Antidiabetic drugs

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Abstract

Achieving good glycaemic control is an important part of the treatment strategy to minimise vascular complications in diabetes. An expanding range of differently acting oral antidiabetic agents provides new choices for type 2 patients. This review considers the attributes and limitations of these agents, and their positioning in the treatment process.

Key words: antidiabetic drugs, type 2 diabetes, metabolic syndrome, metformin, sulphonylureas, meglitinides, thiazolidinediones, acarbose, insulin.

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Introduction

The prevalence of diabetes mellitus continues to rise and is set to reach 300 million people worldwide by the year 2025 (figure 1).[1] In most European countries 3–5% of the adult population has diabetes, with the vast majority (> 95%) of these patients having type 2 (non-insulin dependent) diabetes.

Macrovascular complications are commonplace amongst diabetic patients, particularly those with type 2 diabetes (table 1). Diabetes increases the risk of ischaemic heart disease by up to four-fold,[2,3] hence the increasing overlap of cardiology and diabetology. Indeed, type 2 diabetes is one of several cardiovascular risk factors that comprise the Metabolic Syndrome (table 2).[4,5] Microvascular complications (retinopathy, nephropathy and various neuropathies) are also a serious cause of morbidity amongst diabetic patients.[6]

Long-term trials such as the Diabetes Control and Complications Trial (DCCT) in type 1 patients, and the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 patients have demonstrated that improved glycaemic control delays the onset and reduces the severity of microvascular disease.[7-9] These and other trials have also provided evidence that improved glycaemic control reduces macrovascular disease.[10,11] Additionally there is compelling evidence that rigorous treatment of hypertension, dyslipidaemia, and obesity will reduce vascular complications and extend the life expectancy of diabetic patients.[10,12]

This article updates an earlier review of antidiabetic drugs in this journal.[13] The present review will focus on the use of oral blood glucose-lowering drugs in type 2 diabetes, with brief comment on the use of insulin, mainly as it applies to patients with type 2 diabetes.

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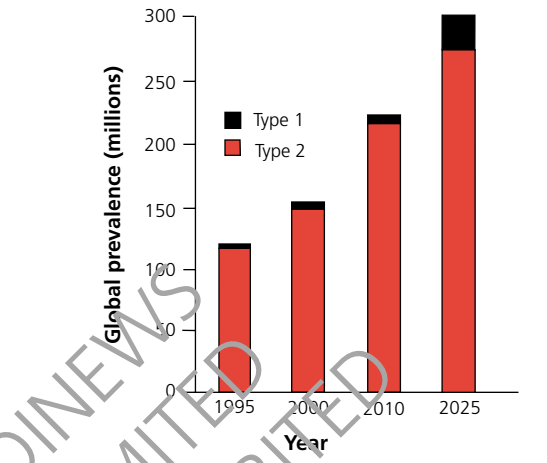
Figure 1. Estimated prevalence of diabetes 1995–2025



Data sourced from Zimmet *et al.* 2001[1]

Table 1. Occurrence of macrovascular complications in type 2 diabetes mellitus

Mortality	
• Death rate	↑ > 2-fold
• Fatal ischaemic heart disease	↑ 2–4-fold
• Fatal stroke	↑ 2–3-fold
Morbidity	
• Ischaemic heart disease	↑ 2–3-fold
• Cerebrovascular disease	↑ > 2-fold
• Peripheral vascular disease	↑ 2–3-fold
• Hypertension	30–50%[a]

Key: ↑ = increase incidence compared with non-diabetic population;
[a] = percentage of patients at diagnosis, dependent on diagnostic criteria

Type 2 diabetes: a progressive disease

The natural history of type 2 diabetes presents a moving target

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Table 2. Cardiovascular risk factors comprising the Metabolic Syndrome[a]

- Insulin resistance
- Hyperinsulinaemia[b]
- Visceral obesity
- Impaired glucose tolerance or type 2 diabetes
- Hypertension
- Dyslipidaemia[c]
- Atherosclerosis
- Pro-coagulant state

