What is type 2 diabetes?

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Abstract

Type 2 diabetes mellitus (T2DM) is a common metabolic disorder characterized by chronic hyperglycaemia. It is associated with reduced life expectancy owing to a greater risk of heart disease, stroke, peripheral neuropathy, renal disease, blindness and amputation. The best-known predictors of increased diabetes risk are elevated fasting plasma glucose, elevated 1- and 2-hour plasma glucose after an oral glucose tolerance test, obesity and evidence of impaired insulin action. However, the mechanisms by which people with impaired fasting glucose and/or abnormal glucose tolerance 'progress' to overt T2DM are not completely understood. Moreover, T2DM is defined in a 'negative' sense (hyperglycaemia not accounted for by autoimmune destruction of islet cells or other known causes). This has two potentially negative consequences: first, T2DM may actually encompass a heterogeneous group of hyperglycaemic disorders with multiple different mechanisms; and second, defining such a complex disease affecting many different metabolic pathways simply in terms of hyperglycaemia may oversimplify the nature of the condition. In this review, we explore some of the mechanisms suggested to underlie T2DM, and attempt to remind readers that hyperglycaemia is only one of its characteristics.

Keywords Incretin hormones; insulin action; insulin secretion; MRCP; pre-diabetes; type 2 diabetes

Key points

- Type 2 diabetes mellitus encompasses a heterogeneous group of hyperglycaemic disorders with multiple different mechanisms
- Established type 2 diabetes is characterized by defective and delayed insulin secretion and abnormal postprandial suppression of glucagon
- Understanding the pathogenesis of type 2 diabetes is complicated by several factors including the varying degrees of insulin deficiency and insulin action, and genetic and environmental influences
- Bariatric surgery has shown promising results in terms of remission of type 2 diabetes as most people go into partial or complete remission afterwards. Remission of type 2 diabetes can occur in people who have not had weight loss surgery, but this is rare
- A large number of commonly used medications can cause hyperglycaemia and lead to development of diabetes. Clinicians should be particularly aware of this possible adverse effect because abnormalities can usually be reversed by discontinuing the culprit

Hyperglycaemia: too simplistic a definition of type 2 diabetes?

Diabetes mellitus is a heterogeneous and complex disease characterized by chronic hyperglycaemia. Hyperglycaemia is the result of defective insulin synthesis, secretion and/or action. There are many known causes of diabetes.

Type 2 diabetes mellitus (T2DM), characterized by a variable defect of insulin secretion and action, is by far the most common cause, accounting for >90% of cases. Type 1 diabetes mellitus (T1DM) is the second most common cause of diabetes, and is characterized by absolute insulin deficiency resulting from an autoimmune destruction of pancreatic β-cells. Myriad genetic defects cause diabetes, but these account for only a very small fraction of cases of diabetes. In practice, it is occasionally difficult (and unnecessary) to distinguish between T2DM and other types of diabetes. In essence, diagnosis of T2DM is a diagnosis of exclusion, being defined largely by what it is not, rather than by a determinate aetiopathogenesis. The absence of a positive definition for diabetes is indicative of the difficulty of succinctly describing T2DM.

The prevalence of T2DM has risen markedly with increasing degrees of obesity over the past few decades. In 2015, the Centers for Disease Control and Prevention estimated that 11–12% of the adult US population had T2DM. T2DM is not only a major cause of morbidity and mortality in the USA, but has increasingly high direct and indirect costs. Like other forms of diabetes, T2DM is defined in terms of glycaemia – fasting plasma glucose ≥7.0 mmol/litre (≥126 mg/dl) or random plasma glucose ≥11.1 mmol/litre (≥200 mg/dl), based on values above which the incidence of microvascular complications begins to increase.

The transition from normal glucose metabolism to T2DM occurs through an intermediate phase characterized by impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG). In these states, although glucose metabolism is abnormal, the criteria for diabetes are not met, i. e a fasting plasma glucose >5.6 mmol/litre (>100 mg/dl) but <7.0 mmol/litre (<126 mg/dl), or a 2-hour plasma glucose after an oral glucose tolerance test (OGTT) >7.8 mmol/litre (>140 mg/dl) but <11.1 mmol/litre (<200 mg/dl), using the thresholds recommended by the American Diabetes Association. IFG and IGT are associated with a high but

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heterogeneous rate of progression to T2DM. For instance, 'only' 40% of subjects with a fasting glucose ≥110 mg/dl develop diabetes in the subsequent 10-year period; i.e. most individuals (60%) do not develop T2DM within this period (Figure 1). Besides the increased risk of progression to T2DM, patients with IFG and/or IGT are at increased risk of developing macrovascular diseases.

