

CLINICAL REVIEW

The challenge of managing coexistent type 2 diabetes and obesity

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Coexistent type 2 diabetes and obesity—often termed “diabesity”—is an emerging epidemic that poses a challenge to the treatment of both conditions.¹ More than 90% of the world’s 285 million people with diabetes have type 2 diabetes, and this number is projected to grow to 438 million by 2030.² In North America about 90% of people with type 2 diabetes are obese (body mass index >30 (weight (kg)/height (m)²), overweight (body mass index 25-29.9), or have a medical history of being so, and those who are not overweight may carry an excess of hidden visceral fat.³ A large cohort study estimated that a body mass index of 30-34.9 (compared with 22) for 16 years increased the risk of type 2 diabetes more than 20-fold in women, and a large cross sectional study of North American men aged 25-54 estimated that a body mass index of 30-34.9 increased the risk more than 10-fold.^{w1 w2}

In principle, lifestyle measures such as diet and exercise could prevent the onset and greatly help the treatment of type 2 diabetes and obesity. In practice this is seldom borne out. Few of the current treatments for type 2 diabetes facilitate weight loss, and some cause weight gain (table 1). Because excess adiposity presents a considerable hurdle to the control of hyperglycaemia, therapeutic approaches that simultaneously deal with glycaemic control and weight management are particularly attractive for the treatment of type 2 diabetes.

This article examines existing and new treatments that have the potential to treat coexistent diabetes and obesity and explores the evidence from recent randomised trials and early experimental research.

How do diabetes and obesity interact?

Metabolic homeostasis is crucially dependent on insulin (fig 1). The hyperglycaemia and associated metabolic disturbances of type 2 diabetes are usually caused by impaired insulin action (insulin resistance) and defective insulin secretion, plus other endocrine abnormalities such as hyperglucagonaemia. These derangements and their attendant morbidity are greatly increased by coexistent obesity, and the risk of death is more than doubled.^{3 4} Each condition arises through a mix of genetic susceptibilities and environmental factors. Genetic

polymorphisms and variations in the expression of genes that affect feeding behaviour and metabolism can result in increased storage of nutrients. This in turn accentuates further genetic vulnerabilities that disturb insulin secretion and interfere with the action of insulin on tissues.⁵ Environmental factors such as inappropriate quality and excess quantity of nutrients, insufficient physical activity, low grade inflammation, and oxidative stress combine with genetic factors to increase adiposity and insulin resistance. For example, excess fatty acids and cytokines from adipose tissue (adipokines) such as tumour necrosis factor α , interleukin 6, retinol binding protein 4, and resistin impair the action of insulin.⁴ Insulin resistance initially leads to a compensatory hyperinsulinaemia, but as insulin output fails to meet the demands for insulin created by insulin resistance, a state of impaired glucose tolerance emerges. Progression to type 2 diabetes will depend on the extent of islet β cell dysfunction and failure, and unintentional weight loss signals severe insulin deficiency.

How do available treatments for diabetes influence diabesity?

Interventions to promote weight loss

In obese patients with established diabetes long term randomised controlled trials have shown that an intentional and sustained reduction in body weight by 5-10% can lower glycated haemoglobin (HbA_{1c}) by 0.5-1% (5-11 mmol/mol) and increase life expectancy by 2-4 years.^{3w3} However, when people with diabetes start to lose weight their insulin sensitivity improves, favouring the anabolic efficacy of insulin and making it harder to lose more weight. Reduced hyperglycaemia prevents the loss of calories through glucosuria.

The intestinal lipase inhibitor orlistat is the only antiobesity drug now available for prescription in the United Kingdom. Randomised trials have shown that orlistat reduces weight by 2-3 kg more than placebo in obese patients with diabetes, with a concomitant reduction in HbA_{1c} of 0.3-0.5% (3-5 mmol/mol).⁶ Orlistat may also help patients adhere to dietary restrictions but

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Summary points

- The presence of obesity with type 2 diabetes increases morbidity and mortality from each condition
- Excess adiposity accentuates insulin resistance and complicates the treatment of type 2 diabetes
- Glucagon-like peptide 1 receptor agonists promote weight loss, whereas metformin, dipeptidyl peptidase 4 inhibitors, and α glucosidase inhibitors are typically weight neutral
- The anabolic effects of increased insulin secretion and action restrict the benefits of treatment in obese patients
- New treatments should ideally reduce hyperglycaemia and excess adiposity
- Potential new treatments include analogues of intestinal and adipocyte hormones, inhibitors of renal glucose reabsorption and cellular glucocorticoid activation, and activators of cellular energy production

Sources and selection criteria

This article is largely based on a search, focused on the treatment of hyperglycaemia, of original articles published between 2005 and 2010 using Medline, PubMed, Cochrane Library, and Google Scholar. The main search terms were hyperglycaemia, diabetes, diabetes, and obesity together with therapy, treatment, or control. Papers identified were English language with full text available. Reference lists of recent reviews were searched, along with abstracts of the American Diabetes Association and European Association for the Study of Diabetes 2007-10.

is not a recognised part of current treatment algorithms for type 2 diabetes.

