increase the risk by a further 20%.[7] The risk of CHD doubles when hypertension is present in patients with diabetes.[8,9] The ratio of triglycerides to high-density lipoprotein (HDL)-cholesterol is much higher in obese than in normal-weight patients, even when patients are treated with lipid-reducing agents (mostly statins).[4]

The established pharmacotherapies for diabetes, such as sulfonylureas (SUs), biguanides, glitazones and insulin, improve glycaemic control and thus reduce the risk of microvascular and macrovascular complications. However, most of these treatments are also associated with concomitant weight gain,[10-13] which could offset this benefit. For example, the 10-year UKPDS (UK Prospective Diabetes Study), looking at the effect of established therapies for diabetes, reported improvements in glycaemic control, but these were coupled with an average weight gain of 5kg in the groups receiving intensive interventions, with the greatest average weight gain of 6.5kg occurring in the insulin-treated group.[10] The exception was treatment with metformin, which, in contrast to SUs and insulin, showed no further weight gain than diet treatment alone. The detrimental impact of weight gain on the prognostic benefits of improving glycaemic control is unknown.

Apart from its association with increased CHD risk factors, weight gain is often cosmetically very unwelcome to patients, and therefore can become a barrier to intensifying diabetes treatment, as patients generally try to avoid gaining weight.[13,14] Although the weight gain *per se* may not be clinically significant, it may jeopardise compliance with the treatment, preventing the achievement of glycaemic targets and limiting the treatment success. Weight gain can affect compliance to the point that some patients manipulate their medication in order to control their weight. In extreme cases, patients choose to omit insulin altogether in an attempt to limit their weight gain. It is important to establish to what extent the benefits associated with improved glycaemic control are counteracted by the potential for an increased risk of CHD due to weight gain.[15]

2. Weight Loss in Diabetes

Evidence that weight gain could be of direct prognostic significance in type 2 diabetes has been provided by studies in which even modest weight loss has improved glycaemic control and cardiovascular risk. For example, calorie controlled diet alone has been shown to decrease plasma glucose and enhance insulin sensitivity in type 2 diabetes patients.[16,17] A reduction in body mass index (BMI) of 4.8 kg/m^2 was shown to improve glycaemic control, based on a reduction in glycosylated haemoglobin (HbA_{1c}) of 2.0%, and a significantly improved lipid profile over a 12-month period.[18] In a 12-year, prospective mortality study, intentional weight loss (up to 5 kg/m^2) was associated with a 25% reduction in total mortality and a 28% reduction in CHD risk.[19] Thus, when individuals with diabetes lose weight, the risk markers for CHD decrease, and they increase their longevity.[18-21] Several studies have shown that weight loss, including the use of diet and exercise programmes, improves insulin sensitivity and reduces the risk for CHD.[16,17] However, it is not clear if this improvement is due to the weight loss *per se,* or due to the fact that inevitably the individuals become fitter. An analysis of 15 studies of CHD risk in obese patients with type 2 diabetes showed that a weight loss of 10kg was associated with reductions in fasting serum cholesterol (−9.9%), low-density lipoprotein (LDL)-cholesterol (−6.8%), triglycerides (−19.3%), systolic and diastolic blood pressure (−4.9% and −3.8%, respectively) and fasting plasma glucose (FPG); the reduction in FPG was related to baseline value, with a higher baseline value resulting in a greater reduction in FPG.[7]

More evidence that weight affects prognosis in patients with type 2 diabetes is provided in a stratified analysis by Ridderstrale et al.,[4] in which obese patients had a very high incidence of hypertension (88%), hyperlipidaemia (81%) and microalbuminuria (29%) in comparison with patients of normal weight. High baseline BMI was a predictor of high blood pressure, high triglycerides and low HDL-cholesterol in this 6-year prospective study of >4000 patients with type 2 diabetes. An increase in BMI during the study period (mean increase in weight was 4–5kg) predicted an increase in blood pressure.[4]

Taken together, the observations described suggest that the weight gain associated with diabetes therapies represents a negative aspect of treatment that can potentially undermine treatment benefits. For this reason, some anti-obesity drugs, such as orlistat, sibutramine and rimonabant, have been studied in patients with type 2 diabetes.[22,23] The use of such compounds may represent an alternative, either as monotherapy or in combination with glucose-lowering therapy, for the management of some overweight or obese patients with type 2 diabetes. Although these weight-lowering agents may have an important role in type 2 diabetes treatment, they are not discussed in detail here, as this review focuses on drugs used primarily to treat type 2 diabetes.

In recent years, a number of new antidiabetic therapies with novel mechanisms of action have been developed. Some of these newer agents may allow diabetes to be treated without causing the degree of weight gain seen in the past. It is therefore timely to critically evaluate the influence of currently available or emerging treatments for type 2 diabetes and to assess their relative influences on both glycaemia and weight gain. In this review, we examine the emerging treatments and attempt to compare the data available with studies of more established treatments as examples. For the purposes of this review, such data have been derived from published clinical trials of the therapies in question. Priority for inclusion was given to those studies initiating or using monotherapy where possible, and studies of a minimum duration of 12 weeks. It is, however, important to be aware of the factors that confound the ability to derive any quantified conclusions about individual therapies from a review of the literature. These include differences in study duration, differences in cohort selection and size, differences in glycaemic targets, concurrent interventions with diet and exercise and the use of concomitant medication.

