Weight loss: Is it quantity or quality that matters?

Balancing weight loss quantity and quality, and the factors contributing to optimised quality, are explored in this review published in *Diabetes, Obesity & Metabolism*. In response to the significant weight loss achievable with weight loss drugs, the review encourages clinicians to think about ten potential weight loss quality targets, and the authors explore how current weight loss methods, including drug treatments, could achieve these. The review highlights the significant role that exercise can have in improving quality of weight loss, including by reducing weight regain.

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Obesity is a growing challenge globally, and injectable weight loss pharmacotherapies offer double-digit weight loss, as well as other benefits, in those who respond to and tolerate them. All weight loss results in loss of lean mass alongside fat mass, and the ratio of fat to lean mass lost varies depending on the method or drug used. Recently there has been exploration and debate about the impact of weight management drugs on muscle, bone and other tissues, including the heart and kidneys.

In the present review, published in *Diabetes, Obesity & Metabolism*, Henriksen and colleagues introduce and explore the concept of weight loss quality. The authors propose weight quality targets for weight loss interventions, which could include:

- Large reduction in fat mass.
- Minimal impact on lean mass.
- Minimal/prevention of bone loss.
- Preserved insulin sensitivity.
- Preserved energy expenditure.
- Resetting of the satiety set point.
- Durability – results sustained over time.
- Improved quality of life.
- Improved mobility.
- Reduced pain.
- Prevention/remission of comorbidities.
- Minimising need for other drugs.

Weight quality targets

Reduction in fat mass

During weight gain and fat accumulation, initially fat cells (adipocytes) are small and insulin-sensitive, but with continued fat storage they become large and insulin-resistant. Adipose tissues become infiltrated with macrophages and inflammatory cytokines increase, resulting in low-grade systemic inflammation. Inflammation is further increased by mitochondrial stress and increased reactive oxygen species due to exposure of the fat cells to excess circulating fatty acids. Subcutaneous fat stores fill up initially and may be protective. In contrast, abdominal or visceral adipose tissue includes deposits around blood vessels (perivascular deposits), the heart (epicardial fat) and the kidneys (perirenal fat), and are associated with insulin resistance, hypertension and other cardiometabolic complications.

The goal during weight loss should be to preserve the adipose tissue oxidation of fatty acids while decreasing the fat deposits, particularly those in the ectopic fat, thus decreasing inflammation.

Protecting lean mass

Lean mass includes skeletal muscle and the heart, kidneys and liver. It contributes 15–40% of total weight lost depending on the method, resulting in decreased muscle strength, energy burning ability and insulin sensitivity, partially reversing the improvement in insulin sensitivity attributed to the weight loss. The goal is, therefore, to preserve skeletal muscle function and muscle mass during weight loss, and the recognised best way to achieve this is with exercise/physical activity.

Citation: Brown P (2025) Diabetes Distilled: Weight loss – is it quantity or quality that matters? *Diabetes & Primary Care* **27**: [Early view publication]

Practice points

1. Consider outcomes beyond the degree of weight loss to prioritise when discussing weight management options.
2. The concept of "weight loss quality" can be useful.
3. Although of limited effectiveness for weight reduction, physical activity has a key role in optimising weight loss quality and minimising weight regain.
4. People must be supported to implement evidence-based lifestyle guidance, particularly physical activity, alongside any pharmacotherapy for weight loss.

Improving insulin sensitivity

According to the authors, skeletal muscle, liver, adipose tissue, kidneys, pancreas, bone, brain, and heart and blood vessels all contribute to insulin sensitivity. Increased free fatty acids in the tissues and blood, combined with local inflammation, increase insulin resistance. In adipose tissue the effect of insulin is blocked, resulting in increased free fatty acids and inflammation, while reduced GLUT4 translocation reduces glucose uptake into muscle.

The goal is to identify drugs that positively impact insulin sensitivity or decrease inflammation, even if they only produce small degrees of weight loss.

Effects on liver and heart

Accumulation of fatty acids in the liver cells results in insulin resistance and inflammation, resulting in metabolic dysfunction-associated steatotic liver disease (MASLD), which can progress to metabolic dysfunction-associated steatohepatitis (MASH), decreasing liver function. Modest weight loss may improve steatosis but greater weight loss is required to reverse more serious liver changes such as fibrosis.

Increasing levels of free fatty acids, fat deposition around the heart and inflammation all contribute to heart failure, particularly heart failure with preserved ejection fraction (HFpEF). Drugs such as semaglutide and tirzepatide have been demonstrated to combine weight reduction with improvements in HFpEF, physical function and quality of life (Kosiborod et al, 2023; Packer et al, 2025).

Preventing bone loss

Obesity and type 2 diabetes result in increased bone mass but lower bone strength (Piñar-Gutierrez et al, 2022), resulting from poor muscle function, insulin resistance, inflammation and inactivity. Significant weight loss, following bariatric surgery for example, results in bone loss and increased fracture risk.

