‘Diabesity’ – interlinking treatments to improve outcomes in diabetes and obesity

Learning objectives

You will learn:

• ‘Diabesity’ is a term used to describe the pathophysiological interlink between obesity and type 2 diabetes mellitus, both of which are characterised by insulin resistance and insulin deficiency
• Significant benefits of weight loss have been observed in type 2 diabetes mellitus prevention and treatment
• Rational use of antidiabetic medications is imperative to optimise long-term management of diabesity, balancing optimal glycaemic control with the most appropriate diabesity management regimen.

Introduction

Over recent decades obesity has emerged as the largest chronic health concern globally, with major driving factors being the consumption of high-calorie, high-carbohydrate and high-fat foods and a shift towards a sedentary lifestyle. Moreover, the incidence of severe obesity (i.e. a body mass index (BMI) >40kg/m²) is increasing rapidly and carries an especially elevated mortality risk. Obesity is associated with more than 45 comorbidities and is known to be the primary risk factor for cardiovascular disease, type 2 diabetes mellitus (T2DM), hypertension, coronary heart disease and certain types of cancer. Obesity is also a cause of diverse psychological problems and various physical disabilities, including a significantly increased risk of developing an arthritic condition. In the context of the COVID-19 pandemic, obesity and diabetes are associated with more severe outcomes of the disease and markedly increased mortality. The infection itself may precipitate acute metabolic complications through direct negative effects on pancreatic β-cell function.1-4

In the context of the COVID-19 pandemic, obesity and diabetes are associated with more severe outcomes of the disease and markedly increased mortality.

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It is important for the clinician to recognise the cycle of insulin resistance and obesity, whereby each gives rise to the other and can result in more severe obesity and T2DM. The term ‘diabesity’ describes the pathophysiological interlink between obesity and diabetes, as both metabolic disorders are characterised by insulin resistance and insulin deficiency. There is a tendency towards decreased treatment success in diabetes whenever weight gain is observed, and weight reduction is considered a key therapeutic goal in the treatment of T2DM. This raises the question of whether weight management and diabetes should be targeted with combined treatment strategies.1,5,6

Diabesity is the pandemic that will stay with us long after COVID-19 has passed. Of the South African adult population, 20% are diabetic or pre-diabetic, and half of these remain undiagnosed; this will place an enormous burden on our health system in the coming decade. To improve long-term metabolic control, Dr Lombard confidently favours diabetic treatments that contribute to weight loss or that are at least weight neutral.

**From obesity to diabetes**

Obesity causes sustained elevation of free fatty acid plasma levels, both in the basal state and following glucose load; this is a major contributing factor to insulin resistance and ultimately the development of diabetes (Figure 1). Hyperglycaemia and compensatory hyperinsulinaemia associated with insulin resistance and glucose intolerance lead to pathological glycation of circulating proteins and the formation of advanced glycation end-products. This progression ultimately leads to pancreatic β-cell secretory failure and apoptosis.6 Click through for further information on these inflammatory pathways (see page 12).

![Diagram of pathways from obesity to diabetes](image)

**What is the importance of body fat distribution?**

A high proportion of body fat is regularly seen in people with a BMI >30kg/m², but this is also observed in one-third of people with normal weight and can usually be identified using waist circumference measurements (women >80cm, men >94cm). Independent of the population-specific BMI thresholds determining overweight and obesity, visceral fat distribution has been found to elevate the risk of mortality.1
What are the benefits of weight loss in diabetes prevention and therapy?

The progression of T2DM can be arrested and often reversed in the first five years after diagnosis by significantly reducing body weight (≥10%); the metabolic dysregulation and inflammatory processes that predispose to T2DM can frequently be corrected.5

The Finnish Diabetes Prevention Study7 showed that in pre-diabetic individuals, intensive dietary and exercise programmes decreased the overall risk of diabetes by 58% (Figure 2). Similarly, the Diabetes Prevention Program8 showed that moderate weight loss with lifestyle intervention in an obese population with impaired glucose tolerance could reduce the incidence of diabetes by 58%, whereas metformin alone reduced diabetes incidence by only 31% (Figure 3).