3. Established Treatments

3.1 Insulin Secretagogues

The first of the oral antihyperglycaemic agents to be developed and still in widespread use for the treatment of type 2 diabetes are SUs, such as glyburide, glipizide, gliclazide and glimepiride. These agents bind to SU receptors on β cells in the pancreas and stimulate insulin secretion.[24] As with other antidiabetic agents, the potency of the SUs to improve glycaemic control is directly related to starting plasma glucose levels; in two multicentre trials, the greatest absolute reduction in FPG and HbA_{1c} occurred in patients with the most severe hyperglycaemia (reduction of HbA_{1c} ranged from −1.50% to −1.82%).[25]

However, one shortcoming of SUs is that the resultant insulin secretion lasts for several hours and therefore increases the risk of hypoglycaemia. Another widely held belief about SUs is that the use of these agents can result in significant weight gain.[26,27] Nevertheless, while some studies do report weight gain, it has not been a universal finding. For example, newly diagnosed patients in the UKPDS gained up to 4.8kg over the 10-year period of the study (the chlorpropamide group gained an average of 3.5kg, the glibenclamide group gained 4.8kg and the diet-only group gained 1.7kg).[28] Patients whose diabetes was not controlled on diet and exercise who were treated with glimepiride showed an improvement in HbA_{1c} of 2.3% over 14 weeks, but also increased their weight by 2.3kg.[26] However, a study of glipizide in patients previously treated with SUs or with controlled diet indicated that an improvement in HbA_{1c} (−1.5% to −1.8% depending on dose) was not associated with weight gain over 16 weeks (−0.3kg).[25]

An analysis of four 1-year trials of patients whose diabetes was not controlled on diet alone showed mean weight gain of 2.6kg with glipizide in contrast to weight loss of 2.0kg with metformin[29] (figure 1). When glimepiride was added to metformin, patients still gained weight, although less (+0.6kg) than when on glimepiride alone (+0.78kg).[30] In the GUIDE (GlUcose control in type 2 diabetes: Diamicron MR vs glimEpiride) study,[31] 845 type 2 diabetic patients were randomised to receive either gliclazide or glimepiride treatment for 27 weeks; HbA_{1c} decreased similarly in both groups (1.1% and 1.0%, respectively) and bodyweight increased from a mean of 83.1 to 83.6kg on gliclazide treatment and from 83.7 to 84.3kg on glimepiride treatment.

Data from four 1-year, double-blind studies were used to compare >3700 patients with type 2 diabetes treated with gliclazide, pioglitazone or metformin. Of these patients, 67% gained weight with monotherapy;[38] mean weight increased with both gliclazide (+1.9kg) and pioglitazone (+2.8kg), but decreased with metformin monotherapy (−2.5kg).[38] In a population-based sample of patients with type 2 diabetes receiving structured, individualised care by primary-care physicians, the bodyweight changes in relation to weight at the start of antidiabetic treatment were measured during the first 5 years.[42] Patients treated only with dietary advice attained an average weight reduction of 5.4kg after 5 years, whereas those on SU monotherapy achieved an average weight loss of 2.9kg (+2.5kg compared with diet alone), and those on SUs plus metformin attained a weight loss of 2.0kg after 5 years (+3.4kg compared with diet alone).[42] In summary, weight gain can occur with SUs, but may be limited if concurrent diet and exercise are used. Where weight gain is associated with SUs, it may in part be a consequence of reduction of glycosuria and/or defensive snacking in order to prevent hypoglycaemia. These issues are elaborated on in section 3.5 describing insulin therapy.

Meglitinides, such as repaglinide and nateglinide, are another class of insulin secretagogue. These agents produce a more rapid and short stimulation of endogenous insulin secretion than SUs, so taken before meals they can help restore the prandial insulin secretory response, which is usually limited in type 2 diabetes.[43] However, as with SUs, meglitinides have also been associated with weight gain.

When patients whose diabetes was not previously controlled on diet and exercise were treated with repaglinide, their HbA_{1c} improved on average by 1.57% but they also gained on average 1.8kg of weight during 16 weeks of treatment.[32] Even patients previously treated with metformin or SU monotherapy gained some weight (1.6kg), while improving their HbA_{1c} by only 0.17% over 24 weeks.[44] However, some recent studies suggest that