IFG and IGT are of considerable interest in terms of understanding the mechanisms underlying the progression to diabetes. Although IFG was considered a relatively benign condition, a recent longitudinal study showed that the rate of conversion to T2DM is similar in people with isolated IFG and isolated IGT, and is half the rate of progression in people with combined IFG and IGT.[1] Moreover, longitudinal studies have demonstrated that the glucose concentration 60 minutes after an OGTT is a better predictor of progression to T2DM than fasting and 2-hour glucose concentrations after OGTT.

Pathophysiological mechanisms proposed to underlie T2DM

Established T2DM is characterized by defective and delayed insulin secretion as well as abnormal postprandial suppression of glucagon. These abnormalities explain, in part, the defective suppression of endogenous glucose production after a meal; this, combined with decreased peripheral glucose uptake, contributes to postprandial hyperglycaemia (Figure 2).

The islets of people with long-standing T2DM have a characteristic appearance, with prominent amyloid deposition and a decrease in functional β-cells. These anatomical defects underlie the decrease in insulin secretion. However, our current ability to quantify islet mass and function reliably *in vivo* significantly limits any attempt to characterize the pathophysiology and evolution of T2DM. Moreover, functional measures of β-cell mass, based on determining islet secretion in response to physiological and supraphysiological stimuli, are often cumbersome, non-standardized and difficult to perform in well-powered longitudinal cohort studies. It is also uncertain whether the abnormal regulation of glucagon secretion results from an inherent defect in the α-cells of people with T2DM, or is instead a manifestation of decreased intra-islet insulin, which normally suppresses α-cell glucagon secretion.