Observational studies have found that bariatric surgery is effective in patients with obesity and diabetes, reinstating near normal glycaemia in 50-80% of patients for several years.⁷ In England bariatric surgery increased more than 10-fold from 238 procedures in 2000 to 2543 in 2007 but is not suitable, acceptable, or affordable for all.^{w4}

Glucose lowering agents

Table 1 lists the currently prescribed glucose lowering agents and fig 2 shows their main sites of action. Because insulin promotes adipogenesis and weight gain, insulin itself and agents that increase its secretion or actions can restrict their own efficacy in obese people unless they also counter weight gain.^{4,8} Randomised controlled trials have shown that metformin is “weight neutral”—it improves the action of insulin but exerts metabolic effects that increase energy dissipation and offset weight gain. Glucagon-like peptide 1 (GLP-1) receptor agonists potentiate insulin secretion and exert a satiety effect that reduced weight by 2-4 kg in most patients during randomised controlled trials. Inhibitors of the enzyme dipeptidyl peptidase 4 (DPP-4) also potentiate insulin secretion, largely through reduced degradation of incretins such as GLP-1, and are also weight neutral, possibly because of a mild satiety effect. Inhibitors of α glucosidase, which slow down carbohydrate digestion, can reduce the amount of prandial insulin secretion and help control weight in some patients. Other oral antidiabetic drugs that increase insulin secretion (sulphonylureas and meglitinides) or improve insulin action (thiazolidinediones) tend to cause weight gain.⁸

Other glucose lowering drugs

Several other drugs that are not approved as glucose lowering agents in Europe are weight neutral or facilitate a small reduction in body weight. These include the amylin analogue pramlintide, a low dose quick release formulation of the dopamine agonist bromocriptine, and the bile sequestrant colestevlam.

Intensive glycaemic control in patients with type 2 diabetes

Although recent high profile prospective trials of intensive glycaemic control found that late intensification of treatment

did not prevent mortality from cardiovascular disease, it did reduce microvascular disease.^{w5} These findings should not detract from observational evidence that early intensive glycaemic control reduces microvascular and macrovascular complications and that it may take a decade or more for macrovascular benefits to be seen.^{w6} This suggests the existence of “glycaemic memory,” and that effective glycaemic control is needed from diagnosis to reduce complications decades later.

Which agents may allow effective treatment of diabetes and obesity in future?

New drugs have the potential to reduce both hyperglycaemia and excess adiposity. GLP-1 receptor agonists (twice daily injected exenatide and once daily injected liraglutide) fit this profile.^{9,w7} Looking to the future, a once weekly subcutaneously injected formulation of exenatide—exenatide QW—is advanced in development.

Exenatide QW

This depot formulation encapsulates exenatide in biodegradable microspheres comprising polymers of lactic acid and glycolic acid, and it has been tested in a series of open label randomised six month studies. In a study of 258 overweight and obese patients with type 2 diabetes already receiving metformin or a sulphonylurea (or both) with a baseline HbA_{1c} of 8.5% (70 mmol/mol), HbA_{1c} was lowered by 1.9% (21 mmol/mol) in patients prescribed 2 mg exenatide QW compared with 1.5% (16 mmol/mol) in patients prescribed standard exenatide 10 μ g twice daily.¹⁰ This reduction was maintained to one year, weight loss averaged more than 4 kg, and the side effect of nausea was less common with QW than with standard exenatide. In 491 overweight and obese patients with diabetes and a baseline HbA_{1c} of 8.5% (70 mmol/mol) already taking metformin, 2 mg exenatide QW reduced HbA_{1c} by 1.7% (18 mmol/mol) and reduced body weight by 2.8 kg at six months, compared with 1.0% (11 mmol/mol) and 0.9 kg in those taking 100 mg sitagliptin once daily and 1.4% (15 mmol/mol) and 3.4 kg in those taking 45 mg pioglitazone once daily.^{w8} Another study compared 2 mg exenatide QW for 26 weeks with insulin glargine (mean daily dose 31 U/day at end point) in 456 overweight and obese patients with diabetes taking metformin with or without