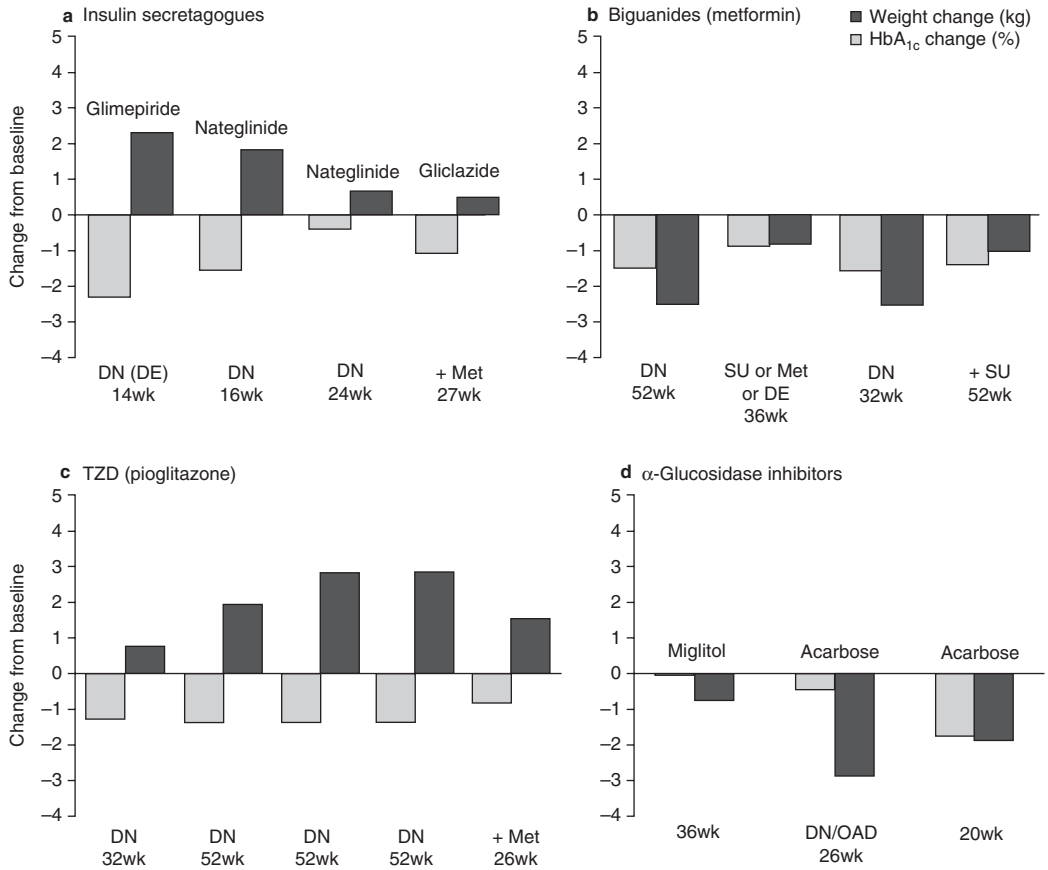

Fig. 1. Representative studies of established oral treatments showing bodyweight change from baseline in patients with type 2 diabetes mellitus. (Duration of studies [14–52 weeks] and baseline treatment characteristics are indicated below each data set. All studies included a minimum of 50 patients.) It should be noted that these agents are not necessarily used at the same point in the disease process. Studies: (**a**) Bautista et al.,[26] Rosenstock et al.,[32] Saloranta et al.,[27] Schernthaner et al.;[31] (**b**) Schernthaner et al.,[33] Chiasson et al.,[34] Pavo et al.,[35] Hanefeld et al.;[36] (**c**) Pavo et al.,[35] Schernthaner et al.,[33] Charbonnel et al.,[37] Belcher et al.,[38] Kendall et al.;[39] (**d**) Chiasson et al.,[34] Goke,[40] Feinbock et al.[41] **DE** = diet and exercise; **DN** = drug naive; **DN/OAD** = drug naive or failed on oral antidiabetic drugs; **HbA_{1c}** = glycosylated haemoglobin; **Met** = metformin; **SU** = sulfonylurea; **TZD** = thiazolidinedione.

the weight gain may be limited by concomitant use of other agents, such as metformin (−0.7kg over 6 months),[45] or that the combination of secretagogues, diet and exercise may result in a reduction in weight gain (−0.4kg over 20 weeks).[41] Interestingly, a prospective observational study in a large cohort suggested that only patients with low BMI gained weight (up to 2kg) with repaglinide, while the heaviest patients lost weight (up to 3kg) over 46 days.[46] However, it seems unlikely that the rapid weight loss was caused by repaglinide; a reduced caloric intake is a possible explanation.

3.2 Biguanides

Metformin is the most commonly used biguanide. It exerts its effect by reducing glucose production and enhancing the sensitivity of hepatic tissue to insulin, which leads to the reduction of FPG.[24] Metformin also improves glucose uptake in muscle tissue.

The greatest advantage of metformin compared with other antidiabetic agents has been the fact that it is associated with weight loss rather than weight gain (figure 1). This seems to be the case for drug-

naive patients,[34] as well as for patients already receiving oral antidiabetic drugs (OADs).[34,36,47] Many studies show weight loss in patients treated with metformin, or limitation of weight gain during combination therapy including metformin; this has been well documented in the literature. For the purpose of this review, a few examples illustrating these weight improvements will be mentioned. For example, in drug-naive patients on metformin, HbA_{1c} decreased by 1.5%, while their bodyweight decreased by 2.5kg over 52 weeks.[33] Comparable improvement in HbA_{1c} (−1.5%) and weight (−2.4kg) was reported in another study of drug-naive patients with type 2 diabetes over 32 weeks.[35] In the population-based study of patients with type 2 diabetes mentioned in section 3.1,[42] individuals treated only with dietary advice maintained an average weight reduction of 5.4kg in 5 years, and patients treated with metformin monotherapy maintained an average weight loss of 4.3kg over the same period (+1.1kg compared with diet alone). In a 29-week study of glyburide by DeFronzo and Goodman,[48] patients whose diabetes was poorly controlled with SUs were either switched to metformin, achieving reductions in both HbA_{1c} (−1.4%) and weight (−3.8kg), or had metformin added to SUs, with HbA_{1c} improving by 1.7% and weight gain limited to +0.4kg.[48] In the large ADOPT (A Diabetes Outcome Progression Trial) study comparing three treatments over a period of 5 years, mean bodyweight increased with rosiglitazone by 4.8kg, but decreased with metformin by 2.9kg. With glyburide, weight gain occurred in the first year (+1.6kg) and then remained stable.[49]

Metformin is often the first-line pharmacological therapy of choice. It is frequently combined with SUs, and used in obese patients in an attempt to reduce the weight gain often associated with these agents.[38,48] Interestingly, the greatest weight loss with metformin occurred in the heaviest type 2 diabetes patients.[38] Furthermore, according to a *post hoc* analysis, randomisation to metformin led to better cardiovascular outcomes than diet alone, but was not clearly better than insulin or SUs.[50]

The mechanism underlying the weight reduction due to metformin is not fully understood, but it has been suggested that metformin enhances glucagon-like peptide (GLP)-1 secretion, without altering glucose metabolism.[51,52] More recently, metformin has also been shown to inhibit dipeptidyl peptidase (DPP)-4 activity in patients with type 2 diabetes.[53]

3.3 α-Glucosidase Inhibitors

The α-glucosidase inhibitors used in type 2 diabetes therapy are acarbose, miglitol and voglibose. These agents delay the breakdown of disaccharides and oligosaccharides into monosaccharides by inhibiting enzymes in the small intestine. This reduces the amount of glucose going into the circulation after meals and hence decreases post-prandial glucose (PPG).[54] However, some gastrointestinal adverse effects have been reported, which might be a consequence of incompletely digested disaccharides and oligosaccharides in the small intestine, resulting in bacterial fermentation in the colon.