Figure 2. Finnish Diabetes Prevention Study: intensive dietary and exercise intervention decreases overall risk of diabetes

Figure 3. Diabetes Prevention Program – Lifestyle modification is superior to metformin for the prevention of T2DM
The American Cancer Society’s Cancer Prevention Study I indicated that intentional weight loss of 10kg in those with T2DM reduced total mortality by approximately 25%. Other clinical trials have demonstrated that a loss of 5-10% of body weight in diabetes patients demonstrates beneficial effects at one year (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Benefits of weight loss in diabetes patients</th>
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<tr>
<td>• Improves overall fitness</td>
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<tr>
<td>• Reduces HbA1c levels</td>
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<tr>
<td>• Improves cardiovascular disease risk factors</td>
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<tr>
<td>• Decreases the use of antihyperglycaemic, antihypertensive and lipid-lowering agents</td>
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<tr>
<td>• Reduces symptoms of depression</td>
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<td>• Reduces severity of, or promotes remission of, symptoms of obstructive sleep apnoea.</td>
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In many ways the treatments for diabetes are similar to those for addressing obesity. The treatment of obesity always entails reduction of body weight through lifestyle interventions, pharmaceutical interventions or metabolic surgery. Canada is the only country to publish clinical guidelines for the management of obesity as a chronic disease. The available treatments for diabetes are variable and based on the type of diabetes with which an individual has been diagnosed. Important factors that need to be considered include a person’s lifestyle habits, diet and their medicine choices.

What is the role of lifestyle in management of weight and diabetes?

Patients’ understanding of the role of diet and exercise in preventing and managing diabetes is critical to long-term health status change. Any recommended lifestyle changes should be specific to the patient; patients that participate in lifestyle reconciliation decision-making have a much greater ability to lose weight. However, the reality is that intensive lifestyle interventions are difficult to achieve and maintain over a long period of time.

Exercise

The effects of physical activity in improving a patient’s metabolic profile are unequivocal. Studies have consistently shown improved glycaemic control, lipid profile, cardiovascular fitness and antioxidant status, along with reduced inflammatory markers, adiposity and atherogenic progression, thereby confirming that physical activity is an evidence-based treatment modality to combat diabesity.

Exercising more than three times per week, averaging 150 minutes of physical activity every week, should entail a combination of aerobic exercise with twice-weekly strength training. Aside from obviously strengthening muscle and bone and improving lean mass, strength training also improves insulin sensitivity and can lower blood glucose. There is an additive effect on weight loss when exercise is combined with an energy-restricted diet.

Diet and nutrition

Nutrition therapy is practical and useful for improving glycaemic control and metabolism. An energy-restricted diet can be achieved either by a low-fat, low-carbohydrate diet, or the Mediterranean-style diet, which is characterised by beneficial metabolic effects. However, it is not the diet type that determines the success of weight loss, but rather...
sustained adherence to the diet of choice. Ideally, a broad spectrum of different diet options should be available to best match the patient’s individual food preferences, lifestyle and medical conditions.

**Clinical focus with Dr Lombard**

**Top tips for motivating patients to adopt a better lifestyle**

Dr Lombard points out that from his clinical experience, the following strategies or interventions work best:

- Motivating patients to lose weight, especially poorly controlled overweight diabetics, is more achievable when they understand the serious implications of their condition. If diagnosed with T2DM at 50 years of age, lifespan is likely to be reduced by 10 years; if diagnosed before the age of 40 years, the individual is unlikely to reach retirement age.

- A weight loss of at least 10kg or 10% of body weight is not easy to achieve and sustain; the addition of anti-obesity drugs is useful, although they are not reimbursed by South African medical aids. Options include orlistat, topiramate, liraglutide and phentermine. Phentermine can only be used short term as it has significant risks; the prescriber should be aware of its indications and contraindications.

- Consultation with a motivated and dedicated dietitian can be of great help; a team effort and regular follow-up are necessary.

- Ensure that other medications are not contributing to weight gain.

- Choose diabetic medications that contribute to weight loss.

**Pharmacotherapy in diabetes – what are the options for combined obesity and diabetes treatment?**

Effective treatment of obesity should simultaneously improve body weight, body composition and glycaemic control. Although metabolic surgery is the best treatment option for patients with diabesity, most patients can only be managed with antidiabetic medications because metabolic surgery is invasive, unacceptable to many patients and expensive, currently around R180 000.

