Tailored use of GLP-1 receptor agonists in type 2 diabetes

Andrew Brewster

Current guidelines do not take into account the phenotypic presentations of type 2 diabetes that manifest as varying degrees of metabolic disturbance, including a spectrum of insulin resistance, dyslipidaemia, and, in some people, deranged liver biochemistry associated with non-alcoholic fatty liver disease. The extent of these biochemical aberrations in people with type 2 diabetes depends on body composition and body fat partitioning. In addition to improvements in glycaemic control, weight reduction is an important clinical benefit of glucagon-like peptide-1 receptor agonist therapies and it underscores the importance of these agents as a major advance in the treatment of type 2 diabetes in overweight and obese people. The author postulates that the use of simple anthropometric measures and metabolic parameters to determine body fat partitioning and adiposity phenotype may allow more targeted use of GLP-1 receptor agonists, independent of BMI category.

Obesity is a major risk factor for the development of type 2 diabetes. A dramatic illustration of the association between body weight and type 2 diabetes was provided by the ADDITION (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care) study, in which 97% of individuals with screen-detected diabetes in Cambridge were overweight or obese (Lauritzen et al, 2000).

It is increasingly recognised that weight reduction and restoration of healthy body composition is possibly the most important therapeutic target for future interventions in the management of type 2 diabetes (Maggio and Pi-Sunyer, 1997; Anderson et al, 2003). Prospective evidence regarding intentional weight loss in people with type 2 diabetes demonstrates significant reductions in mortality, amounting to a 28% reduction in cardiovascular and diabetes-related deaths over a 12-year period (Williamson et al, 2000).

Despite evidence that weight loss can improve fasting glycaemia, HbA_{1c} levels, dyslipidaemia and hypertension, the very drugs that have conventionally been used to treat type 2 diabetes, such as sulphonylureas and insulin are associated with increasing weight (Yki-Järvinen, 2001). These medications are typically associated with a 2 kg gain in weight for every 1 percentage point (10.9 mmol/mol) decrease in HbA_{1c} (UK Prospective Diabetes Study Group, 1998).

With the recent development of the glucagon-like peptide-1 (GLP-1) receptor agonist therapies, it is now possible to offer a licensed treatment approach to managing hyperglycaemia in type 2 diabetes that is associated with a reduction in weight. The injectable GLP-1 receptor agonists exenatide and liraglutide are associated with significant,

Article points

1. This article discusses the benefits of weight reduction associated with the glucagon-like peptide-1 receptor agonist therapies for the management of blood glucose levels in type 2 diabetes.
2. Recent advances in obesity medicine and the more widespread use of imaging techniques to characterise body fat partitioning have served to highlight significant limitations of using BMI to assess health risks and tailor appropriate management strategies.
3. The concept of individual assessment to identify particular "at-risk" phenotypes likely to benefit most from GLP-1 receptor agonist therapy, independent of BMI, is postulated.

Key words

- BMI
- Body composition
- Glucagon-like peptide-1 receptor agonist
- Weight loss

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Page points

1. Endogenous glucagon-like peptide-1 (GLP-1) secretion results from differential processing of the glucagon gene product, proglucagon.
2. GLP-1 secretion in response to meal ingestion provides nutritional feedback as part of the "ileal brake" mechanism, whereby the presence of unabsorbed nutrients in the lower small intestine reduces gastric emptying and gastrointestinal secretion.
3. Central and peripheral satiety mechanisms may be impaired in people with type 2 diabetes as a result of a reduced GLP-1 response. This may provide a reason for the propensity for weight gain in people with type 2 diabetes and may also serve to explain the apparent difficulties these people have in losing weight.

sustained weight loss (Visbol et al, 2007; Klonoff et al, 2008). In this respect, the GLP-1 receptor agonists are distinct from the orally administered dipeptidyl peptidase-4 (DPP-4) inhibitors that protect endogenous GLP-1 from degradation and are also referred to as GLP-1 enhancers. The DPP-4 inhibitors are generally regarded as weight neutral (Kendall et al, 2009) and shall not be the focus of this article.

This review discusses the benefits of weight reduction associated with the GLP-1 receptor agonist therapies rather than the incretin effect *per se,* which is well described elsewhere (Holst et al, 2008).