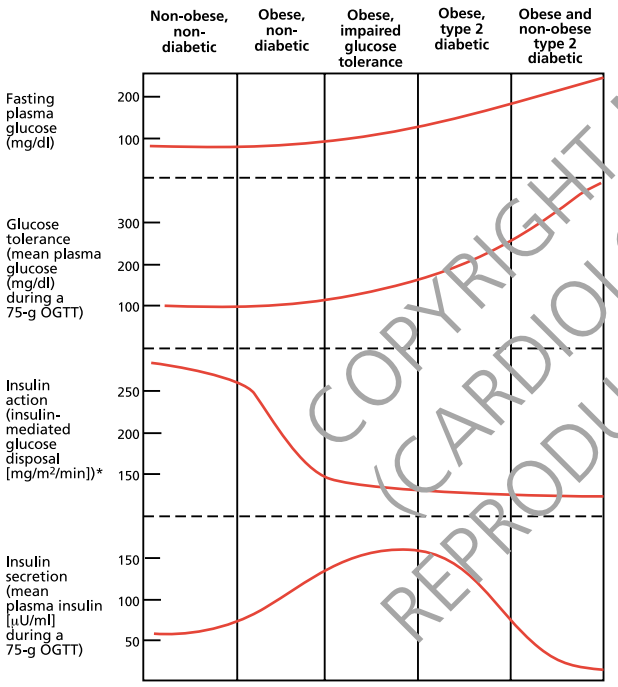
Key: [a] = also known as Insulin Resistance Syndrome, Multiple-metabolic Syndrome, Reaven's Syndrome, Syndrome X, Atherothrombotic Syndrome. Inflammation, hyperuricaemia and microalbuminuria are sometimes included in the list of cardiovascular factors comprising the Metabolic Syndrome [b] = only initially during natural history of type 2 diabetes; [c] = increased circulating triglycerides and small dense low density lipoprotein cholesterol, and decreased high density lipoprotein cholesterol

Table 3. Targets for control of blood glucose and other parameters related to cardiovascular risk in diabetic patients*

	Low risk	At risk	High risk
HbA_{1C} (%)	≤ 6.5	> 6.5	> 7.5
Fasting plasma glucose (mmol/L)	≤ 6.0	> 6.0	≥ 7.0
Serum total cholesterol (mmol/L)	< 4.8	4.8–6.0	> 6.0
Serum triglycerides (mmol/L)	< 1.7	1.7–2.2	> 2.2
Blood pressure (mmHg)	< 140/85	> 140/85[a]	> 140/85[a]

Key: * = guidelines proposed by European Diabetes Policy Group.[17]
[a] = unstated in guidelines, but assumed that increasing blood pressure carries increasing risk

Figure 2. Development of type 2 diabetes: changes in glucose metabolism during a typical progression through obesity and impaired glucose tolerance leading to type 2 diabetes



Key: * = measured during a euglycaemic-hyperinsulinaemic clamp; OGTT = oral glucose tolerance test
Plasma glucose conversion: 18 mg/dl = 1 mmol/L

Based on data from DeFronzo *et al*.[14]

requiring different therapies at different stages of its progression. Typically, insulin resistance is an early feature (figure 2), usually resulting from a genetic susceptibility to reduced insulin sensitivity, compounded by exposure to factors from the internal and external environments (such as high-fat diet, sedentary lifestyle, obesity, stress and chronic infections) which further impair insulin action.[14] Initially insulin resistance is compensated by the adaptive capacity of the pancreatic beta cells to increase insulin concentrations, preventing any serious disturbance to glucose homeostasis. Adaptation of the beta cells depends upon various genetic constraints such as the total beta-cell mass, rates of replication, neogenesis and apoptosis of beta cells, and the activity of key biochemical components of these cells. Environmental influences, including poor interuterine and perinatal nutrition, obesity and diseases of the exocrine pancreas aggravate the genetic constraints. When increased beta-cell function is no longer sufficient to compensate for insulin resistance, glucose tolerance becomes impaired. With progressive beta-cell failure, a state of overt type 2 diabetes supervenes, and the hyperglycaemia continues to increase as hyperinsulinaemia gives way to hypoinsulinaemia.[15]

Diagnosis and treatment targets

Current diagnostic criteria propose that diabetes is confirmed by measurements of plasma glucose > 11 mmol/L on two random occasions or two hours after a 75 g oral glucose tolerance test.[16,17] Two measurements of a fasting plasma glucose level ≥ 7 mmol/L is also a diagnosis of diabetes.