sulphonylurea who had a baseline HbA_{1c} of 8.3% (68 mmol/mol).^{w9} Exenatide QW reduced HbA_{1c} by 1.5% (16 mmol/mol) and reduced weight by 2.6 kg compared with 1.2% (13 mmol/mol) and an increase of 1.4 kg for glargine. A head to head study of 912 patients recently found that 2 mg exenatide QW for 26 weeks reduced HbA_{1c} by 1.3% (14 mmol/mol) compared with a reduction of 1.5% (16 mmol/mol) with 1.8 mg daily liraglutide.¹¹

Possible drawbacks to using longer acting GLP-1 receptor agonists include potential injection site reactions, acute reactions, “resistance,” and the development of antibodies. The prevalence of pancreatitis in patients using exenatide seems to be no higher than for the diabetic population in general, although this remains open to debate. Because exenatide is degraded and eliminated by the kidneys, patients must have adequate renal function.^{w10}

Other GLP-1 based treatments

Other once weekly GLP-1 receptor agonists under study include CJC-1134, a variant of exenatide linked to albumin, and taspoglutide.^{12w11} Albiglutide, is a dimeric GLP-1 analogue (Ala8Gly) that is fused to human albumin and acts for as long as two weeks.¹³ Lixisenatide, a variant of exenatide, is shorter acting but suited to once daily injection in combination with insulin glargine.¹⁴ Limited phase I and phase II data on these drugs suggest that they have similar efficacy to other members of the class. A long chain polymer of GLP-1 that is slowly degraded in the circulation by endopeptidases is at an early stage of testing.¹⁵ Delivery of GLP-1 analogues by buccal, oral, and nasal routes and dermal patches, rather than injections, is being investigated.

Oxyntomodulin is an extended glucagon-like peptide produced by ileal L-cells along with GLP-1.¹⁶ Oxyntomodulin has glucagon receptor and GLP-1 receptor agonist properties, and its analogues are being investigated for the treatment of obesity. They combine the satiety inducing and pancreatic effects of GLP-1 with the lipolytic effects of glucagon—the glucose lowering effect of the GLP-1 moiety overcomes the hyperglycaemic effect of the glucagon.^{w12} Although they may not be ideally suited for diabetes and obesity, other hybrids such as a GLP-1 receptor agonist with a glucagon antagonist have been produced; the glucagon antagonist enables the molecule to occupy the glucagon receptor without triggering post-receptor signalling.¹⁷

Small (non-peptide) GLP-1 receptor agonists and glucagon receptor antagonists suitable for oral administration have recently shown proof of principle in animal studies.^{18 19w13 w14} Neutralisation of glucagon can promptly reduce hyperglycaemia, but this approach may reduce the defence against an episode of hypoglycaemia, because glucagon is a key blood glucose raising hormone. Also, glucagon antagonists may cause a compensatory rise in glucagon and a rebound increase in the effect of glucagon if the antagonism is lifted.

Preclinical and phase I studies have identified small molecule agonists of some G protein coupled receptors such as GPR-119, which act directly on the intestine and pancreas to stimulate secretion of incretins and insulin.²⁰ They have also reduced food intake and curbed weight gain in rodents.

DPP-4 inhibitors

The advantages of current DPP-4 inhibitors (sitagliptin, vildagliptin, and saxagliptin) in lowering blood glucose without weight gain have been reviewed elsewhere.²¹ Other DPP-4 inhibitors, notably linagliptin and alogliptin, are advanced in

development; they have similar efficacy but different pharmacokinetic properties that may make them suitable for use in patients with diabetes and obesity, particularly those with comorbidities or taking other drugs.^{w15 w16}

Agents that exploit lessons learnt from bariatric surgery

As well as reducing weight, bariatric surgery rapidly improves and maintains glycaemic control. Although this approach is not practical for all patients, “metabolic surgery” is now an accepted treatment for obese patients with diabetes.^{7w17} The finding that glycaemic control is promptly reinstated in most patients with diabetes when less food passes through the stomach, duodenum, and proximal jejunum— independently of the amount of weight lost—has focused attention on research into gastrointestinal factors as a potential source of new drugs for treating diabetes.²²

