Antidiabetic Treatment in Obese Patients with Type 2 Diabetes – Effects of Medication on Bodyweight

a report by
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Obesity is a major risk factor for the development of type 2 diabetes;[1–3] moreover, the presence of obesity in type 2 diabetes is associated with an increased risk of vascular complications associated with the disorder.[4,5] The majority of patients are overweight or obese at diagnosis of type 2 diabetes. Recent clinical trials have demonstrated that progression to diabetes in obese patients with impaired glucose tolerance can be prevented through weight reduction and increased levels of physical activity.[6,7] For patients who have developed type 2 diabetes, intentional weight loss has many potential benefits, including improved metabolic control and a reduced need for antidiabetic medications.[8–10]

One of the challenges of using antidiabetic therapy in obese or overweight patients is the prospect of substantial iatrogenic weight gain with many widely used drug classes. Since lifestyle interventions, including weight loss, are usually very difficult to achieve and/or sustain, the practitioner frequently is left with few options when trying to avoid adverse effects of antidiabetic therapy that are counterproductive to efforts directed at weight loss.

New classes of antidiabetic agents mimic or potentiate the activities of incretin hormones, including the injectable glucagon-like peptide-1 (GLP-1) mimetics and the oral dipeptidyl peptidase-4 (DPP-4) inhibitors. These drugs have benefits for glucose-dependent insulin secretion, suppression of glucagon secretion, inhibition of gastric emptying and appetite reduction.[11–14] They are effective in lowering glycated haemoglobin (HbA_{1c}) and are associated with either weight loss (GLP-1 mimetics) or weight neutrality (oral DPP-4 inhibitors). Thus, these drugs promise to be useful in obese/overweight patients with type 2 diabetes.

A new anti-obesity agent, the selective cannabinoid receptor antagonist rimonabant, is effective in reducing weight and improving a range of metabolic defects in patients with type 2 diabetes. Such new agents should improve our ability to treat overweight or obese patients.

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Effects of Traditional Oral Antidiabetic Agents on Bodyweight

Insulin Secretagogues

Sulfonylureas

As insulin secretion is relatively deficient in type 2 diabetes, use of insulin secretagogues is logical for patients in whom the β-cell defect is not too advanced. Treatment with sulfonylureas (SUs) reduces HbA_{1c} by approximately 1–2%. SU treatment in the UK Prospective Diabetes Study (UKPDS) was associated with a significant reduction in microvascular complications and a trend towards reduction of myocardial infarction (MI), but no significant effect on diabetes-related or all-cause mortality.[15] Weight gain and hypoglycaemia – the latter usually asymptomatic or mild – are common side effects with these agents.[16–18] Longer-acting agents (e.g. chlorpropamide, glyburide (glibenclamide) and sustained-release glipizide) are more likely to cause hypoglycaemia than shorter-acting agents.[18] Weight gain averages about 1–4kg and generally stabilises over six months. In the UKPDS, for example, weight gain was 1.7kg with glyburide and 2.6kg with chlorpropamide. Weight increases with SU treatment may be partly due to anabolic effects of increased plasma insulin levels or reduced loss of calories as glucose in the urine.[17] Lesser degrees of weight gain are claimed for some SU formulations (e.g. extended-release glipizide).[19] However, individual metabolic responses to these agents vary, and weight gain should be anticipated with any agents in this class. SUs are, therefore, widely regarded as being less attractive as first-line therapy for obese patients; however, they remain in widespread use, often in combination with other drugs, notably metformin. When used in obese patients, treatment with SUs should be accompanied by a weight control programme of diet and exercise wherever possible.