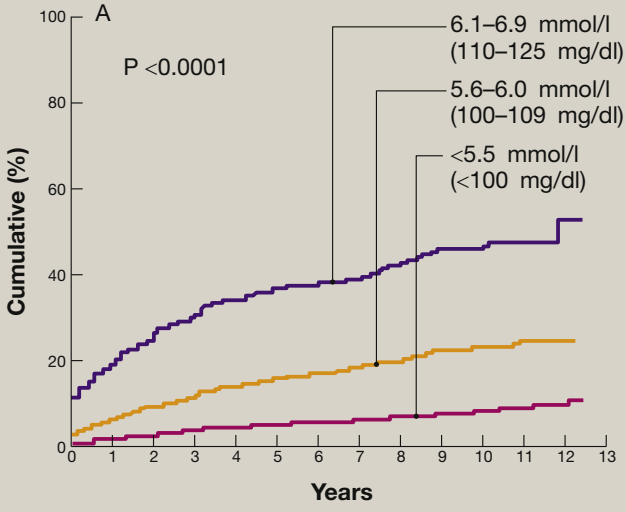

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Figure 1

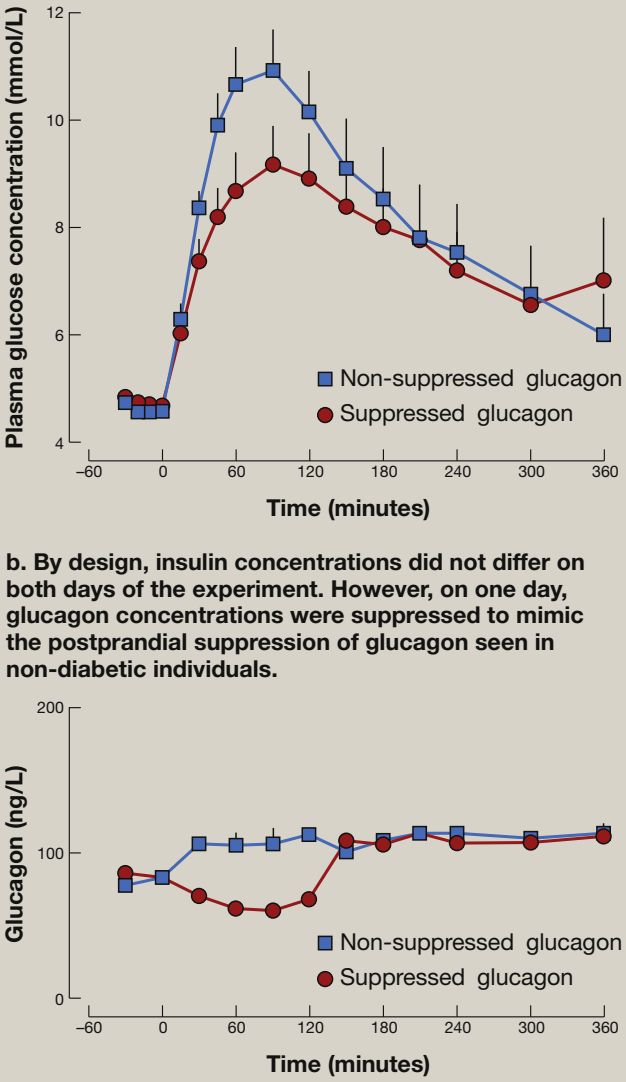

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Figure 2

Insulin secretion: defects in insulin secretion early in the pathogenesis of diabetes, probably preceding the anatomical changes described above, are important. Insulin is secreted in a pulsatile manner, resulting in high-frequency oscillations of insulin concentration in the portal and (to a lesser extent) peripheral circulation. This pulsatility is disordered in people with T2DM as well as in those with IGT, implying that such abnormalities arise early in the course of disease. Another important early abnormality observed in T2DM is a reduced ability of insulin to stimulate glucose uptake and suppress glucose release. This defect in insulin action (referred to colloquially as insulin resistance) is believed to contribute to the pathogenesis of T2DM. Indeed, when insulin secretion is expressed as a function of prevailing insulin action, it is clear that, across the spectrum of IFG and IGT, defects in secretion and action occur in parallel during the progression to T2DM. This effect is modified by differences in body composition attributable in part to sex.

Genetic component: the strong heritability of T2DM argues for a major genetic component to susceptibility. The technique of genome-wide association study has thus been extensively applied, seeking patterns of genetic variation that are seen in people with T2DM but not non-diabetic control populations. These studies have suggested that most such genetic susceptibility factors affect β-cell function rather than insulin signalling; further genetic factors have been found that modulate fasting and post-challenge plasma glucose concentrations independent of diabetes risk. Nevertheless, the basis of most of the observed heritability has yet to be established.

Obesity: although genetic susceptibility is important in the pathogenesis of T2DM, the recent surge in its prevalence is probably largely caused by the obesity epidemic. More than 80% of patients with T2DM are overweight. From a metabolic viewpoint, the increase in fat cell mass that accumulates viscerally is particularly harmful. Many of the mechanisms invoked to explain the link have been based on changes in circulating concentrations of molecules, with actions on the insulin sensitivity of other tissues, that arise from overloaded, unhealthy adipose tissue. These mediators include substrates such as free fatty acids, other lipid species or branched-chain amino acids, adipose-derived hormones called adipokines, and inflammatory cytokines arising from stressed fat cells themselves, or from the heavy infiltrations of macrophages and other immune cells seen in the fat tissue of individuals with obesity and T2DM. However, despite significant bodies of evidence supporting many of these hypotheses, no unifying scheme has yet emerged.

Incretins: it has also been postulated that both impaired insulin and excessive glucagon secretion in T2DM are in part the result of an 'incretin defect', defined as inadequate release of or response to gastrointestinal incretin hormones upon meal ingestion. Incretins, such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide, are produced by endocrine cells in the small intestine and induce insulin secretion after food intake. In patients with T2DM, incretins are present in lower concentrations, an effect that seems to be mediated by obesity as well as the duration and severity of diabetes. There have also been reports of abnormal incretin concentrations in people with IFG and IGT, suggesting an early role in T2DM pathogenesis. As part of decreased responsivity to other secretagogues, the islets themselves may be less sensitive to the effect of incretins.

Increased glucose uptake: another potential contributor to postprandial hyperglycaemia is an enhanced systemic appearance of ingested glucose as a result of increased intestinal absorption of glucose, either alone or in combination with decreased hepatic extraction of glucose. Animal models of T2DM exhibit an enhanced activity and abundance of intestinal sodium glucose co-transporter 1 (SGLT-1 or SLC5A1 for solute carrier family 5 member 1) and solute carrier family 2 member 2 (SLC2A2 (GLUT-2)), thereby increasing intestinal glucose absorption and post-challenge glucose concentrations. SGLT-1 is also significantly increased in the duodenal brush border of people with T2DM, but the significance of this finding is uncertain.