The selection of targets for glycaemic control is arbitrarily based upon evidence from large trials and epidemiological studies showing that patients who maintain near-normal values for HbA_{1C} and fasting glucose carry least risk of long-term complications.[7-9] Guidelines prepared by the European Diabetes Policy Group (table 3) have couched treatment targets in terms of 'low risk' (HbA_{1C} ≤ 6.5% = good control), 'at risk' (HbA_{1C} > 6.5% to 7.5% = could try to do better), and 'high risk' (HbA_{1C} > 7.5% = must strive hard to do better).[17] The National Institute for Clinical Excellence (NICE) has recommended a target range of HbA_{1C} 6.5–7.5% for type 2 diabetes.[18] Ideally glycaemic control should be as close to the normal physiological situation as possible, and suitably individualised to avoid hypoglycaemia and improve the quality of life. In reality, there is no absolute boundary for glycaemic control that is guaranteed to prevent complications, and the UKPDS found that each

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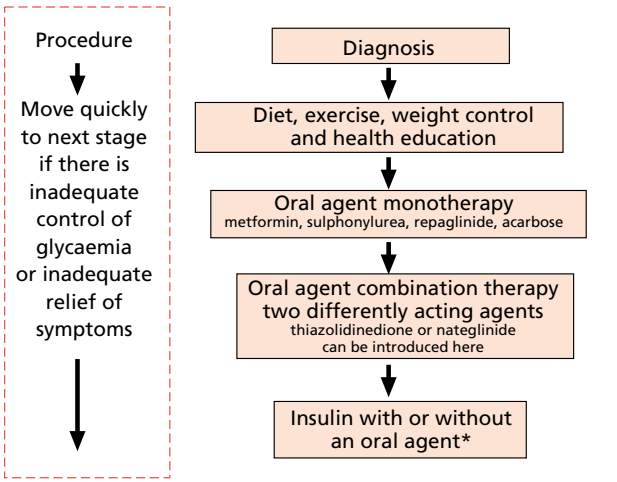
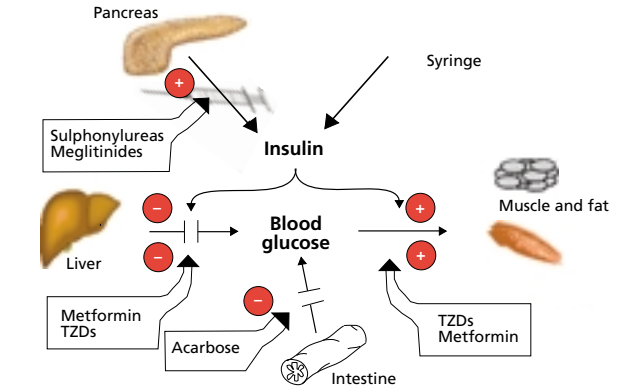
Figure 3. A typical algorithm for the treatment of type 2 diabetes



Key: * = in Europe thiazolidinediones are not indicated with insulin

Figure 4. Main targets of antidiabetic agents



Key: TZDs = thiazolidinediones; + = increase; - = decrease

Table 4. Actions of oral antidiabetic agents currently available in the UK

Class	Examples	Main mode of action
Sulphonylureas	Chlorpropamide, glibenclamide, gliclazide, glimepiride, glipizide, gliquidone, tolbutamide	Stimulate insulin secretion (typically acting 6–24 hour)
Meglitinides[a]	Repaglinide, nateglinide	Stimulate insulin secretion (rapid-onset, short-acting < 6 hour)
Biguanide	Metformin	Improve insulin action
Thiazolidinediones[b]	Pioglitazone, rosiglitazone	Increase insulin action (PPARγ) agonists
Alpha-glucosidase inhibitor	Acarbose	Slow rate of carbohydrate digestion

Key: [a] = also termed 'prandial insulin releasers'; [b] = also termed 'glitazones'

1% decrease in HbA_{1C} (at any level down to euglycaemia) decreased diabetes-related morbidity and mortality by about 21% over 10 years.[11]