Rapid-acting Secretagogues

The non-sulfonylurea secretagogues repaglinide and nateglinide were developed to have a rapid onset and short metabolic half-life, resulting in preferential targeting of post-prandial hyperglycaemia. These agents reduce HbA_{1c} to a degree broadly similar to that observed with SUs (about 1–2%), with repaglinide having a somewhat greater effect in this regard.[16–18] The drugs must be taken before each main meal. As with other insulin secretagogues, hypoglycaemia and weight gain are the most common side effects, although both appear to be reduced in frequency compared with SUs. In a study involving 576 patients with type 2 diabetes, less weight gain was observed with repaglinide than with glyburide (2.5kg versus 3.6kg, respectively) among pharmacotherapy-naïve patients – although previously treated patients did not exhibit less weight gain with repaglinide.[20] In general, no weight loss can be expected in patients switched from an SU to repaglinide. Nateglinide is a D-phenylalanine derivative with a faster onset and shorter duration of action than

repaglinide, a meglitinide derivative. In a large-scale placebo-controlled trial, weight gains were 0.3kg with nateglinide 60mg tid and 0.9kg with 120mg tid.[21] In a direct comparison with repaglinide, weight gain was 0.7kg with nateglinide 360mg/day and 1.8kg with repaglinide 6mg/day.[22]

Insulin Sensitisers

Thiazolidinediones

Thiazolidinediones (TZDs) act to increase insulin sensitivity in adipose tissue, muscle and the liver.[23] Rosiglitazone and pioglitazone reduce HbA$_{1c}$ by about 0.5–1.5%.[16–18] However, these agents are associated with weight gain. A small proportion of patients develop leg oedema, which is attributed to fluid retention; heart failure is a concern in vulnerable patients (and is discussed below). Weight gain is generally similar to that seen with SUs (i.e. about 1–4kg, with stabilisation over six to 12 months). Of note, weight gain may be increased with concomitant treatment with other medications, including insulin.[24] The weight gain with TZDs is partly attributable to adipogenesis, but recent data suggest that fluid retention may in fact be the main cause.[25] There is some evidence that fat is redistributed away from visceral deposits, which are more closely associated with insulin resistance, to subcutaneous deposits.[16–18] TZDs have complex effects on atherogenic lipid profiles with some notable differences between the two agents.[26] In the secondary prevention PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial in high-risk patients with type 2 diabetes, pioglitazone was associated with a statistically significant 16% reduction in the secondary end-point of all-cause mortality, non-fatal MI or stroke. However, an increased frequency of heart failure and oedema without heart failure, as well as a 4kg weight increase compared with placebo, detracted from the positive impact on vascular events.[27,28] In the EU, TZDs are contraindicated in patients with a history of heart failure or current evidence of heart failure; their use in combination with insulin is contraindicated because of a perceived increased risk of heart failure. Recent US guidelines urge a cautious approach to TZD use in patients with evidence of heart failure. TZDs are also contraindicated in patients with active liver disease, although their effects on the liver are still under investigation; reduced levels of hepatic transaminases have been reported in several studies.

Metformin

Metformin, the only widely available biguanide, acts primarily by reducing hepatic glucose production and thereby reducing fasting hyperglycaemia in the presence of a sufficient amount of insulin. The drug improves post-receptor insulin signalling to increase cellular insulin sensitivity.[17,29] Metformin does not stimulate insulin secretion and may decrease hyperinsulinemia, an action regarded as potentially beneficial in obese patients. The agent reduces HbA$_{1c}$ by approximately 1–2%.[16,17,29] Metformin also results in small beneficial changes in the atherogenic lipid profile and may exert positive effects on other cardiovascular risk factors.[17]

In the UKPDS, metformin therapy in obese patients (mean body mass index (BMI) approximately 32kg/m^2) randomised to the drug after an inadequate response to diet was associated with statistically significant reductions of 32% in any diabetes-related end-point, 39% in MI and 42% in diabetes-related mortality.[30] In the Diabetes Prevention Program, metformin therapy reduced the risk of diabetes by 31% in obese patients with impaired glucose tolerance.[7] Metformin is not associated with weight gain and can sometimes promote modest weight loss. In the UKPDS, obese patients randomised to metformin gained 1–2kg compared with gains of 5–7kg in