GLP-1 as a signal of nutritional abundance

Endogenous GLP-1 secretion results from differential processing of the glucagon gene product, proglucagon. This gene is expressed in the alpha-cells of the pancreas and also endocrine L-cells of the gut mucosa (Bell et al, 1983). In the alpha-cells of the pancreas the glucagon sequence of proglucagon is cleaved out and secreted. In the L-cells of the distal ileum, however, the glucagon sequence remains in a larger peptide called "glicentin" with no apparent biological activity, whereas GLP-1 is cleaved out and secreted in response to meal ingestion, and in response to the delivery of nutrients to the terminal ileum (Orskov et al, 1986, Holst, 1997).

In addition to enhancing pancreatic glucose-dependent insulin secretion, GLP-1 has an important role as an enterogastrone – an intestinal hormone that inhibits gastrointestinal (GI) motility and secretion (Layer et al, 1995). GLP-1 secretion in response to meal ingestion provides nutritional feedback as part of the "ileal brake" mechanism, whereby the presence of unabsorbed nutrients in the lower small intestine reduces gastric emptying and GI secretion (Maljaars et al, 2008).

As well as its inhibitory effect on GI motility, GLP-1 also appears to influence central appetite circuits. GLP-1 receptors have been identified in regions of the hypothalamus that are known to be involved in appetite regulation (Göke et al, 1995) and GLP-1 is produced centrally by subgroups of brainstem neurones that have been shown to be activated by gastric distension (Vrang et al, 2003). The central elaboration of GLP-1 in response to gastric distension may therefore represent a physiological signal to terminate ingestion of food. In this way, centrally acting GLP-1 may serve to enhance satiety as part of a "gastric brake" mechanism, complementing the inhibition of gastric motility by peripheral GLP-1 as part of the ileal brake mechanism described earlier.

Central and peripheral satiety mechanisms may be impaired in people with type 2 diabetes as a result of a reduced GLP-1 response (Nauck et al, 2004). This may provide a reason for the propensity for weight gain in people with type 2 diabetes and may also serve to explain the apparent difficulties these people have in losing weight.

The GLP-1 receptor agonist exendin-4 (exenatide) has a superior affinity for the GLP-1 receptor compared with the endogenous GLP-1 ligand (Runge et al, 2008). Interestingly, in a mouse animal model, exendin-4 rapidly crosses the blood–brain barrier following peripheral administration (Kastin and Akerstrom, 2003) and appears to be much more potent than GLP-1 at reducing food intake in Zucker obese rats (De Fonseca et al, 2000).

Figure 1 provides a rationale for the differential effects of GLP-1 receptor agonists and DPP-4 inhibitors in terms of weight profile. A simple explanation is the difference in degree of "GLP-1 receptor agonism" achieved with each therapy. While both types of agent have beneficial effects on pancreatic insulin and glucagon secretion, the greater degree of GLP-1 receptor agonism achieved with injectable GLP-1 receptor agonists results in important extra-pancreatic effects, such as delayed gastric emptying and modulation of appetite and food intake (Holst et al, 2008). However, unwanted GI side-effects such as nausea, vomiting and diarrhoea may arise as a result of the extra-pancreatic effects of injectable GLP-1 receptor agonist therapies.

The importance of the central and GI effects of GLP-1 receptor agonists is illustrated in a recent case study that demonstrates an improvement in glycaemic control that could not be attributable to enhanced insulin secretion (Paisley et al,

2009). This obese person had undetectable C-peptide levels, suggesting that extra-pancreatic GLP-1 receptor agonist effects, such as weight loss due to increased satiety and delayed gastric emptying, in addition to glucagon suppression, resulted in improved insulin sensitivity and glycaemic control following treatment with exenatide (Paisley et al, 2009).

Weight loss benefits of GLP-1 receptor agonist therapy

As well as reductions in blood glucose levels, exenatide, the first licensed GLP-1 receptor agonist, was associated with significant weight loss of 4.4±0.3 kg (95% confidence interval –3.8 to –5.1 kg) during an 82-week period of treatment corresponding to a 4.4% reduction in baseline body weight (Blonde et al, 2006). For the 82-week exenatide completer group (*n*=314), 81% of treated participants had lost weight. An initial concern in this study was whether nausea could account for the observed weight reduction. However, weight loss was observed in people with varying amounts of nausea, including the majority of participants (54%) who had minimal or no nausea (Blonde et al, 2006). Furthermore, the incidence of nausea associated with GLP-1 receptor agonist administration was highest during treatment initiation and dose escalation, with nausea generally decreasing over a period of 4 weeks following initiation and subsequent dose escalation (Blonde et al, 2008).