Several gastrointestinal peptides could provide a basis for new treatments in patients with obesity and diabetes (table 2).²³ Reduced secretion of ghrelin, an orexigenic hormone from the stomach, has been seen after bariatric surgery, but this has not been a consistent finding, and its effects on islet function are variable, casting doubt on the therapeutic value of a ghrelin antagonist.^{w18} Peptide YY (PYY), another hormone produced by the ileal L-cells, is reduced in obese people and those with type 2 diabetes and increased after gastric bypass surgery. As a Y2 receptor agonist, this hormone has an anorectic effect that might be useful in obesity, but its effect on glucoregulation remains to be clarified.²⁴

Although glucose dependent insulinotropic polypeptide (GIP) contributes to the incretin effect, GIP receptor knockout mice and obese-diabetic animals treated with GIP receptor antagonists have shown improved glucose control with reduced weight gain, suggesting that GIP antagonism might be a useful approach.²⁵

SGLT2 inhibition: reduced renal glucose reabsorption

Hyperglycaemia could be reduced and calories lost by increasing the elimination of glucose in the urine. Although this does not tackle the underlying endocrinopathy it could help to control symptoms of glucotoxicity and reduce the morbidity associated with hyperglycaemia. Normally most of the glucose in the glomerular filtrate is reabsorbed by the sodium-glucose cotransporter 2 (SGLT2) in the initial part of the proximal tubule. Remaining glucose is reabsorbed by SGLT1 further along the proximal tubule. Inhibition of these transporters can reduce glucose reabsorption.²⁶ However, SGLT1 is also responsible for glucose absorption by the intestine, and its inhibition may lead to glucose malabsorption. Specific or predominant inhibition of SGLT2 is therefore needed.

Dapagliflozin is the first selective SGLT2 inhibitor to be extensively investigated. In randomised double blind controlled trials over six months to one year it reduced HbA_{1c} by 0.5-1% (5-11 mmol/mol) and lowered body weight by 2-3 kg compared with placebo, either as monotherapy or add-on to other oral antidiabetic agents or insulin in overweight and obese patients with diabetes.^{26w19} This effect is associated with glucosuria of 50-80 g/day (compared with a normal filtered glucose load of more than 200 g/day). The risk of hypoglycaemia is low because a fall in blood glucose below normal allows SGLT1 to reabsorb almost all of the filtered glucose. Moreover, the mechanism is independent of insulin and not reduced by the progressive deterioration of insulin secretion or action as diabetes gets worse. Adverse effects include infections in the urinary tract and urogenital region. A modest persistent osmotic diuresis was

evident, which may have contributed to the consistent small reduction in blood pressure. Other SGLT2 inhibitors in early stages of clinical development show similar glucose lowering and weight lowering properties.²⁶

Glucocorticoid antagonists

Because raised concentrations of glucocorticoids promote truncal obesity, insulin resistance, and hyperglycaemia, strategies have been developed to reduce the action of glucocorticoids by targeting hepatic glucose production and adipogenesis. One mechanism for delivering glucocorticoid receptor antagonists to the liver has been conjugation with a bile salt, so that the antagonist is recycled in the enterohepatic circulation.^{w20} This has reduced hepatic glucose production and improved glycaemic control in obese-diabetic animal models.

Another approach has exploited the cellular conversion of less active cortisone to more active cortisol by the enzyme 11 β hydroxysteroid dehydrogenase 1.^{w21} In a 12 week randomised double blind placebo controlled trial of 302 overweight and obese patients with type 2 diabetes inadequately controlled with metformin, addition of INCB-13739 (up to 200 mg/day), a selective inhibitor of 11 β hydroxysteroid dehydrogenase 1, improved insulin sensitivity, lowered body weight by 1-2 kg, improved the plasma lipid profile, and reduced HbA_{1c} by 0.6% (6 mmol/mol).²⁷

Enhancers of insulin activity

Several new mechanisms to improve the action of insulin have shown beneficial effects on glycaemic control in obese and diabetic rodents without reducing excess adiposity, but they have yet to be assessed in human patients.²⁸

Considerable interest has focused on agents that activate AMP activated protein kinase, an energy regulating enzyme that is activated by metformin, thiazolidinediones, and adiponectin.²⁹ Stimulation of this enzyme reduces the expression of rate limiting enzymes for gluconeogenesis in the liver, thereby reducing hepatic glucose production. AMP activated protein kinase also increases fatty acid oxidation in liver and muscle and promotes mitochondrial biogenesis. Various novel activators of this protein kinase have shown proof of principle by improving glycaemic control in insulin resistant obese and diabetic animals with a variable effect on weight control.^{30w22}

Hypothalamic targets

Centres within the hypothalamus continually sense neural flux rates for glucose and fatty acid metabolism and initiate vagally mediated adjustments to hepatic glycogenolysis and gluconeogenesis.³¹ The extent to which hypothalamic control of glucose homeostasis inter-relates with the hypothalamic control of appetite and satiety is not clear.