The effect of α-glucosidase inhibitors on HbA_{1c} is often perceived to not be as great as that of other agents, but they do not seem to affect bodyweight; in fact, some studies report a significant weight loss in patients taking α-glucosidase inhibitors during the study period[34,40,41] (figure 1). For example, drug-naive patients treated with acarbose for 20 weeks lost 1.9kg in weight and their HbA_{1c} improved by 1.8%.[41] Also, newly diagnosed patients not controlled on OADs lost 2.1kg, while their HbA_{1c} decreased by 0.48% in 26 weeks.[40] A meta-analysis of 41 studies on α-glucosidase inhibitors reported an HbA_{1c} change of −0.77% and a statistically significant effect on BMI of −0.17 kg/m^2, but the authors reported the effect on bodyweight as not statistically significant.[55]

Several mechanisms have been suggested to explain the effect of α-glucosidase inhibitors on bodyweight. It was thought that the gastrointestinal adverse effects may cause patients to change dietary habits, but this idea has not been supported by research.[56] Another suggestion has been that these agents may be modulating the release of some gut peptides (e.g. GLP-1) that play an important role in postprandial satiety signals.[57]

3.4 Thiazolidinediones

The thiazolidinediones (TZDs) rosiglitazone, and pioglitazone enhance glucose uptake into peripheral tissues. This in turn has beneficial effects on adipose

tissue and redistributes body fat from visceral to subcutaneous sites.[58] The insulin-sensitising effect of the TZDs is mediated through activation of the peroxisome proliferator-activated receptor-γ, a nuclear receptor present in high concentrations in adipocytes.

Patients typically gain weight when treated with TZDs, with the increase in fat mass proportional to improved glycaemic control.[59] In a 52-week comparison[37] of pioglitazone and gliclazide in drug-naive patients, HbA_{1c} decreased by 1.4% in both groups, but patients treated with pioglitazone reported a substantial weight gain of 2.8kg, with the greatest increase in weight occurring in the first 42 weeks. The weight gain with gliclazide was 1.9kg.[37] An improvement in HbA_{1c} (−1.1%) together with weight gain (1.3kg) was also reported in a 26-week study by Goke and colleagues,[40] and subsequent studies have reported consistent findings.[33,35] Also in the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study of 5238 patients with type 2 diabetes, a mean bodyweight increase of 3.6kg was observed in the pioglitazone group (n = 2605) over 3 years.[59] Many studies have shown that rosiglitazone produces significant weight gain and fluid retention, which is seen with both TZDs.[60] As mentioned in section 3.2, the recent ADOPT study has shown weight gain with rosiglitazone of 4.8kg over 5 years.[49]

Although body adiposity contributes to an insulin-resistant state,[61] TZDs reduce insulin resistance despite the increase in weight. There are several explanations for this apparent contradiction. The redistribution of fat from the visceral depot to abdominal subcutaneous sites increases insulin sensitivity,[58] and by reducing fat in the liver and muscles, insulin signalling in these organs might improve despite the weight gain.[62] Furthermore, insulin action is enhanced by the increase in number of small adipocytes that results from TZD treatment, as these are more sensitive to insulin than large adipocytes.[62,63] It has also been suggested that pioglitazone increased total body water, and that this accounted for approximately 75% of the total weight gain.[64] A recently published observation suggested that water retention and weight gain associated with rosiglitazone can be prevented with fenofibrate.[65] This is an important finding, as weight gain and fluid retention are important limiting factors in the use of TZDs. Because of the potential plasma volume expansion, TZDs should be used with caution in patients with oedema or a history of congestive heart failure.[66]

3.5 Insulin

Insulin therapy is the most effective treatment in type 2 diabetes when other agents, such as OADs, begin to fail. However, the improvement of glycaemic control with insulin has always been associated with an increase in bodyweight, which can be substantial and greater than that found in patients undergoing treatment with OADs.[67,68] Unfortunately, the weight gained by patients on insulin treatments appears to increase in direct proportion to the insulin dose and improved plasma glucose concentrations.[6,69]

Studies in which insulin treatment has been initiated in type 2 diabetes often show weight gain of 2–3kg over study periods of 4–12 months[67] (figure 2). However, weight gain is often more limited when insulin is added to OADs rather than used as a substitute. For example, in a 12-month trial of insulin-naive patients on OADs (SUs or metformin), NPH insulin was either added to OADs or used as monotherapy.[70] HbA_{1c} decreased by 0.8% in the combination treatment group and by 1.2% in the NPH insulin monotherapy group; weight increased by 1.3kg and 4.2kg, respectively.[70] In a study by Strowig et al.,[71] patients already on insulin were assigned either NPH insulin monotherapy, NPH insulin plus metformin, or NPH insulin plus troglitazone. The three groups displayed similar levels of glycaemic control (change in HbA_{1c} −1.7%, −1.7% and −2.1%, respectively). However, weight gain in the NPH insulin monotherapy and NPH insulin plus troglitazone groups was higher (+4.4kg) than in the NPH insulin plus metformin group (+0.49kg) over the 16 weeks of the study.[71] As a final example, a trial of insulin-naive patients on OADs, in which premixed 70% regular/30% human NPH insulin was used, reported an HbA_{1c} decrease of 1.31% but weight gain of 2.1kg in 24 weeks.[72] A small but interesting study has provided some additional information about combined therapy resulting in less weight gain than insulin monotherapy in patients with type 2 diabetes;[73] patients previously on glipi-