Table 1: Treatment-emergent Adverse Effects Occurring in ≥5% of Exenatide Patients in Three 30-week Placebo-controlled Trials

Event (%)	Placebo bid (n=483)	Exenatide bid (n=963)
Nausea	18	44
Vomiting	4	13
Diarrhoea	6	13
Feeling jittery	4	9
Dizziness	6	9
Headache	6	9
Dyspepsia	3	6

Adapted from Byetta [package insert]. San Diego, Calif; Amylin Pharmaceuticals; 2006.[44]

Table 2: Vildagliptin Adverse Event Profile (Incidence ≥5%) in Monotherapy Trials with 100mg/day

Event (%)	Vildagliptin 100mg daily* (n=1,530)	Metformin to 2g daily (n=252)	Rosiglitazone 8mg daily (n=267)	Placebo (n=255)
Any	63.6	75.4	64.0	60.0
Nasopharyngitis	7.6	9.5	7.5	7.1
Headache	7.1	7.1	5.2	5.9
Dizziness	5.8	6.0	4.1	4.3
Upper respiratory tract infection	4.6	6.0	3.0	2.7
Diarrhoea	3.1	26.2	2.6	3.1
Nausea	2.9	10.3	0.7	3.9
Abdominal pain	1.2	7.1	0.7	1.2

*Pooled data from monotherapy trials with 50mg bid and 100mg qd. Adapted with permission from Nathwani A. Presented at: American Diabetes Association 66th Scientific Sessions, Washington, DC, June 13, 2006.[61]

patients receiving SU or insulin treatment.[30] In the Diabetes Prevention Program, metformin was associated with weight loss of 2.1kg.[7]

Co-administration of metformin with insulin has the potential to reduce insulin-associated weight gain.[31] The mechanisms of weight neutrality or weight loss associated with metformin in this context are not completely understood. Suggestions include a reduction in hyperinsulinaemia, a reduced risk of hypoglycaemia and hence lower calorie consumption, or decreased food intake as a consequence of the well-recognised gastrointestinal (GI) side effects of the drug; these often include a degree of anorexia.

Overall, these characteristics of metformin make it a preferred therapy for obese patients with type 2 diabetes. Use of the drug is limited, however, by risk of lactic acidosis – a rare condition but one associated with a high case-fatality rate. For this reason, metformin is limited to patients with renal function sufficient to avoid drug accumulation and is contraindicated in patients with cardiac or respiratory insufficiency (e.g. congestive heart failure (CHF)), other conditions associated with hypoxia or reduced perfusion, hepatic dysfunction, alcoholism or history of metabolic acidosis.[16–18] Use of metformin is also limited by the high frequency of GI adverse effects; a lesser proportion of patients cannot tolerate metformin at higher doses, whereas a minority are unable to tolerate the drug at any dose.

a-Glucosidase Inhibitors

The a-glucosidase inhibitors (AGIs) reduce the rate of polysaccharide digestion in the proximal small intestine, thereby reducing post-prandial

Table 3: Adverse Event Categories and Most Frequent Adverse Events (≥5%) in Patients Receiving Rimonabant 5mg or 20mg or Placebo in RIO-Diabetes

	Placebo (n=348)	Rimonabant 5mg (n=358)	Rimonabant 20mg (n=339)
Safety data at 1 year (% of patients)			
Overall drop-out rate	34	35	32
Any adverse event	79	82	85
Serious adverse event	4	8	8
Discontinuation due to adverse event	5	8	15
Adverse events with incidence ≥5% in any group (% of patients)			
Nausea	6	6	12
Nasopharyngitis	21	16	12
Dizziness	5	3	9
Arthralgia	8	10	9
Headache	9	8	8
Diarrhoea	7	6	7
Back pain	7	6	7
Upper respiratory tract infection	9	8	7
Vomiting	2	4	6
Hypoglycaemia	2	1	5
Fatigue	4	5	5
Anxiety	3	1	5