Antidiabetic adipokines

Glucoregulatory and weight modulating hormones from adipose tissue may prove useful in the treatment of diabetes and obesity.³² The adipocyte hormone leptin, in addition to its centrally mediated satiety and thermogenic effects, can suppress the secretion of glucagon, alter the production of insulin-like growth factor binding protein-2, and exert direct effects on cellular nutrient metabolism.^{w23} Each of these effects could help lower blood glucose, so leptin has recently been considered as an adjunctive treatment for type 1 and type 2 diabetes, either alone or combined with other antiobesity agents.³³ The development of antibodies and resistance to persistently high

concentrations of leptin interfere with such treatment, however, so leptin analogues and non-peptide receptor agonists are being investigated.

Another adipocyte hormone, adiponectin, activates AMP activated protein kinase, improves insulin sensitivity, lowers blood glucose concentrations, improves weight control and vascular reactivity, and reduces inflammation in obese and diabetic animals.³²

A further adipokine, zinc- α_2 -glycoprotein has recently been shown to induce weight loss and improve glycaemic control in obese diabetic rodents.³⁴

Conclusion

The burgeoning epidemic of coexistent diabetes and obesity and the lack of available drugs, despite substantial research, is worrying.

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- 1 Astrup A, Finer N. Redefining type 2 diabetes: "diabesity" or "obesity dependent diabetes mellitus"? *Obes Rev* 2000;1:57-9.
- 2 International Diabetes Federation. Diabetes atlas. 4th ed. 2009.
- 3 Gregg EW, Cheng YJ, Narayan KM, Thompson TJ, Williamson DF. The relative contributions of different levels of overweight and obesity to the increased prevalence of diabetes in the United States: 1976-2004. *Prev Med* 2007;45:348-52.
- 4 Kahn SE, Hull KL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006;444:840-6.
- 5 McCarthy MI. Casting a wider net for diabetes susceptibility genes. *Nat Genet* 2008;40:1039-40.
- 6 Hennessy S, Perry CM. Orlistat: a review of its use in the management of obesity. *Drugs* 2006;66:1625-56.
- 7 Dixon JB. Obesity and diabetes: the impact of bariatric surgery on type-2 diabetes. *World J Surg* 2009;33:2014-21.
- 8 Nathan DM, Buse JB, Davidson MB, Ferannini E, Holman RR, Sherwin R, et al. Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetologia* 2009;52:17-30.
- 9 Flatt PR, Bailey CJ, Green BD. Recent advances in antidiabetic drug therapies targeting the enteroinsular axis. *Curr Drug Metab* 2009;10:125-37.
- 10 Buse JB, Drucker DJ, Taylor KI, Kim T, Walsh B, Hu H, et al. Duration-1: exenatide once weekly produces sustained glycemic control and weight loss over 52 weeks. *Diabetes Care* 2010;33:1255-61.
- 11 Lilly. DURATION-6 top-line study results announced. 2011. <https://investor.lilly.com/releasedetail2.cfm?ReleaseID=554248>.
- 12 Conjuchem. PC-DAC Exendin-4 (CJC-1134-PC). <http://conjuchem.hyphenhealth.com/products/PCDACExendin4.shtml>.
- 13 Rosenstock J, Reusch J, Bush M, Yang F, Stewart M. Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing. *Diabetes Care* 2009;32:1880-6.
- 14 Ratner RE, Rosenstock J, Boka G. Dose-dependent effects of the once daily GLP-1 receptor agonist lixisenatide in patients with type 2 diabetes inadequately controlled with metformin: a randomised, double blind placebo-controlled trial. *Diabet Med* 2010;27:1024-32.
- 15 Ma X, Hui H, Liu Z, He G, Hu J, Meng J, et al. Poly-GLP-1, a novel long-lasting glucagon-like peptide-1 polymer, ameliorates hyperglycaemia by improving insulin sensitivity and increasing pancreatic beta-cell proliferation. *Diabetes Obes Metab* 2009;11:953-65.
- 16 Day JW, Ottaway N, Patterson JT, Gelfanov V, Smiley D, Gidda J, et al. A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. *Nature Chem Biol* 2009;5:749-57.
- 17 Pan CQ, Buxton JM, Yung SL, Tom I, Yang L, Chen H, et al. Design of a long acting peptide functioning as both a glucagon-like peptide-1 receptor agonist and a glucagon receptor antagonist. *J Biol Chem* 2006;281:12506-15.