Since type 2 diabetes is part of the Metabolic Syndrome of atherothrombotic risk factors linked to insulin resistance and (initially) hyperinsulinaemia,[4,5,14] it is pertinent to consider the diabetologist's versions of desirable targets for blood lipids and blood pressure (BP) (table 3).[17] NICE guidelines for type 2 diabetes are similar: offer a statin if total cholesterol is > 5 mmol/L, and consider a fibrate if the triglyceride remains > 2.3 mmol/L.[19] For type 2 diabetes NICE recommends a BP < 140/80 mmHg.[19] The high risk of coronary heart disease and the need for especially stringent targets in diabetic patients are well appreciated.[20] Indeed, in the UKPDS a sustained lowering of systolic BP by 10 mmHg decreased the occurrence of diabetic complications by 24%.[12]

The treatment algorithm

The first step in any treatment algorithm should be a package of dietary and healthy living advice (figure 3). Since this underpins treatment throughout life it should be reinforced at every opportunity, although only a small proportion of patients (< 20%) actually achieve good control with such measures alone. Disease progression dictates that most patients will require oral drug therapy within three years of diagnosis.[8,9] The oral antidiabetic agents currently available in the UK and their main modes of action are listed in table 4. Continued progression of the natural history of type 2 diabetes, mainly due to ongoing loss of beta-cell function, requires that most patients will eventually need a combination of two *differently acting* classes of oral agents.[21,22] In pursuit of good glycaemic control there is justification for early recourse to two different oral drugs before beta-cell failure deteriorates into absolute hypoinsulinaemia. Indeed, newly diagnosed type 2 diabetic patients who remain markedly hyperglycaemic (e.g. fasting plasma glucose > 12 mmol/L or HbA_{1C} > 10%) after dietary intervention are unlikely to achieve good control (e.g. HbA_{1C} < 6.5%) with one oral antidiabetic agent. These patients may be candidates for starting oral antidiabetic therapy with (or moving promptly to) a combination of two differently acting agents. When oral agents fail to achieve or maintain adequate control it is recommended to switch to insulin therapy, in some cases supplemented with an oral agent. In the USA about one-third of patients with type 2 diabetes receive insulin.

Use of an anti-obesity agent (e.g. sibutramine or orlistat), or various dietary adjuncts such as fibre preparations (e.g. guar gum), minerals (e.g. magnesium and trivalent chromium) or antioxidants (e.g. vitamins C and E), is supported by some specialists, but these adjuncts do not hold a generally accepted position in the treatment algorithm.

Choice of antidiabetic drugs

Different antidiabetic agents target different aspects of the path-

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Table 5. Oral antidiabetic agents

	Daily dosage (mg)	Duration of action*	Activity of metabolites	Main elimination route	Tablet strength (mg)
Sulphonylureas[a]					
Chlorpropamide	100–500	Long	Active	Urine > 90%	100, 250
Glibenclamide	2.5–15	Intermediate–long	Active	Bile > 50%	2.5, 5.0 (scored)
Glimepiride	1–6	Intermediate–long	Active	Urine ~60%	1,2,3,4 (all scored)
Gliclazide MR[b]	30–120	Intermediate–long	Inactive	Urine ~65%	30 (scored)
Gliclazide	40–320	Intermediate	Inactive	Urine ~65%	80 (scored)
Glipizide	2.5–20	Short–intermediate	Inactive	Urine ~70%	2.5, 5.0 (scored)
Gliquidone	15–180	Short–intermediate	Inactive	Bile ~95%	30 (scored)
Tolbutamide[c]	500–2000	Short	Inactive	Urine ~100%	500
Meglitinides[c]					
Repaglinide	0.5–16	Very short	Inactive	Bile ~90%	0.5, 1, 2
Nateglinide[d]	60–540	Very short	Inactive	Urine ~80%	60, 120, 180
Biguanide					
Metformin[c]	500–3,000	Short–intermediate	Not metabolised	Urine ~100%	500, 850
Thiazolidinediones[d]					
Rosiglitazone	4–8	Intermediate–long	Very weakly active	Urine ~65%	4, 8
Pioglitazone	15–30	Intermediate–long	Active	Bile > 70%	15, 30
Alpha-glucosidase inhibitor					
Acarbose[c]	50–300	Short	Inactive[e]	Urine ~35%[e]	50, 100