Antidiabetic agents may affect diabesity outcomes because of their effects on body weight and other metabolic parameters. Consequently, rational use of antidiabetic medications is imperative to optimise long-term management of diabesity. The focus of a suitable antidiabetic treatment for obese/overweight patients should at the very least be the prevention of additional weight gain. Glucose-lowering agents that support weight reduction or are weight neutral should be the first choice after the obligatory metformin therapy.\(^1,15\)

**Metformin**

Although metformin is generally considered weight-neutral, weight loss ranging from 0.6 to 2.9 kg has been shown in multiple studies with HbA\(_1c\) reduction of ≥1%, especially when coupled with lifestyle interventions. Antidiabesity effects arise from inhibition of hepatic gluconeogenesis, improvement of muscle insulin sensitivity and the agent’s appetite-suppressing effect. Metformin treatment in combination with lifestyle modifications has shown improvements in polycystic ovary syndrome (PCOS), gestational diabetes mellitus, non-alcoholic fatty liver disease (NAFLD) and cancer, all of which are health problems directly or indirectly linked to diabesity.\(^5,15\)
GLP-1 RAs

The glucagon-like peptide-1 receptor agonists (GLP-1 RAs) can lead to weight loss by decreasing appetite, delaying gastric emptying and enhancing satiety. Collectively, these effects result in a significant improvement in diabesity, with protective effects on the heart, kidneys and liver (Figure 4). Variations in weight loss potential are seen among individual GLP-1 RAs and in different patient groups. Liraglutide is the most potent and best researched for weight loss in the GLP-1 class, with a 3mg daily dose found to be beneficial as an anti-obesity treatment in patients without diabetes (Box 1).

Variations in weight loss potential are seen among individual GLP-1 RAs and in different patient groups

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Box 1. Anti-obesity treatments: Liraglutide and weight management

- Individuals without T2DM, BMI >30kg/m² or >27kg/m² in the presence of treated or untreated dyslipidaemia or hypertension
- 3.0mg liraglutide injected subcutaneously vs placebo; all subjects received counselling on lifestyle modification
- At 56 weeks, the liraglutide group had lost a mean of 8.4±7.3kg of body weight and the placebo group had lost a mean of 2.8±6.5kg
- Of patients in the liraglutide group, 63.2% lost at least 5% of their body weight compared with 27.1% in the placebo group (P<0.001); 33.1% and 10.6%, respectively, lost more than 10% of their body weight (P<0.001)
- Liraglutide treatment was associated with reductions in cardiometabolic risk factors, including waist circumference, blood pressure and inflammatory markers, along with modest improvements in fasting lipid levels.

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Figure 4. The physiological roles of GLP-1 and therapeutic benefits of GLP-1 RAs

- Reduced gastric motility and gastric acid secretion
- Increase sodium and water excretion
- Insulin secretion
- Glucagon secretion
- β cell proliferation
- β cell apoptosis
- Insulin sensitivity
- Glucose production
- Cardioprotection
- Cardiac function
- Neuroprotection
- Reduced appetite
- Early satiety
Are all GLP-1 RAs equal with regard to weight loss?

A recent comparison of dulaglutide and liraglutide in the AWARD-6 study showed a statistically significantly greater weight loss with liraglutide (Figure 5), with a difference of 700g in six months. However, once-weekly dulaglutide has similar glucose-lowering efficacy as the 1.8mg liraglutide dose and good cardiovascular outcomes. Treatment with exenatide has been associated with only modest weight loss (2.49±0.66kg) in a cohort of obese non-diabetic women. Exenatide has not shown any cardiovascular benefit.

The SUSTAIN-7 trial, a head-to-head comparison between semaglutide and dulaglutide as add-on to metformin, demonstrated significantly greater weight loss at 40 weeks with semaglutide. As T2DM and lifestyle factors are the usual consequences of obesity, clinicians should consider this treatment option in very obese subjects not willing or able to undergo metabolic surgery.

SGLT-2 inhibitors

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) reduce glucose reabsorption by the kidneys, leading to increased urinary glucose excretion. This may result in weight loss via direct caloric loss in the form of glycosuria, as well as improved glucose control. Major adverse effects reported are urinary tract infections and genital fungal infections (from increased glucose excretion through the kidney) that may lead to discontinuation of the drugs. A beneficial class effect is renoprotection – a more than 40% reduction of renal disease, renal failure, renal replacement therapy and worsening renal function on average. There is also significant benefit in heart failure, with hospitalisation reduced by nearly 40%. Empagliflozin data show a lowering of cardiovascular mortality by an impressive 38% (relative risk reduction) in patients with established cardiovascular disease.
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DPP-4 inhibitors

DPP-4 inhibitors are weight neutral. While use of dipeptidyl peptidase-4 (DPP-4) inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) have a low risk of hypoglycaemia and have been associated with improved glycaemic control, insulin secretion and β-cell function, they are considered to be weight neutral or associated with minimal changes in weight. They are very safe drugs, seldom give rise to side effects and are ideal for use in the elderly or those patients at high risk of hypoglycaemia. DPP-4 inhibitors are generally neutral from a cardiovascular point of view, but some should not be used in patients with heart failure.