Reprinted from Scheen AJ, et al., Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study, Lancet, 2006;368:1660–1672,[60] with permission from Elsevier.

hyperglycaemia, by inhibiting intestinal a-glucosidase enzymes.[16–18] These agents (acarbose, miglitol, voglibose) are taken three times daily with meals that contain digestible carbohydrates. They reduce HbA_{1c} by 0.5–0.8%. Acarbose treatment was associated with a 25% reduction in risk of progression to diabetes in patients with impaired glucose tolerance in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial.[32] AGIs pose little risk for hypoglycaemia as monotherapy, but hypoglycaemia that occurs when they are used in combination with other drugs, such as SUs, must be treated with oral glucose rather than complex carbohydrates. AGIs may be associated with a small reduction in bodyweight. Carbohydrate malabsorption and associated marked weight loss do not occur with these agents, since carbohydrate absorption is moved more distally along the intestinal tract. However, greater amounts of undigested oligosaccharides are passed to the large bowel, resulting in troublesome GI side effects, including abdominal discomfort, flatulence and diarrhoea. GI side effects have resulted in discontinuation of AGIs in 25–45% of patients in clinical trials.

Insulin

Insulin, the most effective glucose-lowering drug, is sometimes the treatment of choice in patients with type 2 diabetes and is often required when glycaemic goals cannot be obtained using oral agents.[33] However, the adverse effects of insulin often lead to sub-optimal results in clinical practice. Most important from the perspective of the patient is the substantial weight gain, ranging from 2kg to nearly 10kg with various formulations, that so often accompanies insulin treatment.[34–37] This weight gain poses particular problems for overweight or obese patients who usually have pre-existing insulin resistance, weight-related health issues and longer-

term health risks. Gains in bodyweight appear to increase in proportion to daily insulin dose and plasma insulin concentration.[24] The magnitude of weight gain may, to some extent, also reflect the timing of insulin injections, co-administration of oral antidiabetic agents and risk of hypoglycaemia. In fact, the risk of severe hypoglycaemia is relatively low in obese insulin-resistant patients treated with insulin in the early course of the disorder.[33]

New Antidiabetic Agents

The incretin hormone GLP-1, secreted by the enteroendocrine L cells of the GI tract in response to eating, is rapidly degraded by the proteolytic enzyme DPP-4. GLP-1 mimetics (or GLP-1 receptor agonists) are parenteral formulations that resist degradation by DPP-4 and competitively bind to G-protein-coupled cellular GLP-1 receptors on islet α and β cells,[13,14] thereby mimicking the effects of endogenous GLP-1. The DPP-4 inhibitors are orally active agents (incretin enhancers) that selectively bind to DPP-4 and block the action of the enzyme in degrading GLP-1; this results in persistent higher levels of active GLP-1 after eating. As already mentioned, the biologic actions of GLP-1 include improvements in glucose-dependent β-cell function, suppression of glucagon secretion, reduced gastric emptying, and increased satiety. In addition, GLP-1 has been shown to stimulate β-cell expansion in pre-clinical studies, a finding that has also been observed with chronic DPP-4 inhibition using the DPP-4 inhibitor vildagliptin in animal models.[11,12,38]