Key: * = very short < 6 hour; short < 12 hour; intermediate 12–24 hour; long 18 – ~24 hour
[a] = large dosages should be divided and related to meal pattern
[b] = gliclazide MR (Diamicron MR) is a modified release formulation: 30 mg of the MR formulation is approximately therapeutically equivalent to 80 mg of standard gliclazide
[c] = should be taken immediately before meals
[d] = first-line drug therapy excluded in UK: use in combination therapy only
[e] = degraded mainly in intestine. Some metabolites absorbed but very little parent drug absorbed

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Table 6. Main precautions associated with antidiabetic drugs

	Insulin	Sulphonylureas and meglitinides	Metformin	Thiazolidinediones	Acarbose
Main exclusions	-	? Liver, renal	Renal, liver, hypoxia[b]	CHF[g], liver[h], oedema, anaemia	GI[i]
Tolerability	Injection	-	GI[c]	-	GI[c]
Safety	Hypoglycaemia[d]	Hypoglycaemia[d]	LA[e]	Oedema, anaemia	-
Monitor[d]	-	-	Creatinine, vitamin B_{12} or haemoglobin[f]	LFT[h]	? LFT[j]

Key: [a] = if liver or renal disease, select sulphonylurea with appropriate pharmacokinetics and monitor accordingly. Caution drug interactions; [b] = excluded by renal impairment, serious liver disease and any condition predisposing to hypoxia; [c] = take with meals and titrate slowly to reduce gastrointestinal symptoms; [d] = monitor glucose with all antidiabetic drugs, especially during titration to avoid hypoglycaemia ('hypo'); [e] = rare risk of lactic acidosis (LA); [f] = check creatinine and vitamin B_{12} or haemoglobin annually; [g] = CHF (congestive heart disease/failure) [h] = check liver function (e.g. serum alanine transaminase) before treatment and at intervals thereafter; [i] = avoid if intestinal disease; [j] = check liver function (e.g. serum alanine transaminase) if taking high dose

ogenic process (figure 4). Historically, sulphonylureas have been most widely used to start oral drug therapy for non-obese type 2 patients, while metformin has been preferred for obese patients. More recently there has been interest in a wider use of metformin: this reflects growing acceptance that insulin resistance is an early pathogenic feature of most cases of type 2 diabetes, and evidence that initial therapy with metformin reduced macrovascular complications in overweight patients during the UKPDS.[9,23] Acarbose and repaglinide are less widely used as initial therapy, but may be preferred in individuals with mostly postprandial hyperglycaemia or irregular eating patterns. Thiazolidinediones and nateglinide can be added in as second-line agents for oral combination therapy. General information on the use of antidiabetic agents is summarised in tables 5–7.

For all oral antidiabetic drugs it is customary to check first for contraindications, start with a low dose and titrate up slowly

Table 7. Synopsis of effects of antidiabetic drugs

	Insulin	Sulphonylureas	Meglitinides	Metformin	Thiazolidinediones	Acarbose
Basal glucose	↓ ↓	↓	-/ ↓	↓	↓	↓-/
Postprandial glucose	↓ ↓	↓	↓ / ↓ ↓	↓	↓	↓
Insulin concentration	↑ ↑	↑	↑	-/ ↓	-/ ↓	-/↓
Body weight	↑	↑	↑ /-	-/ ↓	↑	-
Free fatty acids	↓	-/ ↓	-	-/ ↓	↓	-
Triglycerides	-	-	-	-/ ↓	↓ /-	-/↓
Total cholesterol	-	-	-	-/ ↓	↓/- / ↑	-

Key: ↓ = decrease; ↑ = increase; - = no change

while monitoring blood glucose concentrations. Sulphonylureas and metformin usually produce a maximum effect before the maximum dose is reached, so a titration step that gives no added benefit can be reversed. As noted previously, early recourse to combination therapy is justified if monotherapy is inadequate. The same procedure of checks and titration is again applied. The main exclusions and precautions for use of antidiabetic drugs are summarised in table 6.[24]