Tips for non-specialists

Every consultation is an opportunity to reinforce healthy lifestyle advice

Advise patients to switch to diet drinks, avoid snacking, generate a taste for "healthy" foods, and take non-strenuous exercise in any way and at any time that they can

Encourage weight loss by overweight and obese family members to support the patient

Be cautious in the treatment of comorbidities with agents that can cause weight gain (for example, steroids, some antipsychotics)

If a drug does not benefit glycaemic control or weight loss within three months, consider discontinuation

Trying to lose weight can improve glycaemic control even without weight loss

Future research

How to introduce practical measures to reinstate a culture of healthy living that includes physical activity

Identifying new treatments to prevent pancreatic β cell failure and to dissipate energy without reducing lean body mass

Predicting who will be most responsive to a particular treatment

Determining early markers of susceptibility for increased appetite, metabolic efficiency, and sedentary choices

Additional educational resources*Resources for healthcare professionals*

Each of the following sites provides a range of well structured and authoritative educational resources for all healthcare professionals

European Association for the Study of Diabetes (www.easd.org/)

International Diabetes Federation (www.idf.org/)

Association for the Study of Obesity (www.aso.org.uk/)

International Association for the Study of Obesity (www.iaso.org/about-iaso/history/)

National Obesity Forum (www.nationalobesityforum.org.uk/)

Australian Diabetes Society (www.diabetessociety.com.au/)

Obesity Society (www.obesity.org/)

Resources for patients

Each of the following sites offers straightforward yet comprehensive information together with practical advice, answers for frequently asked questions and locations of relevant services

American Diabetes Association (www.diabetes.org/)

Diabetes UK (www.diabetes.org.uk/)

Canadian Diabetes Association (www.diabetes.ca/)

- 18 Madsen P, Kodra JT, Behrens C, Nishimura E, Jeppesen CB, Pridal L, et al. Human glucagon receptor antagonists with thiazole cores. A novel series with superior pharmacokinetic properties. *J Med Chem* 2009;52:2989-3000.
- 19 Jones RM, Leonard JN, Buzard DJ, Lehmann J. GPR119 agonists for the treatment of type 2 diabetes. *Expert Opin Ther Patents* 2009;19:1339-59.
- 20 Green BD, Bailey CJ, Flatt PR. Gliptin therapies for inhibiting dipeptidyl peptidase-4 in type 2 diabetes. *Eur Endocrinol* 2010;6:19-25.
- 21 Verspohl EJ. Novel therapeutics for type 2 diabetes: incretin hormone mimetics (glucagon-like peptide-1 receptor agonists) and dipeptidyl peptidase-4 inhibitors. *Pharmacol Ther* 2009;124:113-28.
- 22 Vetter ML, Cardillo S, Ricketts MR, Iqbal N. Narrative review: effect of bariatric surgery on type 2 diabetes mellitus. *Ann Intern Med* 2009;150:94-103.
- 23 Pourmaras DJ, Le Roux CW. Ghrelin and metabolic surgery. *Int J Pept* 2010; online 27 January.
- 24 Karra E, Chandarana K, Batterham RL. The role of peptide YY in appetite regulation and obesity. *J Physiol* 2009;587:19-25.
- 25 Flatt PR. Gastric inhibitory polypeptide (GIP) revisited: a new therapeutic target for obesity-diabetes. *Diabet Med* 2008;25:759-64.
- 26 Bailey CJ. Renal glucose reabsorption inhibitors to treat diabetes. *Trends Pharmacol Sci* 2011;32:63-71.
- 27 Rosenstock J, Banarer S, Fonseca VA, Inzucchi SE, Sun W, Yao W, et al. The 11- β -hydroxysteroid dehydrogenase type 1 inhibitor INCB-13739 improves hyperglycemia in patients with type 2 diabetes inadequately controlled by metformin monotherapy. *Diabetes Care* 2010;33:1516-22.
- 28 Bailey CJ. Treating insulin resistance: future prospects. *Diab Vasc Dis Res* 2007;4:20-31.
- 29 Bei B, Zhang G, Li C. AMPK: an emerging drug target for diabetes and the metabolic syndrome. *Cell Metab* 2009;9:407-16.
- 30 Yu, LF, Qiu BY, Nan FJ, Li J. AMPK activators as novel therapeutics for type 2 diabetes. *Curr Top Med Chem* 2010;10:397-410.
- 31 Lam CK, Chari M, Lam TK. CNS regulation of glucose homeostasis. *Physiology (Bethesda)* 2009;24:159-70.
- 32 Billyard T, McTernan P, Kumar S. Potential therapies based on antidiabetic peptides. *Clin Endocrinol Metab* 2007;21:641-55.
- 33 Wang MY, Chen L, Clark GO, Lee Y, Stevens RD, Ilkayeva OR, et al. Leptin therapy in insulin-deficient type 1 diabetes. *Proc Natl Acad Sci USA* 2010;107:4813-9.
- 34 Russell ST, Tisdale MJ. Antidiabetes properties of zinc- α 2-glycoprotein in ob/ob mice. *Endocrinology* 2010;151:3948-57.