Circadian rhythm: more recently, circadian disruption, defined as an asynchrony between endogenous circadian rhythm and the earth's 24-hour dark/light cycle, has been associated with an increased risk of T2DM. Adequate sleep and eating patterns, both established inputs that affect circadian function, have been shown to affect glucose regulation. In large epidemiological studies, shift work is an independent risk factor for T2DM, probably because the circadian system regulates insulin synthesis and signalling.

Can T2DM be cured?

Once the diagnosis of T2DM has been established, is there, in the absence of short-term contributing factors, any hope of remission?

Lifestyle: the effectiveness of aggressive lifestyle modification in preventing progression from IFG and/or IGT to diabetes in a high-risk group was clearly established by the Diabetes Prevention Program. Weight loss achieved through intensive lifestyle interventions has been shown to improve T2DM in many aspects, including glycaemic control.

Despite the clear benefits of weight loss, the reality is that the vast majority of patients cannot attain and/or maintain it. Therefore, only a small fraction of patients with T2DM achieve partial or complete correction of glucose parameters in the short term, and an even a smaller fraction of individuals maintain this over time. For instance, an ancillary analysis of the Look AHEAD longitudinal trial showed that a 9% weight loss at year 1 was associated with a 9.3% rate of partial remission of T2DM.[2] The rate of remission dropped in time to (3.5% at 4 years for a 5% weight loss). Rates of complete remission were <1.5%, and relapse rates were high. Therefore, although it is certainly theoretically possible to reverse T2DM, in practical terms this is very difficult. Moreover, it remains to be ascertained whether intervention significantly alters the underlying pathophysiology of the disease or merely retards it.

Surgery: given the difficulties of achieving and maintaining weight loss with lifestyle modifications alone, bariatric surgery has been proposed as a 'cure' for diabetes.[3] After bariatric surgery, diabetes remission occurs in 40–95% of patients, depending on the type of surgery performed and the amount of weight loss achieved. Interestingly, a dramatic improvement in plasma glucose profile and even a remission of diabetes can occur within the first week after the procedure, before any weight loss ensues. When the intense caloric restriction necessary in the immediate postoperative period after such alterations in gastrointestinal anatomy were replicated in matched controls with T2DM who did not undergo surgery, similar glucose profiles and indices of β-cell function were obtained. Thus, caloric restriction per se is an important contributor to the amelioration of hyperglycaemia seen soon after bariatric surgery.

The mechanisms involved are multiple and poorly understood. For instance, total GLP-1 concentrations are higher in patients who have undergone bariatric surgery because of the accelerated delivery of calories to the distal small intestine. The physiological effects of GLP-1 (stimulation of insulin secretion, suppression of postprandial glucagon secretion, decrease of gastric emptying) provided a neat explanation for many of the effects on glycaemic control after bariatric surgery. However, blocking the GLP-1 receptor with exendin 9-39 in Roux-en-Y gastric bypass patients showed only small, albeit significant, effects on insulin secretion and action. This indicates that factors other than GLP-1 may play an important role in remission of T2DM. Other mechanisms involved include decreased hepatic insulin resistance, decreased lipotoxicity, increased peripheral insulin action, increased β-cell responsivity and increased gut glucose utilization, among others. Bariatric surgery is thus an attractive option for improving glucose metabolism, although the exact mechanism by which this happens and the sustainability of such an effect are still unknown. Although bariatric surgery remains the most effective method of weight loss and resolution of its co-morbidities, complications are not negligible. For instance, cholelithiasis, nutritional deficiencies, electrolyte imbalances, metabolic derangements and mechanical obstruction are complications that can affect a significant proportion of patients.