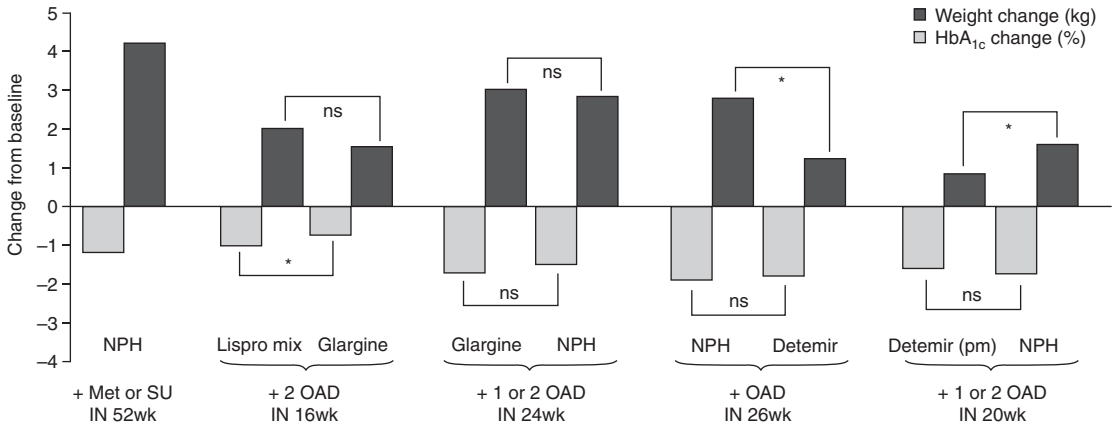

Fig. 2. A representative study of NPH insulin and comparative studies of insulin treatments showing bodyweight change from baseline in patients with type 2 diabetes mellitus (*p < 0.01). Studies: Goudswaard et al.,[70] Jacober et al.,[68] Riddle et al.,[74] Hermansen et al.,[75] Philis-Tsimikas et al.[76] **HbA_{1c}** = glycosylated haemoglobin; **IN** = insulin naive; **Met** = metformin; **ns** = not significant; **OAD** = oral antidiabetic drug; **SU** = sulfonylurea.

zide or glyburide were treated with NPH insulin plus metformin or NPH insulin alone. HbA_{1c} decreased similarly in both groups (−2.9% and −2.5%, respectively), but bodyweight increased over 12 months by 3.8kg in the group using metformin and by 7.5kg in the NPH insulin-only group. Also, body fat content increased in both groups, but the increase was lower in the metformin group (+2.8kg) than in the NPH insulin group (+5.2kg). The improvement in glycaemic control was similar in both groups, but the metformin group required 47% less insulin than those in the insulin-only group, supporting the idea of an insulin-sparing effect with metformin.

Several mechanisms may play a role in weight gain in patients treated with insulin. One important issue relating to weight gain is the conservation of calories. When glycosuria is corrected by improving glycaemic control, energy loss in the urine is reduced, and patients' weight increases if they do not reduce their energy intake.[69] Other mechanisms (no hierarchy implied) may also contribute to weight gain; the anabolic effect of insulin on muscle and fat is well recognised.[77] The risk of hypoglycaemia is also an important factor; some patients may actually increase their calorie intake in an attempt to prevent hypoglycaemia ('defensive snacking'). Furthermore, mild hypoglycaemia may stimulate appetite,[78] and patients have an increased freedom to eat, as insulin use will prevent hyperglycaemia.[6] Insulin also has an important effect in the CNS, where it plays a role in signalling satiety and suppressing appetite, and this mechanism may be impaired in type 2 diabetes.[79] Another potential cause of weight gain with insulin therapy concerns the inherently unphysiological nature of the subcutaneous route of administration. In a healthy individual, insulin is secreted into the portal vein, suppressing endogenous glucose production; only about half passes through to the systemic circulation, increasing peripheral glucose uptake and suppressing lipolysis. However, when insulin is administered subcutaneously, the muscle and adipose tissue is exposed to an excessively high proportion of insulin relative to the liver.[12] This effect could enhance lipogenesis.

The factors affecting the magnitude of weight gain are not yet fully understood, but it has been suggested that the timing of insulin injections, and their use in combination with OADs, may play a role. For example, at similar levels of glycaemic control, weight gain is usually greater with regular insulin several times a day than with a single injection of NPH insulin at bedtime.[80] However, the greatest risk for weight gain seems to be poor glycaemic control before insulin initiation together with a good treatment response.[69]

3.6 Insulin Analogues

Compared with human insulin, insulin analogues have either delayed and prolonged absorption (insulin detemir and insulin glargine), which results in a more physiological basal insulin profile, or a faster onset and rapid absorption (insulin aspart, insulin lispro and insulin glulisine). These analogues can be combined in regimens that produce an insulin profile that comes closer to that seen in normal physiology, that is, a low, flat and relatively constant basal level of secretion, coupled with rapidly generated and relatively short bursts of insulin release in response to meals. In clinical trials, insulin analogues achieve comparable or better glycaemic control together with a lower incidence of hypoglycaemia than human insulins.[81]