GLP-1 Mimetics – Exenatide, Liraglutide

In 2005 exenatide, the first licensed incretin-based treatment, was approved as a twice-daily subcutaneous injection before meals in patients who are receiving metformin and/or SU and who have not achieved glycaemic control. The addition of exenatide to metformin and/or SU reduced HbA_{1c} by approximately 1.0% and produced significant weight loss ranging from 0.9kg (when added to metformin/SU) to 2.5kg (when added to metformin) at the approved 5µg and 10µg doses in six-month studies.[39–41] In a relatively small group of overweight metformin-treated patients followed for 82 weeks, there was maintained reduction in HbA_{1c} and continued weight loss (5.3kg).[42] In a comparison with insulin glargine, both treatments reduced HbA_{1c} by 1.1%, and exenatide produced a 2.3kg weight loss compared with a weight gain of 1.8kg with insulin glargine.[43] Severe hypoglycaemia has been infrequent with use of exenatide, but hypoglycaemia occurred in 14–36% of patients receiving SU or metformin/SU; accordingly, a dose reduction in SU is recommended when the agents are combined.[44] In addition to its need for twice-daily injection, exenatide use may be limited by a high frequency of GI adverse events, including nausea and, less commonly, vomiting (see *Table 1*). A new long-acting formulation to be administered once weekly is in development that may offer substantially better prospects in terms of patient acceptability.

Liraglutide is an acylated GLP-1 mimetic in development that has a half-life long enough to permit once-daily subcutaneous dosing. In a recent 14-week study in obese patients, liraglutide once daily significantly reduced HbA_{1c} at doses of 0.65, 1.25 and 1.9mg (1.7% reduction at highest dose); liraglutide therapy was associated with dose-dependent reductions in bodyweight of 3.0kg at the highest dose compared with a loss of 1.2kg with placebo.[45] GI adverse effects were common but appeared to decrease over time.

DPP-4 Inhibitors – Sitagliptin, Vildagliptin

Of the oral DPP-4 inhibitors in development, sitagliptin and vildagliptin are at the most advanced stage, the former having been approved for use in patients with type 2 diabetes in October 2006 in the US and the latter approved for use in Europe in October 2007. Both agents have been shown to be effective in reducing HbA_{1c} as monotherapy and when added to metformin, SU or TZD therapy in patients with type 2 diabetes.[12,46–52] HbA_{1c} reductions generally have ranged from 0.5 to 1.1%, with greater reductions seen in patients with higher baseline HbA_{1c}.[12] A pooled analysis of 1,301 drug-naïve patients receiving vildagliptin 100mg/day indicates reductions of 1.1% overall, 1.3% in patients with baseline HbA_{1c} >8.0% and 1.7% in those with baseline levels >9.0%.[12]

Modelling studies have indicated improved β-cell function during treatment with these agents.[11–13,53,54] A 52-week meal-test study showed improved β-cell function (insulin secretion measured as suprabasal C-peptide area under the curve divided by glucose area under the curve during standardised meal) at 12 weeks in patients who had vildagliptin added to metformin compared with metformin; this improvement was maintained over 52 weeks.[53] In another study, improved secretory tone was observed, whereby treatment increased the insulin secretory rate at any given glucose level compared with placebo.[54]

The DDP-4 inhibitors appear to have side effect profiles similar to placebo[12] (see *Table 2*) and are not associated with any marked risk of hypoglycaemia as monotherapy. For example, in trials hypoglycaemia in vildagliptin-treated patients has been mild and infrequent, with rates similar to those observed with rosiglitazone (one event in each group over six months)[51] and metformin (<1% of patients over one year);[48] in an add-on study with insulin, vildagliptin treatment was associated with a decrease in the frequency and severity of hypoglycaemia compared with ongoing insulin treatment as monotherapy.[55]

The DPP-4 inhibitors generally appear to be weight-neutral,[12,46,49,51] although some significant reductions in bodyweight have been observed in comparative studies. For example, vildagliptin produced a 0.3kg reduction in weight compared with a 1.6kg increase with rosiglitazone;[51] among obese patients, vildagliptin was associated with a 1.1kg decrease and rosiglitazone with a 1.7kg increase. Similarly, a 52-week study in metformin-treated patients with inadequate glycaemic control showed that sitagliptin was associated with a 1.5kg decrease compared with a 1.1kg increase with glipizide.[12] Conversely, a recent 24-week study with sitagliptin in patients who had inadequate glycaemic control while on glimepiride alone or in combination with metformin found that sitagliptin add-on therapy was associated with a modest but statistically significant bodyweight increase in the entire patient cohort compared with placebo.[56] Other potential benefits of these medications are suggested by a significant reduction in GI side effects with the addition of vildagliptin to metformin, compared with ongoing metformin treatment as monotherapy.[49]