Clinical studies have shown that the effects on food intake are maintained over several years and lead to a sustained or progressive weight loss. Exenatide has been demonstrated to achieve a significant average weight loss of 5.3±0.4 kg maintained over 3 years (P<0.0001) (Figure 2), which is likely to be due to its actions of inducing satiety and reducing food intake independent of any GI side-effect (Edwards et al, 2001).

In addition to clinical trial data, weight loss with exenatide has been demonstrated within a primary care setting. Clinical effectiveness of exenatide in people with type 2 diabetes was evaluated by extractions of data from a primary care electronic records database over a period of 6 months. Average weight loss among the 1785 people was 2.8 kg, from an average baseline

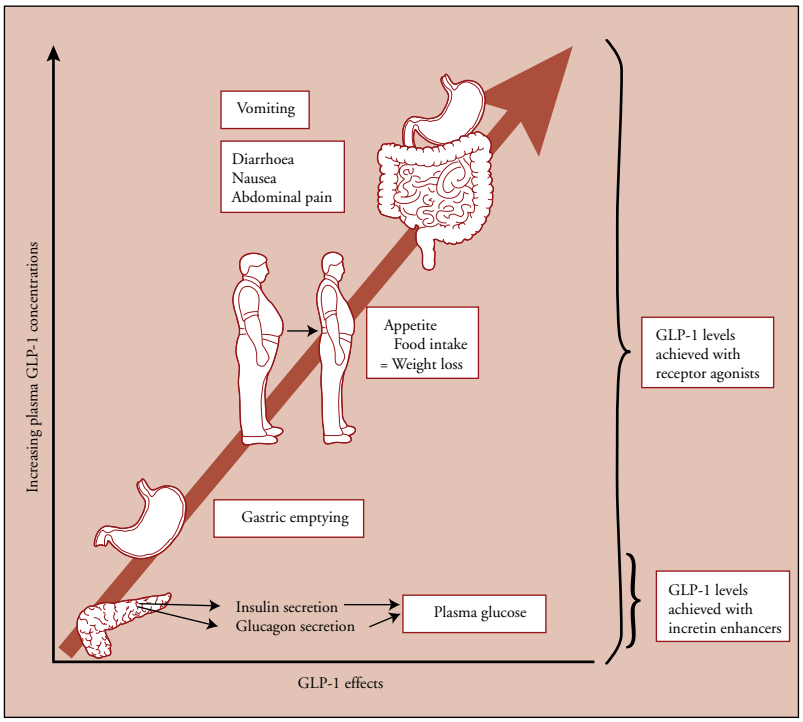

Figure 1. The dose–response relationships for the effects of glucagon-like peptide-1 (GLP-1). This figure illustrates the relationship between the plasma concentrations of endogenous GLP-1 or GLP-1 receptor agonists and their clinical effects and side-effects, as observed during treatment with GLP-1 receptor agonists or incretin enhancers. With modestly elevated GLP-1 levels, as obtained both with GLP-1 receptor agonists and incretin enhancers, there are significant effects on the pancreatic islets. Higher concentrations are needed to slow down gastric emptying and to reduce appetite and food intake. At even higher concentrations, which can be reached with GLP-1 receptor agonists, side-effects such as nausea, diarrhoea and vomiting might result. Reproduced from Holst et al (2008) with permission from Elsevier.