Sulphonylureas

Sulphonylureas reduce hyperglycaemia mainly by stimulating insulin secretion.[25] They bind to the sulphonylurea receptor-1 (SUR-1) in the plasma membrane of the pancreatic beta cells. SUR-1 is part of the complex containing the ATP-sensitive Kir 6.2 potassium channel (K-ATP channel).[26] Binding of a sulphonylurea to SUR-1 closes the K-ATP channel, preventing potassium efflux. This favours membrane depolarisation and the opening of voltage-dependent calcium channels. The influx of calcium raises intracellular calcium concentrations and activates calcium-dependent proteins that control the exocytosis of insulin. The surge of insulin released into the portal vein suppresses excessive output of glucose by the liver in type 2 diabetes, and the extended rise in plasma insulin concentrations facilitates peripheral glucose disposal. Minor direct extra-pancreatic effects of sulphonylureas have been reported to assist glucose-lowering, for example glimepiride may facilitate translocation of glucose transporters into the plasma membrane.[27]

The blood glucose-lowering efficacy of sulphonylureas has been affirmed in many trials.[8,9,25] Typically the reduction in blood glucose is initially 2–3 mmol/L (decrease in HbA_{1C} by 1–2% after two months). The effectiveness of sulphonylureas is obviously dependent on the patient having adequate residual beta-cell function. In general a similar efficacy can be achieved by appropriate titration and dosing schedule with any sulphonylurea, and choice is based on pharmacokinetic features that determine the rate of onset and duration of action, metabolism and route of elimination (table 5).

Sulphonylureas are well tolerated, but the risk of hypoglycaemia must be appreciated, especially with long-acting preparations and in patients with irregular life-styles who skip meals. Potential interaction with other protein-bound drugs should be remembered. Sulphonylurea therapy is likely to cause weight gain, but there is little effect on lipids (tables 6 and 7).

Meglitinides (prandial insulin releasers)

Repaglinide and nateglinide are rapid-acting and short-acting insulin releasers.[28] They can be taken immediately before or during a meal so that their duration of action coincides with the period of meal digestion. These agents stimulate insulin release in a similar manner to sulphonylureas, but they bind to a different site (the benzamido site) on SUR-1.

Repaglinide is a derivative of meglitinide, which is the non-sulphonylurea portion of glibenclamide. Nateglinide is a phenylalanine derivative that is structurally similar to meglitinide. Repaglinide and nateglinide are rapidly absorbed (peak concentration within 1 hour) followed by rapid elimination (plasma half-life [$t^1/_2$] < 1 hour) mainly through hepatic metabolism. Repaglinide metabolites are eliminated mostly into the bile, and nateglinide metabolites into the urine. With these features, meglitinides are suited to mealtime administration so that insulin release corresponds with glucose absorption to reduce the extent of postprandial hyperglycaemia (hence the term prandial insulin releasers). The short duration of action should also reduce the risk of interprandial hypoglycaemia and suit individuals with irregular feeding habits.[28]

Meglitinides can be slightly more effective than sulphonylureas in lowering postprandial hyperglycaemia. Although there is some carry-over reduction in basal glucose, meglitinides are less effective in lowering basal hyperglycaemia. The overall glucose-lowering efficacy of repaglinide can be similar to glibenclamide, but the shorter acting nateglinide has less carry-over effect on basal glycaemia and is not licensed as first-line therapy. Repaglinide and nateglinide can be combined with metformin to give an additive glucose-lowering effect.[28]

Repaglinide and nateglinide can cause weight gain and, being protein bound, they have the potential to interact with other protein-bound drugs.

Metformin

The biguanide metformin lowers blood glucose concentrations

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in type 2 diabetes by countering insulin resistance. The therapeutic efficacy of metformin requires a presence of insulin, improving some metabolic actions of insulin and exerting additional effects that are independent of insulin.[29] Metformin reduces hepatic gluconeogenesis by potentiating insulin action, reducing hepatic extraction of gluconeogenic substrates and suppressing the effects of glucagon. Hepatic glycogenolysis is also reduced by metformin, in part by decreasing the activity of glucose-6-phosphatase. Metformin also enhances insulin-stimulated glucose uptake and glycogenesis by skeletal muscle, and acts independently of insulin to reduce fatty acid oxidation and increase splanchnic glucose turnover.