The findings with oral DPP-4 inhibitors are promising. Although they appear to lack the consistently significant reduction in bodyweight associated with GLP-1 mimetics, the weight neutrality of these agents together with the absence of a need for injection, the apparent absence of significant GI adverse effects and the low risk of hypoglycaemia suggest utility particularly, although not exclusively, in obese patients. If experience in clinical practice substantiates the benefits suggested in these data, clinicians will have an exciting new option for obese patients with type 2 diabetes.

Anti-obesity Drugs – Rimonabant

Rimonabant is a selective cannabinoid-1 receptor blocker that has been approved for use in Europe as an adjunct to diet and exercise in obese patients or overweight patients with cardiometabolic risk factors such as type 2 diabetes or dyslipidaemia. While it is not primarily a glucose-lowering agent, the effect of rimonabant on bodyweight, glycaemia and a range of cardiometabolic risk factors may make it useful in obese patients with diabetes. The Rimonabant-in-Obesity (RIO) series of trials in overweight or obese individuals has shown that rimonabant consistently reduces weight and waist circumference and improves lipid profile and other aspects of cardiovascular risk.[57–60]

The RIO-Diabetes trial compared rimonabant 5mg or 20mg with placebo for one year in more than 1,000 overweight or obese patients with type 2 diabetes who were receiving metformin (~65%) or SU (~35%).[60] The 20mg dose produced a weight reduction of 5.3kg and reduced HbA_{1c} by 0.6%. At this dose, a significantly greater proportion of patients with metabolic syndrome at baseline no longer met the criteria for metabolic syndrome at one year (although there was no significant difference between rimonabant and placebo with regard to proportion of patients developing metabolic syndrome during the study).

Discontinuation rates were high in both rimonabant and placebo groups in all of the RIO trials, a finding that has been observed in some other anti-obesity drug trials. Although discontinuation rates were similar in all patient groups in RIO-Diabetes (see *Table 3*), discontinuation due to adverse events was more frequent in patients receiving rimonabant 20mg (15%) compared with placebo (5%). The most frequent reasons for discontinuation in the 20mg group were depressed mood disorders (11 patients, 3%), nausea (five patients, 1.5%) and dizziness (three patients, 0.9%). There is concern over the frequency of depression and depressed mood disorders observed in rimonabant-treated patients; monitoring for such effects is prudent, and additional study and experience are necessary to quantify any risks associated with these effects.

Conclusions

Obesity is a major – and modifiable – contributor to an alarming increase in type 2 diabetes worldwide. Overweight and obese patients should be encouraged to start and maintain a diet and exercise programme to lose weight; this should help in moving towards glycaemic goals and improving other metabolic risk factors. Unfortunately, although lifestyle interventions can be effective in achieving metabolic control, patients find it very difficult to maintain lifestyle changes.

The recent consensus statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends initial treatment with lifestyle intervention and metformin – where safe and tolerated – for all patients with type 2 diabetes, whether obese or not. The statement also emphasises the need for rapid addition of complementary medications or changes in regimens to promptly achieve and maintain glycaemia at levels as close to normal as possible.[18] When considering treatment of overweight and obese patients with type 2 diabetes, practitioners must remain aware of the potential for weight gain that is associated with many antidiabetic medications. Avoiding iatrogenic weight gain is a first step towards improved metabolic control

and, it is to be hoped, better long-term outcomes. For obese patients with multiple cardiometabolic risk factors, rimonabant may prove to be a useful intervention. Other new agents such as the incretin-enhancing oral DPP-4 inhibitors and the incretin mimetics also represent major advances in therapy. These agents seem likely to have considerable utility in overweight and obese patients with type 2 diabetes. ■

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