Despite their pharmacokinetic advantages, most insulin analogues appear to cause a similar increase in bodyweight to human insulins.[74] However, one exception is the long-acting insulin analogue detemir, which in clinical trials has consistently been shown to cause less weight gain in patients than NPH insulin.[75,82] Insulin detemir differs from human insulin in that a C14 fatty-acid chain has been attached to enable reversible albumin binding. Self-association and consequently slow systemic absorption of insulin detemir molecules from the injection site prolong its action. The absorption is further extended by the reversible binding of insulin detemir to albumin in the plasma, 'buffering' any changes in absorption rate.[83]

In studies of patients with type 1 diabetes, insulin detemir has generally been reported as being weight neutral, whereas comparator groups of patients receiving NPH insulin have typically gained weight of up to 1.5kg over periods of up to 12 months.[82] In type 2 diabetes, four trials comparing insulin detemir with NPH insulin have been published to date.[75,76,84,85] All reported comparable improvements in HbA_{1c}, but weight gain was consistently less with insulin detemir than with NPH insulin[75,76,84,85] (figure 2). For example, in a study in which insulin was initiated by the addition of either insulin detemir or NPH insulin to OADs, HbA_{1c} decreased similarly over 26 weeks with detemir (−1.8%) and NPH (−1.9%), while weight gain with detemir was less than half of that for NPH (+1.2 vs 2.8kg; $p < 0.001$).[75] Interestingly, weight gain fell with increasing BMI for insulin detemir and remained constant for NPH in this study,[75] but in a pooled analysis of two other trials, weight gain was more constant with BMI with insulin detemir, but increased with increasing BMI for NPH insulin[86] (figure 3).

One 52-week, parallel trial comparing insulin detemir with insulin glargine as add-on therapy to OADs showed that bodyweight increased less with

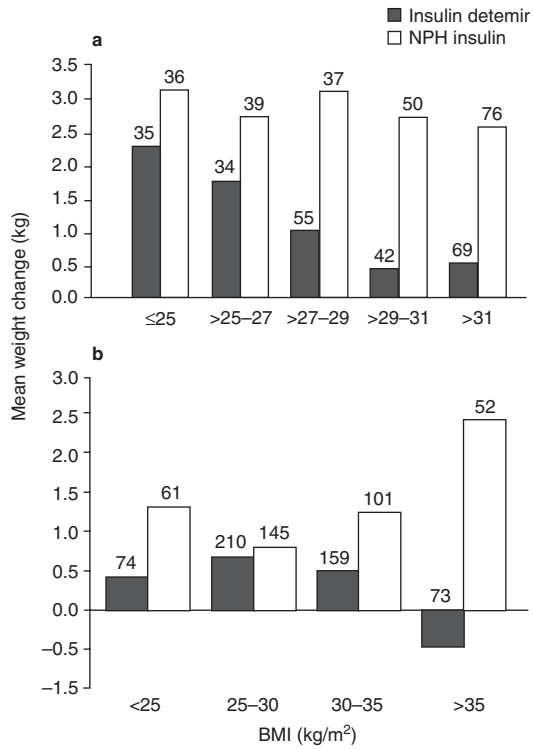

Fig. 3. (**a**) In a treat-to-target study of 475 patients with type 2 diabetes mellitus, a difference in bodyweight change between insulin detemir and NPH insulin was lowest at 24 weeks for patients with the highest body mass index (BMI) at entry. With increasing baseline BMI, patients gained less weight with insulin detemir (weight gain 5.37–0.15 × BMI; $p = 0.01$); no relationship was found for NPH insulin. [Copyright © 2006 American Diabetes Association. From *Diabetes Care*, Vol. 29, 2006; 1269-1274.[75] Reprinted with permission from The American Diabetes Association]. (**b**) Data pooled from two randomised, parallel group trials[84,85] of 900 patients with type 2 diabetes show that patients treated with insulin detemir had minimal weight gain (mean <1kg), regardless of their BMI at entry, whereas in patients treated with NPH insulin, weight gain increased as baseline BMI increased ($p = 0.025$). Numbers over bars indicate number of participants. [Reproduced from Raslova et al.,[86] with permission.]

insulin detemir than with insulin glargine (3.0 vs 3.9kg, respectively).[87] Although the insulin detemir weight advantage still applies, data from this study should be interpreted with caution, as different dosing algorithms were used for the two types of insulin, and as a consequence the dosing schedules were not comparable. Direct comparisons of equivalent regimens with insulin detemir and insulin glargine are still needed. It should also be noted, however, that it is unknown whether this difference in weight gain is of clinical significance, since it is generally assumed that only weight gains of ≥5kg are clinically relevant. Long-term studies are needed to clarify whether the weight difference in favour of insulin detemir is of clinical relevance or will be greater under long-term exposure.