Oral agents: the use of oral agents such as acarbose, metformin or thiazolidinediones in people without T2DM has also led to the suggestion that early pharmacotherapy might prevent diabetes or induce remission. However, discontinuation of pharmacotherapy is not always associated with a sustained improvement in glycaemia. There is also some evidence that intensive insulinization by means of continuous subcutaneous insulin infusion soon after the diagnosis of T2DM can lead to substantial improvements in the plasma glucose profile, with some patients demonstrating near-normal glycaemic patterns of fasting plasma glucose, HbA_{1c}values and intravenous glucose tolerance tests at 1 year.[4]

β-Cell restoration: as diabetes is characterized by decreased β-cell functional mass because of increased cell apoptosis, some strategies have focused on β-cell restoration. Although these strategies had originally been reserved for patients with T1DM, they are currently being applied in a subgroup of patients with T2DM, namely those with insulin-dependent T2DM with end-stage complications. The leading restoration strategy is based on pancreas transplantation, which is generally considered only in patients with serious progressive metabolic complications of diabetes whose quality of life is unacceptable. Although pancreas transplantation has been shown to have generally favourable outcomes, it is an invasive procedure that requires life-long immunosuppressive therapy. Pancreas graft survival rates, defined as independence from exogenous insulin therapy, are around 80% after 1 year and 30–50% after 10 years. Isolated transplantation of cadaveric islets is an evolving strategy currently performed only within the context of clinical research studies in patients with T1DM.

Drugs and diseases associated with diabetes

Numerous medications, most of which are listed in Table 1, can affect glucose metabolism and cause diabetes. These drugs can decrease insulin secretion, increase hepatic glucose production and/or impair insulin action (i.e. increase insulin resistance).[5] Drug-induced diabetes is potentially reversible when the pharmaceutical insult in discontinued.

Drugs that exacerbate diabetes

Antiviral therapy	Interferon
	Protease inhibitors
Immune system suppressants	Cyclosporin
	Tacrolimus
	Sirolimus
Hormones	Glucocorticoids
	Growth hormone and growth hormone analogues
	Progestin (megestrol, combination oral contraceptives)
	Gonadotropin-releasing hormone analogues
Atypical antipsychotics	Clozapine
	Risperidone
	Olanzapine
	Quetiapine
	Chlorpromazine
Tyrosine kinase inhibitors	Imatinib
	Nilotinib
Others	Niacin
	Pentamidine
	β-Adrenoceptor blockers
	Thiazide diuretics
	Fluoroquinolones
	Diazoxide
	Epinephrine
	Norepinephrine

Table 1

Glucocorticoids: these are one of the most commonly used medications and can overall double the risk of developing diabetes. This risk is dependent on glucocorticoid dose and duration of therapy. Glucocorticoids induce postprandial hyperglycaemia through impaired insulin action. Reports suggest that decreased insulin secretion, increased hepatic gluconeogenesis and increased lipolysis are involved as well.

Antipsychotics: although weight gain related to the use of antipsychotics probably accounts for most cases of new-onset diabetes occurring in people affected by schizophrenia, there is a substantial proportion of patients in whom rapid, dramatic development of hyperglycaemia occurs independent of adiposity. Data from pharmaco-epidemiological studies suggest a 3-fold increased risk of diabetes in patients with schizophrenia treated with antipsychotics compared with those with drug-naïve schizophrenia, reflecting a direct impairment of β-cell function by these agents. An additional suggested mechanism includes antagonistic actions on the M_2 muscarinic receptors, centrally and peripherally (particularly at the level of the pancreas). The risk of antipsychotic-induced diabetes is higher with olanzapine and clozapine than with typical antipsychotics or other atypical agents such as aripiprazole or risperidone.

Post-transplantation: diabetes occurs in a substantial number of patients after solid organ transplantation. Immediate postoperative use of glucocorticoids plays a major role, and their use has been optimized in recent years to aim for lower doses and shorter courses. Calcineurin inhibitors, such as tacrolimus and cyclosporin, are part of all post-transplant immunosuppressive therapies. Both medications affect transcriptional regulation of insulin expression because of direct islet cell toxicity. Additional mechanisms may include decreased β-cell volume, insulin content and insulin release. Mechanistic target of rapamycin (mTOR) inhibitors, such as sirolimus, have also been used as post-transplant immunosuppressants and can cause diabetes because of decreased secretion and action of insulin. Tacrolimus and sirolimus are more diabetogenic than cyclosporin.

HIV: although the incidence of HIV has declined, the overall prevalence has stabilized and even increased in some countries, probably because of increased survival resulting from antiviral therapy. With increased survival, there has been a rise in the incidence of diabetes in this population. Protease inhibitors and nucleoside reverse transcriptase inhibitors, widely used to treat HIV, are the culprit. Proposed mechanisms include lipodystrophy, impaired lipolysis suppression, impaired insulin-stimulated glucose uptake in skeletal muscle and adipocytes, and impaired β-cell function.