The glycaemic control achieved with metformin is similar to sulphonylureas: fasting glucose concentrations decrease by 2–3 mmol/L and HbA_{1C} by 1–2%. This is achieved without stimulation of insulin release. Indeed, insulin concentrations may be reduced in hyperinsulinaemic patients, demonstrating the amelioration of insulin resistance. Metformin does not cause overt hypoglycaemia, hence it is regarded as 'antihyperglycaemic' rather than 'hypoglycaemic'.[30] Also, metformin does not cause weight gain and may enhance weight loss in overweight patients. The lipid profile is often improved by metformin, usually involving a reduction of triglyceride concentrations and sometimes a reduction in LDL-cholesterol in hyperlipidaemic patients. Improvements of some parameters of vascular function have been noted with metformin, such as a decrease in PAI-1 and increased fibrinolysis. In the UKPDS, overweight patients starting antidiabetic therapy with metformin incurred lower mortality and fewer micro- and macrovascular complications than patients started with a sulphonylurea or insulin.[9,23,31]

Metformin can be used in combination with a sulphonylurea to produce an additive glucose-lowering effect, but introducing the risk of hypoglycaemia. The risk of hypoglycaemia is likely to be less when metformin is combined with a meglitinide, and less still when combined with a thiazolidinedione or acarbose.

The principal exclusion for metformin is renal impairment (table 6) since the drug is excreted unchanged in the urine (table 5). Excess accumulation of metformin promotes hyperlactataemia and carries the rare possibility of lactic acidosis. Thus, conditions giving rise to hypoxia such as heart failure, or advanced liver disease exclude use of metformin.[30,31] Gastrointestinal side effects are prone to occur during the initiation of metformin therapy. Thus, it is important to start with a low dose, titrate up slowly and take the drug with meals. The gastrointestinal disturbances often resolve with time and usually remit with a reduction in dosage. By improving insulin action metformin can reinstate ovulation in anovulatory polysystic ovary syndrome.

Acarbose

Acarbose competitively inhibits the activity of alpha-glucosidase enzymes (glycoamylase > sucrase > maltase > isomaltase) at the brush border of the small intestine, and weakly inhibits alpha-amylase.[32] Thus, acarbose slows the rate of digestion of complex carbohydrates, and extends the digestive process further along the intestinal tract. In turn, this slows the appearance of glucose within the circulation, reducing postprandial hyperglycaemia. It must be emphasised that the efficacy of acarbose is dependent upon its use in conjunction with meals that are rich in complex carbohydrate. While the antihyperglycaemic effect of acarbose is mostly restricted to the postprandial period, some continued benefit is reflected in lower basal glucose concentrations, although the reduction in HbA_{1C} tends to be substantially less than achieved with sulphonylureas or metformin. Reductions in postprandial insulin and triglyceride concentrations can occur during acarbose treatment, and decreases in the frequency and severity of interprandial hypoglycaemia have been noted.

Acarbose can be used as monotherapy or additively in combination with any other class of antidiabetic drug, including insulin. Particular care is required to titrate the drug dose slowly, and to correlate drug use with the complex carbohydrate content of meals. Predictably, some carbohydrate malabsorption often occurs, causing excessive flatulence, diarrhoea and abdominal discomfort. Rarely, serum transaminases are increased in patients on a high dose of acarbose.

Thiazolidinediones

Thiazolidinediones (TZDs), also termed 'glitazones,' are insulin sensitisers. Two TZDs – rosiglitazone and pioglitazone – were introduced in Europe in 2000. TZDs improve insulin action mainly by activation of the nuclear peroxisome proliferator-activated receptor-gamma (PPARγ).[33] PPARγ is strongly expressed in adipose tissue where it promotes lipogenesis and the differentiation of new adipocytes. PPARγ is weakly expressed in skeletal muscle, liver and various other tissues. Stimulation of PPARγ by TZDs increases transcription of certain genes that are also sensitive to insulin. These genes include those which code for lipoprotein lipase, fatty acid transporters, acyl CoA synthase, glycerol kinase and the glucose transporter Glut4. This facilitates fatty acid uptake, lipogenesis and glucose uptake, particularly in subcutaneous adipose deposits.