In type 2 diabetes, therefore, insulin detemir seems to provide an improvement in the balance between glycaemic control and weight gain that can be achieved with insulin therapy. The mechanism of the weight advantage has not been determined; lower within-subject variability has been documented when comparing the effects of insulin detemir with NPH insulin and insulin glargine,[88] and this might contribute to a reduced risk of hypoglycaemia and hence reduce the 'defensive snacking' commonly associated with insulin therapy. Compared with subcutaneously administered human insulin, insulin detemir has a relatively greater effect on endogenous glucose production than on peripheral glucose uptake, potentially reducing peripheral lipogenesis.[89,90] Another possibility is that insulin detemir has increased access to CNS receptors compared with human insulin, possibly as a result of its lipophilic side chain or the relative decrease in albumin concentration in cerebrospinal fluid. An increased CNS effect might help to normalise impaired satiety signalling.[91]

4. Emerging Treatments

4.1 Glucagon-Like Peptide-1 Agonists

The incretin GLP-1 is a 31-amino-acid peptide that is secreted from L cells in the gastrointestinal system in response to calorie intake, and binds to GLP-1 receptors on pancreatic β cells.[92,93] GLP-1 secretion might be impaired in patients with type 2 diabetes, resulting in a reduction in meal-induced GLP-1 response.[94] In contrast to other agents such as SUs, GLP-1 lowers glucose by stimulating secretion of insulin depending on glucose levels, and therefore incurs a very low risk of hypoglycaemia.[95] GLP-1 also suppresses inappropriately high glucagon secretion, leading to inhibition of hepatic glucose output, [96] and increases feelings of satiety by slowing gastric emptying and inhibiting gastric acid secretion.[97] It has been shown to increase β-cell mass in animals[98] and restore some β-cell function in isolated human islets.[99] Natural GLP-1 has a short half-life because of rapid degradation by the enzyme DPP-4, but the development of incretin mimetics and GLP-1 analogues has led to pharmacological agents with prolonged durations of action.

One of the newer incretin mimetics, exenatide, is a 39-amino-acid peptide derived from exendin-4, a naturally occurring peptide that has similar actions to GLP-1, and is not degraded by DPP-4. Kendall et al.[100] reported reductions in HbA_{1c} of 1.0% and weight loss of 1.6kg when exenatide was given to patients on metformin and SUs for 30 weeks. Another study[101] of patients on maximum doses of SUs demonstrated dose-dependent weight reduction. At 10μg twice daily, exenatide was associated with a weight loss of 1.6kg, together with an HbA_{1c} decrease of 0.86% over 30 weeks.[101] In patients with type 2 diabetes receiving metformin (>1500 mg/day), the group treated with exenatide displayed a dose-dependent weight reduction (−2.8kg at 10μg and −1.6kg at 5μg twice daily, respectively).[102] A 26-week study comparing the effects of the addition of exenatide or insulin glargine in patients suboptimally controlled with metformin and SUs showed similar improvements in HbA_{1c} (−1.1%), but bodyweight decreased by 2.3kg with exenatide and increased by 1.8kg with insulin glargine.[103] This progressive weight loss is consistent with the suggestion that exenatide reduces food intake.[104,105]

A long-acting GLP-1 analogue, liraglutide, has been developed by making two modifications to the amino acid sequence of GLP-1: a fatty acid is acylated to lysine at position 26 and the lysine at position 34 is replaced with arginine. This increases self-association, which slows absorption of the drug from the subcutaneous fat depot. Liraglutide binds

to albumin and has reduced susceptibility to DPP-4. Both of these properties prolong its plasma half-life and therefore extend its action.[106] HbA_{1c} decreased in patients on liraglutide monotherapy by −0.98%, −1.40% and −1.45% in a 14-week, placebo-controlled study at doses of 0.65, 1.25 and 1.90mg, respectively.[107] These patients were previously treated with diet or OADs, but were only included in the study after a 4-week washout period. Furthermore, there was a dose-dependent reduction in bodyweight, as shown in figure 4: the highest weight loss of 2.99kg was in the group on the highest dose of liraglutide (1.9 mg/day). Similar findings of improvements in HbA_{1c} (−0.75%) and weight loss (−1.2kg) over a 12 week period have been reported by others.[108]

4.2 Dipeptidyl Peptidase-4 Inhibitors

DPP-4 inhibitors such as vildagliptin and sitagliptin prevent the degradation of endogenous GLP-1 in patients with type 2 diabetes, and also enhance insulin secretion, inhibit glucagon secretion and improve β-cell function.[114] Vildagliptin was shown to reduce HbA_{1c} levels compared with placebo in patients with type 2 diabetes not previously treated with OADs or insulin.[110] After 12 weeks of treatment, there was a reduction in HbA_{1c} of 0.31%, 0.27%, 0.56% and 0.53% with vildagliptin dosages of 25mg twice daily, 25mg once daily, 50mg once daily and 100mg once daily, respectively. This difference was significant for the 50mg and 100mg groups compared with the placebo group (−0.13%). β-cell function was significantly increased in the vildagliptin 100mg treatment group.[110] However, the changes in weight were small and not significantly different from baseline or between the treatment groups (+0.06kg, −0.55kg, +0.04kg, −0.07kg and −0.73kg for 25mg twice daily, 25mg once daily, 50mg once daily, 100mg once daily and placebo, respectively). Another study[109] of patients on metformin treatment reported an HbA_{1c} change of −0.6% with added vildagliptin in 12 weeks (vs +0.1% with placebo), but similar weight change for both groups (−0.4kg and −0.5kg, respectively). In 52 weeks, there were no further changes in HbA_{1c} in the vildagliptin group, but it increased from 12 weeks onwards in the placebo group. The bodyweight change from baseline to 52 weeks was