Thiazolidinediones

The thiazolidinediones are associated with weight gain, making pioglitazone less favourable for patients with diabesity. However, pioglitazone improves NAFLD, although its use is associated with increased risk of heart failure, urinary bladder cancer, secondary osteoporosis and fractures. Thiazolidinediones can be useful in patients with extreme insulin resistance and have demonstrated good stroke prevention data in the IRIS study.

Insulin

Because it is an anabolic hormone, insulin causes weight gain through inhibition of protein catabolism, stimulation of lipogenesis, slowing of basal metabolism and increasing the accumulation of fat. Increase in body weight and fat mass is strongly associated with the intensity of the insulin regimen, as well as worsening of diabesity. Insulin in high doses, as often used in obese diabetics, can cause massive weight gain. Yet insulin and sulphonylureas (gliclazide, glimepiride, glipizide, glyburide) are frequently used early in the management of T2DM. Gliclazide is the only sulphonylurea recommended by the Society for Endocrinology, Metabolism and Diabetes of South Africa and is associated with minimal weight gain.

For patients with obesity and T2DM requiring insulin therapy, the Endocrine Society Clinical Practice Guideline recommends concomitantly prescribing at least one weight loss-promoting medication (e.g. metformin, GLP-1 RAs or pramlintide) to mitigate associated weight gain from insulin use. With all the new agents available, especially the weight-friendly GLP-1 RAs and SGLT-2 inhibitors, these drugs should be optimised before insulin is considered. Insulin should only be used if no other options are left.

Clinical focus with Dr Lombard

Multidrug treatment for glycaemic control – keeping weight top of mind

Drugs with prognostic (survival) benefits should be used first. It is interesting to note that the only classes that have prognostic benefits are also those medications that contribute to weight loss - metformin, SGLT-2 inhibitors and GLP-1 RAs. Variations in drug efficacy within classes imply that the right choices need to be made for each patient – ‘the art of medicine’. Dr Lombard observes how very unfortunate it is that medical funders usually do not see the point of individualised management, and these drugs are often poorly reimbursed. They would rather pay for the complications than pay to prevent them. Fixed combinations are entering the market and will offer many more excellent choices, with very robust published data to support their use.

Most patients with T2DM require more than one antidiabetic agent for glycaemic control at some point on their diabetes journey. In these cases, rational drug combinations with the least potential for worsening diabesity and with maximum benefits in preventing its complications, such as cardiovascular disorders and renal disease, should be chosen when devising the appropriate management strategy. In patients without contraindications...
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Rational drug combinations with the least potential for worsening diabesity and with maximum benefits for preventing its complications, such as cardiovascular disorders and renal disease, should be chosen when devising the appropriate management strategy.

Summary of interventions

- Addition of insulin to metformin is the best approach for rapid reversal of severe hyperglycaemia and glucotoxicity. However, every attempt should be made to switch from insulin to another antidiabetic agent with weight loss potential or that is weight neutral once glycaemic control is achieved.

- Although addition of sulphonylureas to metformin worsens diabesity because of the weight gain potential, this combination is economical and effective in controlling hyperglycaemia and therefore still preferred by many funders.

- Because of the weight loss potential and beneficial effects on an adverse lipid profile, the combination of GLP-1 RAs with metformin is potentially a very promising regimen for patients with diabesity.

- Combination therapy with metformin and a SGLT-2 inhibitor is encouraging for medical management of diabesity, showing reduction in body weight and improvement of β-cell function.

- Because of weight neutrality and different mechanisms of action, a combination of a DPP-4 inhibitor and metformin is promising in the early management of diabesity in patients reluctant to use injections or intolerant of GLP-1 RAs; a fixed combination should be considered early on.

- Addition of pioglitazone to metformin raises concerns about the management of diabesity, although it may be an appropriate choice among patients with NAFLD and PCOS.

Clinical focus with Dr Lombard

And do not forget about other medications

Many medicines tend to increase body weight (Table 2). In general, net weight gain varies between individuals and from drug to drug. Take time to distinguish between weight gain related to a specific treatment and weight gain that is due to other factors, such as a poor diet or lack of exercise.1,20

It is important to note significant comorbid association between diabesity and neuropsychiatric disease, particularly depression. Importantly, not only is the prevalence of mood disorders elevated in patients with T2DM, but depressed patients are also more prone to develop diabetes. Similarly, there is an association between mood disorders and obesity. Some antidepressants, antipsychotics and anti-epileptic medications lead to an increased appetite, whereas other medicines such as beta-blockers slowly induce weight gain over time due to associated fatigue and thus lower patient activity levels. Importantly, treatment of obesity improves depressive symptoms in patients with mood disorder; and patients being treated for depressive symptoms show improved weight loss and weight management.20,21
### Table 2. Different drug types and their observed trends in weight gain