Malignancy: tyrosine kinase inhibitors have demonstrated promising anti-tumour activity and have increasingly been used for a myriad of malignancies. Although these medications can cause hypoglycaemia, and some have been postulated as potential therapeutic options for T1DM and T2DM, 30–50% of patients treated with these agents develop hyperglycaemia as a result of decreased insulin action and possibly decreased insulin secretion. Second-generation nilotinib induces a worse glycometabolic profile than imatinib. Patients treated with these medications should be closely monitored for development of hyperglycaemia and diabetes.

Rare causes: finally, uncommon endocrine conditions such as acromegaly, Cushing's syndrome, phaeochromocytoma and glucagonoma can cause T2DM or unmask an underlying predisposition to it. IGT or T2DM in acromegaly and Cushing's syndrome, for example, are reported to be present in at least 20% of patients. Most hormones have a physiological effect on glucose and lipid metabolism. High levels of growth hormone and cortisol can result in increased plasma glucose and increased free fatty acid concentrations, which in turn impair insulin action. With phaeochromocytoma, there is impaired insulin secretion, possibly via overstimulation of the adrenergic receptors on the pancreatic islets. Hypersecretion of glucagon from α-cell tumours induces endogenous hepatic glucose production that usually results in diabetes. ◆

KEY REFERENCES

1 Han SJ, Kim HJ, Kim DJ, Lee KW, Cho NH. Incidence and predictors of type 2 diabetes among Koreans: a 12-year follow up of the Korean Genome and Epidemiology Study. *Diabetes Res Clin Pract* 2017; **123:** 173–80.

2 Arterburn DE, O'Connor PJ. A look ahead at the future of diabetes prevention and treatment. *J Am Med Assoc* 2012; **308:** 2517–8.

3 Cho YM. A gut feeling to cure diabetes: potential mechanisms of diabetes remission after bariatric surgery. *Diabetes Metab J* 2014; **38:** 406–15.

4 Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet* 2008; **371:** 1753–60.

5 Jain V, Patel RK, Kapadia Z, Galiveeti S, Banerji M, Hope L. Drugs and hyperglycemia: a practical guide. *Maturitas* 2017; **104:** 80–3.

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 62-year-old man presented for a yearly evaluation. He had no complaints. He had a strong family history of type 2 diabetes. On clinical examination, his body mass index was 38.9 kg/m^2

Investigations

- Fasting plasma glucose 8.3 mmol/litre (3.0–6.0)

What is the next most appropriate step?

A. Recommending weight loss and physical activity.
B. Repeating a fasting plasma glucose and/or checking a HbA_{1c}
C. Initiating metformin
D. Initiating insulin
E. Referral to bariatric surgery

Question 2

A 55-year-old woman presented with poor blood sugar control. Three months previously, she had been found to have diabetes. Dietary changes had had no effect, and she had been commenced on metformin and later gliclazide. However, there had been little improvement of either her troublesome symptoms or her blood glucose test results. She had also recently been found to have raised blood pressure from earlier readings and osteoporosis with thoracis compression fractures.

On clinical examination, her blood pressure was 145/98 mmHg, and body mass index 29.5 kg/m^2. Cardiovascular and respiratory examination was normal. The abdomen was obese with purple striae. She has supraclavicular and dorsocervical fat pads and proximal muscle weakness.

What is the most likely cause for the failure to respond to treatment?

A. Cortisol excess
B. Type 1 diabetes
C. Poor concordance with medication
D. Excess weight
E. High level of islet cell antibodies

Question 3

A 36-year-old man was found to have an elevated blood glucose. Three months previously, he had been found to have schizophrenia. He also had hypertension, gastro-oesophageal acid reflux and back pain. He had recently been treated with olanzapine and was also taking amlodipine, lisinopril, omeprazole and paracetamol.

Clinical examination was normal.

Investigation

- Fasting blood glucose readings 11.7 and 11.2 mmol/litre (3.0–6.0)

What is the most likely explanation for his hyperglycaemia?

A. Paracetamol
B. Amlodipine
C. Lisinopril
D. Olanzapine
E. Omeprazole

Correct answer: D. The only medication known to cause type 2 diabetes among the options is olanzapine, an antipsychotic medication. Antipsychotic medications are commonly used, and clinicians should be aware of this possible adverse effect.