Reduced joint pain

Osteoarthritis (OA) is triggered by the combination of excess weight's impact on the joints and increased inflammation, and the resulting pain, disability and immobility can have a negative effect on muscles and further impact on function. Weight loss of around 10% is usually needed to improve OA. Some of the incretin drugs (e.g. semaglutide 2.4 mg) appear to have an anti-inflammatory effect as well as weight reduction, and may therefore improve OA knee pain (Bliddal et al, 2024).

Durable and sustained weight loss

Weight regain results from a lower resting metabolic rate, lower energy expenditure of weight-bearing activities, and increased appetite or hunger (due to increases in PYY and ghrelin) during and after weight loss. Significant levels of physical activity and the corresponding preservation of muscle mass may at least partially prevent weight regain. However, studies have demonstrated that around two-thirds of weight lost may be regained when drug treatment stops despite ongoing support (Wilding et al, 2022; Aronne et al, 2024).

What impacts weight loss quality?

Many factors influence the amount of, and benefit from, weight loss in individuals, including age, genetics, gender and comorbidities such as type 2 diabetes and chronic kidney disease. The impact of current weight loss methods on the different elements of weight loss quality are summarised in *Table 1* (overleaf).

Studies have demonstrated that although physical activity may contribute little to weight loss, it may produce good reductions in fat mass whilst protecting lean and bone mass.

Bariatric surgery achieves high rates of type 2 diabetes remission and improvements in cardiovascular conditions and MASH, as well as improving mortality risk. However, loss of muscle and bone and increased risk of fractures have been demonstrated. Although quality of life is improved for many people, some suffer depression, substance misuse and other issues.

Semaglutide suppresses appetite and can change food preferences, resulting in significant weight loss with higher doses. Improvement in cardiovascular conditions has been demonstrated (Lincoff et al, 2023; Kosiborod et al, 2023). Preclinical data had suggested that incretin therapies would protect against bone loss, but this has not since been demonstrated in humans.

Tirzepatide, a dual GLP-1 and GIP receptor agonist, is highly effective for weight loss and

glycaemic control. The SURMOUNT-MMO trial is exploring tirzepatide's cardiovascular benefits, and studies on MASH and OA are ongoing. GIP agonism may be involved in inhibition of bone resorption, may improve insulin sensitivity (independent of weight loss) and may improve tolerance compared with other incretin therapies.

Implications for practice

The concept of weight loss quality rather than just quantity may be new to many clinicians and builds on recent discussions around the possible impact of significant weight loss on muscle and bone loss, with all the attendant risks of sarcopenia, frailty, falls, fractures and rapid weight regain when drugs are stopped.

Weight loss drugs targeting multiple receptors are in development and may have individualised beneficial effects on the different aspects of weight loss quality and comorbidity management discussed here. These may allow personalised approaches to weight loss in future.

The quantity and multiple actions of new weight loss drugs in development can seem overwhelming. However, at least over the next few years, our use of weight loss drugs will be guided and closely monitored as we implement the latest NICE guidance according to local policy. Our role will be in supporting people to implement evidence-based lifestyle guidance, particularly physical activity as discussed here, alongside their drug therapy, to optimise weight loss quality and minimise weight regain. I feel strongly that our support should extend to those who are choosing to fund weight loss drugs privately. However, time constraints in primary care are already making this challenging. ■

Table 1. Weight loss quality aspects of various interventions (adapted from Henrikson et al, 2025).

Intervention	Percentage weight loss	Associated benefits	Challenges
Diet, exercise	<5%	All the benefits of exercise and healthy diet	Adherence
Very-low-calorie diet	>10%	Improved comorbidities	Unsustainable Lean and bone mass ↓
Bariatric surgery	30–35%	Remission of comorbidities Durable	Lean and bone mass ↓ Supplements needed QoL may deteriorate Invasive
Older anti-obesity medications*	Up to 5%		Tolerability Anxiety
Semaglutide (subcutaneous)	15–17%	Cardiovascular benefits QoL Type 2 diabetes management Knee osteoarthritis	Lean mass ↓ Effects lost when stopped Less weight loss in type 2 diabetes Bone impact unclear
Tirzepatide	18–20%	Tolerability HFpEF benefits Insulin sensitivity ↑	Mostly weight-related benefits to date
Oral semaglutide, orforglipron		Improved adherence	Weight loss less than with injectables
Cagrilintide	8–9%	Greater weight loss in type 2 diabetes than expected	Diabetes benefit less than incretins
Bimagrumab	5–6%	Lean mass ↑	Unknown as yet

*Older drugs: orlistat, naltrexone–bupropion, phentermine–topiramate, liraglutide 3 mg.
QoL=quality of life.

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The Goldilocks for chronic weight management – Balancing quantity with quality of weight loss

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