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Tables

Table 1 | Current treatments for type 2 diabetes

Agent	Main mechanisms of action	Reduction in HbA _{1c} (%; mmol/mol)	Reduction in fasting plasma glucose (mmol/L)	Body weight	Cautions and contraindications*
Agents administered orally					
Metformin	Reduces insulin resistance† and hepatic glucose output; increases peripheral glucose utilisation and glucose turnover between intestine and liver	~1-2 (~11-22)	1-4	↓/-	Gastrointestinal side effects; lactic acidosis (rare); contraindicated if renal impairment or any hypoxaemic condition
Sulphonylureas (glibenclamide, gliclazide, glimepiride, glipizide, tolbutamide)	Directly increase insulin secretion‡; bind to SUR1 receptor on β cells	~1-2 (~11-22)	2-4	↑	Risk of severe hypoglycaemia; use restricted by severe liver disease, renal disease, or porphyria
Meglitinides (repaglinide, nateglinide)	Directly increase insulin secretion‡§; bind to benzamido site on SUR1 receptor; rapid onset, short duration of action	~0.5-1.5 (~5-16)	1-3	↑/-	Less of a risk of hypoglycaemia (than with sulphonylureas); use restricted by liver disease or severe renal disease
Gliptins (DPP-4 inhibitors: sitagliptin, vildagliptin, saxagliptin)	Increase insulin secretion‡; prevent degradation of incretin hormones by DPP-4, which allows incretins longer potentiation of nutrient induced (prandial) insulin secretion	~0.6-1.5 (~6-16)	0.6-1.2	-	Small risk of hypoglycaemia (seldom severe), mostly when used with other glucose lowering agents; use restricted by substantial renal disease or liver disease
Thiazolidinediones, such as pioglitazone	Increase insulin action† and adipogenesis; stimulate PPAR-γ; alter glucose-fatty acid cycle	~0.6-2.0 (~6-22)	2-3	↑	Caution concerning heart failure, oedema, fluid retention, anaemia, fractures precluded by cardiac disease, severe liver disease, or renal disease
α glucosidase inhibitor (such as acarbose)	Slows carbohydrate digestion¶	~0.5-1.0 (~6-11)	~0.5	-	Gastrointestinal discomfort; avoid if intestinal diseases, severe kidney, or liver disease
Agents administered by subcutaneous injection					
GLP-1 receptor agonists (exenatide, liraglutide)	Increase insulin secretion‡ and decrease glucagon secretion; resistant to degradation by DPP4; potentiate nutrient induced (prandial) insulin secretion	~0.5-2.0 (~6-22)	0.7-2.5	↓	Nausea; risk of hypoglycaemia when used with other glucose lowering agents; avoid in severe renal disease or gastroparesis; stop if pancreatitis is suspected
Insulins	Decrease lipolysis and hepatic glucose output; increase peripheral glucose uptake, storage, and utilisation	Adjust dose and regimen as needed	Adjust dose and regimen as needed	↑	Risk of severe hypoglycaemia; substantial lifestyle adjustments needed; glucose monitoring

*Most agents can rarely cause hypersensitivity reactions.

†Requires presence of circulating insulin.

‡Requires presence of a functional β cell mass.

§Take with meals to reduce the risk and severity of hypoglycaemia.

¶Take with meals rich in complex carbohydrate.

DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; PPAR-γ, peroxisome proliferator activated receptor γ; SUR, sulphonylurea receptor; ↑, increase; ↓, decrease; -, no change.

Table 2| Actions of gastrointestinal hormones that can affect appetite, satiety, and gluoregulation*

Hormone	Plasma concentration of hormone			Effects of hormone		
	In type 2 diabetes	Bariatric surgery		Appetite/meal size	Insulin secretion	Glucagon secretion
		Bypass	Restriction			
Cholecystokinin	↑	?	?	↓	↑	↑
Gastrin	–	?	?	–	↑	–/↑
Ghrelin	↓	–/↓?	↑?	↑	↑/↓	?
GIP	–/↑	–/□	–	–	↑	–/↑
GLP-1	–/↓	↑	–	↓	↑	↓
Peptide YY	↓	↑	–?	↓	↓	–/↓
Secretin	–/↑	?	–?	–/↓	↑	↑
Somatostatin	–/↓	?	?	↓?	↓	↓

*GIP, glucose dependent insulinotropic polypeptide (gastric inhibitory polypeptide); GLP-1, glucagon-like peptide 1; –, no change; ?, not clear (inconsistent reports or the reliability of some of the studies is questionable); □, increase; ▢, decrease.

Figures

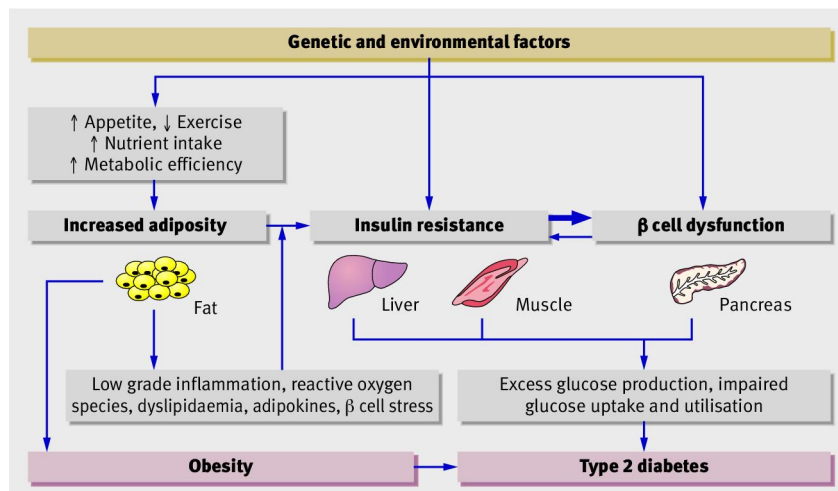


Fig 1 Pathogenesis of type 2 diabetes with obesity. Genetic factors and environmental impositions confer susceptibility to weight gain, insulin resistance, and pancreatic β cell dysfunction. Excess adiposity promotes insulin resistance, which is initially compensated for by increased insulin concentrations. When the insulin concentrations are unable to overcome the insulin resistance then hyperglycaemia develops. Continued deterioration of β cell function causes further impairment of glucose homeostasis into type 2 diabetes

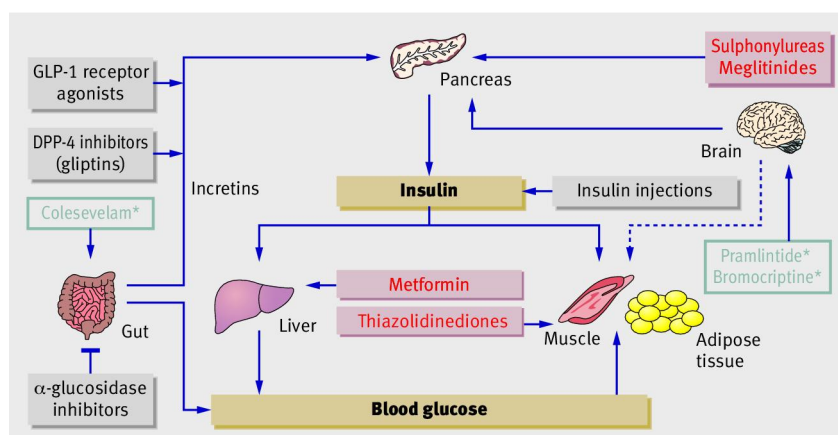


Fig 2 Main sites of action of agents currently used to treat hyperglycaemia in type 2 diabetes. *Bromocriptine, coleselam, and pramlintide are not licensed for the treatment of hyperglycaemia in Europe. DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1