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Weight effect</th>
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<tbody>
<tr>
<td><strong>Antidepressant agents</strong></td>
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<tr>
<td>Tricyclic antidepressants</td>
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<tr>
<td>Amitriptyline, nortriptyline</td>
<td>+/-</td>
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<tr>
<td>MAO inhibitors</td>
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<tr>
<td>Phenelzine, tranylcypromine</td>
<td>+++</td>
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<tr>
<td>Moclobemide</td>
<td>0/-</td>
</tr>
<tr>
<td><strong>SSRI</strong></td>
<td></td>
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<tr>
<td>Citalopram, fluoxetine, paroxetine, sertraline</td>
<td>+/-</td>
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<tr>
<td><strong>SNRI</strong></td>
<td></td>
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<tr>
<td>Duloxetine, venlafaxine, milnacipran</td>
<td>0/-</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>0/-</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>++</td>
</tr>
<tr>
<td>Lithium</td>
<td>+++</td>
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<tr>
<td><strong>Antipsychotic agents</strong></td>
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<tr>
<td>Clozapine</td>
<td>+++</td>
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<tr>
<td>Olanzapine</td>
<td>+++</td>
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<tr>
<td>Risperidone</td>
<td>++</td>
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<tr>
<td>Quetiapine</td>
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<tr>
<td>Aripiprazole</td>
<td>0/+</td>
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<td>Ziprasidone</td>
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<td>Haloperidol</td>
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<td>Phenerphenazine</td>
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<td><strong>Antiepileptics</strong></td>
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<tr>
<td>Valproic acid</td>
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<tr>
<td>Carbamazepine</td>
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<tr>
<td>Gabapentin</td>
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Steroid hormones

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Oral corticosteroids (prednisone)</td>
<td>+ to + + (+)</td>
</tr>
<tr>
<td>Hormone therapy-contraception (DMPA)</td>
<td>+ to ++</td>
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</table>

Miscellaneous agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Beta-adrenergic blockers (propanolol, metoprolol, atenolol)</td>
<td>+ to ++</td>
</tr>
</tbody>
</table>

1+++ Significant, ++ moderate, + slight weight gain; 0/+ slightly increasing effect; +/- inconsistent data; 0/– minimal to no weight reduction; – – moderate; – – – significantly weight loss.

Key learnings

- Insulin resistance and obesity each give rise to the other, potentially resulting in more severe obesity and T2DM.
- Weight reduction is considered a key therapeutic goal in the treatment of T2DM, demonstrating numerous beneficial health effects.
- Metabolic surgery is the best treatment option for patients with diabesity, although most patients can only be managed with combined lifestyle interventions and antidiabetic medications.
- Of the available antidiabetic medications, GLP-1 RAs are associated with the greatest weight loss, with variation among individual GLP-1 RAs and in different patient groups.
- The thiazolidinediones, insulin and sulphonylureas are associated with weight gain.
- Medications for treatment of other conditions may increase body weight.

References

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From obesity to diabetes

When diet-derived fat intake is increased, fat storage occurs within and around other tissues and organs including the liver, skeletal muscle and β-cells, which under normal conditions do not store lipids. This in turn results in excessive mitochondrial production of toxic reactive lipid species that cause organ-specific oxidative damage and cellular dysfunction, leading progressively to the development of insulin resistance, impaired glucose metabolism and finally to diabetes. The accumulation of toxic metabolites within the β-cells in particular affects insulin secretion and enhances β-cell apoptosis.6

Obesity-associated inflammation may be due to increased circulatory pro-inflammatory cytokines, decreased anti-inflammatory cytokines, reactive oxygen species, increased lipids, free fatty acids, endoplasmic reticulum stress, mitochondrial dysfunction and activation of diverse signalling cascades. In the initial stages, inflammatory responses are triggered by a pro-inflammatory imbalance in the brain and adipose, leading to dysregulated insulin and leptin sensitivity. Over time, ectopic lipids accumulate in the muscle, liver and blood vessels, leading to activated tissue leukocytes, organ-specific diseases and exacerbated systemic insulin resistance. Obesity also induces inflammation via lipopolysaccharide-related endotoxaemia involving gut microbiota. Inflammation is characterised by an upsurge of T-lymphocytes and macrophages secreting proinflammatory cytokines that act to perpetuate systemic inflammation and induce insulin resistance. Increasing evidence suggests that chronic low-grade inflammation in adipose tissue affects the pathogenesis of diabetes in obese patients.8