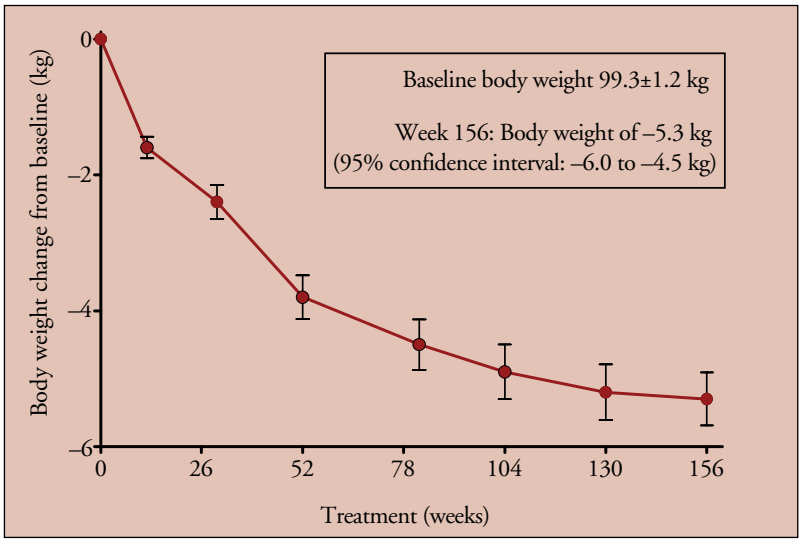

Figure 2. Effects of exenatide on metabolic parameters in people with type 2 diabetes inadequately controlled by metformin, sulphonylurea, or combined metformin and sulphonylurea therapy. Reproduced with permission from Klonoff et al (2008).

Page points

1. As a prerequisite to understanding the benefits of moderate weight loss as an important therapeutic strategy for people with type 2 diabetes, it is necessary to appreciate the high-risk "adiposity phenotype" that frequently presents in those with type 2 diabetes.
2. Evidence suggests that excess fat deposition in the liver is uniformly present before the onset of classic type 2 diabetes, and indeed liver fat content has impressive prognostic power in predicting onset of type 2 diabetes.
3. Resolution of high-risk sites of fat accumulation may explain the mechanism by which relatively modest amounts of weight loss are often associated with seemingly disproportionate health benefits in at-risk groups.
4. Interesting evidence is now emerging regarding the possible beneficial impact of glucagon-like peptide-1 receptor agonist therapy in relation to resolution of specific high-risk body fat depots, although further confirmatory research is required.

weight of 110 kg, with 70% of people losing weight (Brixner et al, 2008).

Weight loss as a therapeutic strategy in people with type 2 diabetes

As a prerequisite to understanding the benefits of moderate weight loss as an important therapeutic strategy for people with type 2 diabetes, it is necessary to appreciate the high-risk "adiposity phenotype" that frequently presents in those with type 2 diabetes, and also to consider the significant benefits of moderate weight loss, achieved via preferential mobilisation of the high-risk sites of fat accumulation.

The accumulation of intra-abdominal, or "visceral" fat, liver fat and ectopic fat in skeletal muscle underlies the dyslipidaemia and glucose dysregulation seen in people with type 2 diabetes (Brewster, 2008). With respect to glucose dysregulation, visceral adipose tissue deposition has been shown to correlate consistently with degree of peripheral insulin resistance (Banerji et al, 1997; Ross et al, 2002). There is a also a direct association between atherogenic dyslipidaemia and propensity to store visceral fat (Després et al, 1990). It is therefore not surprising that visceral fat deposition is associated with cardiovascular disease (Mathieu et al, 2009) as dyslipidaemia is the major risk factor for coronary artery disease (Turner et al, 1998). Indeed, almost 90% of obese people with ischaemic heart disease have evidence of visceral fat accumulation (Matsuzawa et al, 1994).

The associations between visceral fat, dyslipidaemia and coronary heart disease have important implications for people with type 2 diabetes since as 50% of all deaths in such people are attributable to coronary heart disease (Hu et al, 2002). Notwithstanding the important association between visceral fat and cardiovascular risk, visceral fat deposition is also identified as an independent predictor of all-cause mortality (Kuk et al, 2006).

The accumulation of liver fat in people with type 2 diabetes also has important implications. Evidence suggests that excess fat deposition in the liver is uniformly present before the onset of classic type 2 diabetes (Sattar et al, 2007; Shibata et al, 2007), and indeed liver fat content has impressive prognostic power in predicting onset of type 2 diabetes (Shibata et al, 2007; Kim et al, 2008). Interestingly, just as visceral fat has been implicated in insulin resistance, supranormal liver fat accumulation in type 2 diabetes is also associated with the degree of insulin resistance (Younossi et al, 2004).