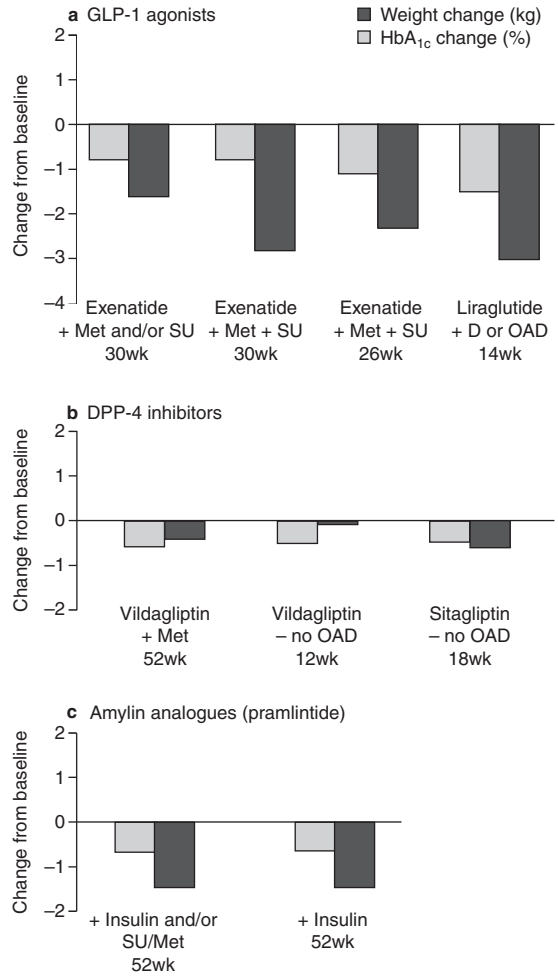

Fig. 4. Representative studies of emerging diabetes treatments showing bodyweight change from baseline in patients with type 2 diabetes mellitus. Studies: (**a**) Kendall et al.,[100] DeFronzo et al.,[102] Heine et al.,[103] Vilsbøll et al.;[107] (**b**) Ahren et al.,[109] Ristic et al.,[110] Raz et al.;[111] (**c**) Hollander et al.,[112] Ratner et al.[113] **D** = diet; **DPP-4** = dipeptidyl peptidase 4; **GLP-1** = glucagon-like peptide 1; **HbA_{1c}** = glycosylated haemoglobin; **Met** = metformin; **OAD** = oral antidiabetic drug; **SU** = sulfonylurea.

–0.2kg in both groups.[109] In a study of sitagliptin monotherapy, HbA_{1c} reductions ranged from 0.6% to 0.8%, and there was no change in weight over the 12-week study period.[115] A recent 18-week study of sitagliptin monotherapy reported only small differences in weight change in the sitagliptin groups relative to placebo (−0.7kg for sitagliptin 100mg, −0.6kg for 200mg and −0.2kg for placebo).[111]

4.3 Amylin Analogues

Human amylin is produced by pancreatic β cells and released with insulin in response to food intake.[116] The dysfunction of β cells in type 2 diabetes may cause a deficiency in insulin and amylin postprandial responses.[117] Amylin complements the actions of insulin in PPG homeostasis by suppressing postprandial glucagon secretion, and by slowing the rate of gastric emptying.[118,119] Human amylin precipitates out of solution, preventing its administration via injection, which is the reason for the development of the amylin analogue pramlintide.

The two studies of pramlintide published to date examined the addition of pramlintide to OADs and/or insulin and reported further glycaemic improvements beyond those achieved with pre-existing treatments.[112,113] Both studies of type 2 diabetes patients reported a mean reduction in HbA_{1c} of at least 0.6% at 52 weeks, and a weight reduction of 0.4–1.4kg, whilst patients in the placebo groups had a weight gain of 0.7–0.8kg. When the authors conducted a *post hoc* analysis of the above trials, they found that in obese patients HbA_{1c} was reduced by 0.59% over 26 weeks and the placebo-corrected weight reductions ranged from 1.6kg for the group of patients on pramlintide and insulin, to 2.5kg for the group of patients on pramlintide, insulin and metformin. When the sample was stratified by BMI, the greatest weight reduction was in the most obese patients.[120]

Possible mechanisms underlying the observed weight effect of pramlintide have not yet been systematically studied in humans. One possible mechanism may be the slowing of gastric emptying and nausea as an adverse effect. Some evidence from studies in rodents implicates amylin as a centrally acting postprandial satiety signal.[121] Unlike anti-obesity agents, which may improve glycaemic control as the result of a reduction in bodyweight, the ability of pramlintide to simultaneously improve glycaemic and weight control appears to occur via two independent mechanisms. Pramlintide selectively reduced postprandial, but not fasting, glucose concentrations,[122] and HbA_{1c} was reduced regardless of whether patients gained or lost weight.[112]

5. Conclusion

Some of the established treatments of type 2 diabetes have been associated with weight gain, and weight gain can be especially problematic with insulin therapy. Results of some studies, however, suggest that even with traditional treatments, it is possible to limit weight gain by using a combination of oral agents, some of which actually reduce weight, for example, metformin, and the α-glucosidase inhibitors, or by making simultaneous interventions with diet and exercise. However, as patients with type 2 diabetes often have difficulty losing weight and changing their lifestyle, it is important to be able to use treatments that do not significantly increase weight.[6] Concurrent use of metformin largely prevents the weight gain otherwise seen with SUs or insulin; thus routine use of these combinations is often seen in everyday practice. Some of the newly developed treatments are also able to control both glucose and weight, as well as incurring a low risk of hypoglycaemia. Even when insulin therapy is needed, it is possible to choose analogues, such as insulin detemir, to improve glycaemic control, while at least limiting weight gain. It is not yet known, however, whether using insulin detemir rather than NPH insulin or insulin glargine will have a long-term or clinically significant weight advantage. Also, the weight reduction effects of exenatide already evident through widespread use in the US suggest that the new GLP-1 agonists may help further reduce weight in type 2 diabetes patients.

In summary, such new developments, together with an increased understanding of the pharmacological basis for weight gain in the therapy of type 2 diabetes, suggest that weight gain need no longer be regarded as inevitable.

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