Moderate weight loss using conventional diet and lifestyle techniques is associated with the preferential mobilisation and resolution of "high risk" visceral and liver fat depots relative to subcutaneous fat depots (Goodpaster et al, 1999; Smith and Zachwieja, 1999; Chaston and Dixon, 2008). In one study over a 7-week period, a loss of 8% body weight was associated with an 80% decrease in hepatic fat (Petersen et al, 2005). Resolution of high-risk sites of fat accumulation may explain the mechanism by which relatively modest amounts of weight loss are often associated with seemingly disproportionate health benefits in at-risk groups. Notably, weight loss is expected to result in improved insulin sensitivity (Dengel et al, 2006).

In one meta-analysis of weight management people with type 2 diabetes, a 12-week energy restricted diet was associated with a 9.6% reduction in body weight and a 25.7% reduction in fasting glucose (Anderson et al, 2003). Other benefits included reductions in the following cardiovascular risk factors: serum cholesterol, 9.2%; serum triglycerides, 26.7%; systolic blood pressure, 8.1%; and diastolic blood pressure, 8.6% (Anderson et al, 2003).

Metabolic benefits of GLP-1 receptor agonist-associated weight loss

Interesting evidence is now emerging regarding the possible beneficial impact of GLP-1 receptor agonist therapy in relation to resolution of specific high-risk body fat depots, although further confirmatory research is required.

For example, measurement of total body fat, percentage fat, and lean tissue composition via a dual energy X-ray absorptiometry (DEXA) scan, as well as visceral, subcutaneous and liver fat measurement via a computed tomography (CT) scan was undertaken in a subgroup of 160 people in the LEAD-2 (Liraglutide Effect and Action in Diabetes) trial (Jendle et al, 2008). A

significant reduction in visceral adipose tissue was seen with liraglutide at all doses compared with the sulphonylurea glimeperide (13–16% vs. 5% $P<0.05$) over a 26-week period. The study also demonstrated preferential mobilisation of visceral fat in respect to subcutaneous fat loss (5–9%) with liraglutide at doses of 1.2 mg and 1.8 mg ($P<0.05$).

Assessment of liver fat via liver-to-spleen attenuation ratio using CT scanning was also made in the study. This ratio is constant in individuals with healthy livers, with reduced attenuation used as an indication of liver fat deposition. Importantly, reduced hepatic steatosis was identified in the group treated with 1.8 mg liraglutide, as evidenced by a significantly increased liver attenuation ratio (+0.10) in this group compared with the unchanged attenuation ratio in the glimepiride group ($P<0.05$) (Jendle et al, 2008).

There are currently no corresponding trial data regarding the effect of exenatide on body composition. There is, however, a case report of a 73% reduction in liver fat, as measured by magnetic resonance spectroscopy, in the case of a 59-year-old Caucasian man, following 44 weeks of exenatide therapy at a dose of 20 µg twice daily (Tushuizen et al, 2006). This person also benefited from a weight reduction of 4.7% (88.5 kg at baseline to 84.3 kg) and from significant beneficial changes in several cardiovascular disease risk factors. It is noteworthy that the Dutch recipient in this case study had a baseline BMI of 28.7 kg/m^2.

While not providing information on body composition, a study by Klonoff et al (2008), involved 217 people (64% male, average age 58±10 years, mean weight 99±18 kg, mean BMI of 34±5 kg/m^2, HbA_{1c} 8.2±1.0% [66±10.9 mmol/mol]) who completed more than 3 years of exenatide treatment. The majority of exenatide-treated participants (68%) not only lost weight but also had a reduced HbA_{1c} level. In addition, improvements were observed in hepatic biomarkers: people with an elevated serum alanine aminotransferase (ALT) at baseline (n=116) had significantly reduced ALT at the end of the 156-week study period (–10.4±1.5 IU/L; $P<0.0001$), and 41% of this subset achieved normal ALT. The study also demonstrated improvements in cardiovascular risk factors: in a subset of people who had serum lipids available for analysis (n=151), triglycerides decreased by 12% ($P=0.0003$), total cholesterol decreased by 5% ($P=0.0007$), LDL-C decreased by 6% ($P<0.0001$), and HDL-C increased by 24% ($P<0.0001$) compared with baseline (Klonoff et al, 2008).

GLP-1 receptor agonist therapy: A NICE time to move beyond BMI?

Readers should remember that GLP-1 receptor agonists are licensed for the management of glycaemic control in type 2 diabetes. However, due to the weight loss associated with their use, clinical guidelines have included BMI criteria in the recommendations concerning these agents. For example, the recently published NICE (2009) CG87 update in relation to blood glucose lowering agents sanctions the use of exenatide (liraglutide was not available at the time of guideline publication) in people who have a BMI ≥ 35 kg/m^2 in addition to specific psychological or medical problems associated with a high body weight, or <35 kg/m^2 where insulin therapy would have significant occupational implications or if weight loss would benefit other significant obesity-related comorbidities.

In previous guidance, NICE recommend the use of exenatide only in those people with a BMI greater than 35 kg/m^2 (National Collaborating Centre for Chronic Conditions, 2008). The recent update and more liberal approach to the use of these agents is welcome, particularly as clinical evidence supports the use of GLP-1 receptor agonists in people with type 2 diabetes who have a BMI less than the proposed NICE BMI "watershed" of 35 kg/m^2.

Significant weight loss (–3.9±0.7 kg; $P<0.0001$) has been demonstrated in a subgroup of people (n=63) with a baseline BMI of <30 kg/m^2 treated with exenatide for 3 years (Klonoff et al, 2008). BMI ranges in insulin comparator trials have also been below the NICE cut-off value, involving participants whose BMI values were >27 kg/m^2 (Heine et al, 2005) and >25 kg/m^2 (Nauck et al, 2007) – both studies demonstrated non-inferiority in HbA_{1c} reduction.

Page points

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Page points

1. Recent advances in obesity medicine and the more widespread use of imaging techniques to characterise body fat partitioning have served to highlight significant limitations of using body mass index (BMI) to assess health risks and subsequent management plans.
2. In considering the use of glucagon-like peptide-1 (GLP-1) receptor agonist therapies, rather than simple reliance on BMI criteria it may therefore be prudent to consider a more targeted approach to identify people most likely to benefit from the moderate weight loss associated with these agents.
3. Tailoring of GLP-1 receptor agonist therapy may be achieved following the measurement of waist circumference and biomarkers of ectopic fat deposition to establish the exact nature of the presenting adiposity phenotype, independent of BMI category.

Consideration as to the origins of BMI casts some doubt regarding the rationale of using rather arbitrary BMI cut-off values to guide GLP-1 receptor agonist therapy. The concept of BMI – a simple ratio of weight in relation to height – was the work of Belgian statistician Adolfe Quetelet, who published his "Quetelet Index" in 1832. It is important to emphasise that Quetelet had no interest in obesity when he developed this index; Quetelet's mission was simply to use an index of relative weight to study the growth of normal man, having established that during normal growth, weight tends to increase in relation to height in metres squared (Eknoyan, 2008).

As Quetelet was a statistician rather than a physician it becomes easy to understand why it was not within his remit to consider the importance of body fat distribution and its impact on health when he formulated the idea behind the BMI. A further consideration is that Quetelet's relative weight data were obtained solely from a Caucasian population and the validity of the established BMI cut-off values has recently been questioned when applied to other ethnic groups (World Health Organization [WHO] Expert Consultation, 2004).

The importance of fat topography was not understood when Quetelet's concept of a simple ratio of weight relative to height was adopted first by the insurance industry after World War II and later by the medical profession as a tool to categorise obesity. The lack of understanding regarding importance of body fat distribution may explain why, until recently, the extrapolation of BMI to assess health risk associated with excess body weight has remained unquestioned.

Recent advances in obesity medicine and the more widespread use of imaging techniques to characterise body fat partitioning have served to highlight significant limitations of using BMI to assess health risks and tailor appropriate management strategies. This ratio does not take into account specific patterns of body fat partitioning and corresponding "adiposity phenotype" (Stefan et al, 2008). Thus, two people with exactly the same BMI can have very different patterns of body fat distribution and therefore have very different insulin sensitivities and cardiovascular risk profiles.

The WHO (2009) defines obesity as abnormal or excessive fat accumulation that presents a risk to health. Waist circumference measurement has been demonstrated to predict distribution of adipose tissue in the abdominal region, including visceral fat mass both in overweight and healthy weight individuals (Lemiuex et al, 1996). Waist circumference, therefore, reflects the most clinically significant fat distribution and adiposity phenotype, there apparently being little value in measuring BMI (Chan et al, 2003).

A recent prospective analysis involving over 350 000 people followed-up over almost 10 years underscores the importance of waist circumference measurement (Pischon et al, 2008). The study demonstrated a 17% increase in relative risk of death for men and 13% for women for every 5 cm increase in waist circumference independent of BMI category, and suggests the use of waist circumference to predict risk, particularly in those with lower BMI values.

In considering the use of GLP-1 receptor agonist therapies, rather than simple reliance on BMI criteria it may therefore be prudent to consider a more targeted approach to identify people most likely to benefit from the moderate weight loss associated with these agents. Tailoring of GLP-1 receptor agonist therapy may be achieved following the measurement of waist circumference and biomarkers of ectopic fat deposition to establish the exact nature of the presenting adiposity phenotype, independent of BMI category.

Tailored use of GLP-1 receptor agonists

Evidence presented to support the use of GLP-1 receptor agonists for blood glucose lowering in overweight and obese people with type 2 diabetes includes significant, sustained weight loss and radiological and biochemical data suggesting a possible tendency towards preferential resolution of high-risk fat depots, as discussed earlier in this article. Raised ALT is the most important marker of hepatic steatosis and non-alcoholic fatty liver disease (NAFLD) (Marchesini et al, 2001), and raised triglyceride levels are a recognised marker of visceral fat accumulation (Couillard et al, 1998). The author of the present article postulates that a trend towards radiological resolution of visceral

and liver fat and improvement of biomarkers representative of these depots may therefore encourage the clinician to identify candidates for GLP-1 receptor agonist therapy who have evidence of visceral and liver fat accumulation, irrespective of BMI category. Such people may have the most to gain from GLP-1 receptor agonist therapy. Indeed, they may also have the most to lose from weight gain associated with some other classes of blood glucose lowering therapy.

Identification of the "hypertriglyceridaemic waist" phenotype following screening for increased waist circumference measurement and elevated fasting triglyceride levels is a useful clinical concept and serves to identify individuals who have accumulated visceral fat mass. Importantly, the use of waist circumference >90 cm for men, together with plasma triglyceride concentration >2 mmol/L, has shown to be highly discriminatory for the development of coronary heart disease (Lemieux et al, 2000). Such people may therefore benefit from weight loss associated with GLP-1 receptor agonist therapy and the resulting improvement in cardiovascular risk factors.

Evidence regarding improvements in liver fat content and serum ALT levels in people with type 2 diabetes and associated NAFLD following GLP-1 receptor agonist therapy may also be considered in attempts to tailor GLP-1 receptor agonist therapy. Intuitively, such individuals would appear most likely to gain additional benefit from GLP-1 receptor agonist therapy via normalisation of deranged hepatic biomarkers as a result of moderate weight reduction and resolution of liver fat accumulation.

Conclusion

Weight loss is an important therapeutic strategy in the management of type 2 diabetes. GLP-1 receptor agonist therapies represent a major advance in diabetes care and their blood glucose lowering action is accompanied by weight loss. It is becoming increasingly apparent that the effects of GLP-1 receptor agonist therapies are not confined to the pancreas. Additional beneficial effects of these agents are likely to reflect the role of GLP-1 as an enterogastrone hormone – signalling nutritional abundance to promote weight loss and possibly preferential resolution of high-risk fat depots.

Data presented in this article support the concept of individual assessment to identify particular at-risk "adiposity phenotypes" likely to benefit most from the tailored use of GLP-1 receptor agonist therapies, independent of BMI category.

GLP-1 receptor agonists represent an exciting new voyage of discovery in the management of type 2 diabetes and the potential of these agents is rapidly becoming clearer. In light of positive outcome data and increasing experience of GLP-1 receptor agonist therapy, it is perhaps time to consider less reliance upon Adolphe Quetelet and his concept of BMI to navigate the future course of our voyage. In the spirit of person-centred care, NICE may in the future be encouraged to extend the use of these promising agents "beyond BMI". ■

Conflict of interest:
The author has participated in advisory boards for both Lilly and Novo Nordisk.

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Page points

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"GLP-1 receptor agonists represent an exciting new voyage of discovery in the management of type 2 diabetes and the potential of these agents is rapidly becoming clearer."

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