While this tends to promote adiposity, associated changes in the glucose-fatty acid (Randle) cycle improve glucose utilisation by muscle and reduce the energy supply for hepatic glucose production. Although changes in the glucose-fatty acid cycle appear to mediate much of the blood glucose-lowering effect of TZDs, a direct stimulation of PPARγ in muscle and liver, and possibly actions that are independent of PPARγ, may also be involved. In Europe TZDs are licensed for oral combination therapy (not first-line therapy).

The blood glucose-lowering effect of TZDs is similar to metformin when used as a second agent. However, the onset of action is slower and may take two to three months to produce maximum efficacy. TZDs require adequate insulin to achieve their glucose-lowering potential, and may reduce insulin concentrations, but in Europe they are not licensed for use with insulin. TZDs typically lower free fatty acid concentrations, often lower triglyceride levels, and raise high density lipoprotein. Pioglitazone can lower low density lipoprotein (LDL) while rosiglitazone may increase LDL, although this appears to reflect an increase in larger (more buoyant and less atherogenic) LDL subfractions.

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A former TZD, troglitazone, was introduced and immediately withdrawn in the UK in 1997 due to evidence of hepatotoxicity from use in other countries. Rosiglitazone and pioglitazone do not show this hepatotoxicity, but nevertheless precautionary monitoring of liver enzymes is required. Evidence of liver disease by raised enzymes such as alanine aminotransferase (ALT) > 2.5 times the upper limit of normal (ULN) contraindicates the use of a TZD.[34]

An important side effect of rosiglitazone and pioglitazone is fluid retention which can lead to oedema and dilutional anaemia. Hence heart disease or a history of heart disease contraindicates use of TZDs. Oedema is likely to occur in 5–10% of patients. Many will respond to thiazide diuretics but withdrawal of the TZD may be preferred. Like metformin, the improvement in insulin action can re-activate ovulation in anovulatory polycystic ovary syndrome. Weight gain often occurs with the use of a TZD, but these agents do not intrinsically cause hypoglycaemia, although hypoglycaemia can occur in combination with an insulin-releasing agent (sulphonylurea or meglitinide).

PPARγ is found in macrophages and vascular tissue and TZDs are presently being investigated for possible effects to decrease macrovascular disease and renal vascular disease that are independent of their glucose-lowering effects.

Combinations

If monotherapy with one oral antidiabetic agent does not produce the desired glycaemic target, or glycaemic control deteriorates to values outside the desired range, oral combination therapy is indicated. The second agent must act by a different mechanism to the first in order to achieve an additive glucose-lowering effect. The efficacy of oral combination therapy is also dependent upon adequate remaining beta-cell function. If beta-cell function is already almost completely lost, hyperglycaemia is either severe or rising quickly, often accompanied by unintentional weight loss. Under these circumstances it is unlikely that any combination of currently available oral antidiabetic agents will provide more than a very temporary respite, and the patient should be switched to insulin.

The most widely used oral antidiabetic drug combinations are shown in table 8. Metformin, sulphonylureas, repaglinide and acarbose are presently licensed for first-line oral therapy. A TZD or nateglinide can be added as second-line therapy. The European regulatory recommendations are somewhat tortuous. Currently they specify that a TZD can only be used with metformin or a sulphonylurea if a metformin-sulphonylurea combination proves to be inappropriate, e.g. if metformin is not tolerated or the sulphonylurea is deemed responsible for episodes of hypoglycaemia. Also nateglinide is only for combination with metformin.

It is important to consider exclusions, contraindications and interactions for both agents before instituting oral combination therapy, and to titrate up the second agent with the usual monitoring of glycaemic control. Early use of two differently acting oral agents may beneficially produce additional efficacy at lower dosages. Hence, it may be appropriate to temporarily lower the dosage of the first agent when moving quickly to the introduction of a second agent.

Table 8. Oral antidiabetic agents that can be used together for combination therapy

Monotherapy: first agent	Combination therapy: agent to add
Metformin	Sulphonylurea or meglitinide, acarbose, thiazolidinedione*
Sulphonylurea or repaglinide	Metformin, acarbose, thiazolidinedione
Acarbose	Sulphonylurea, repaglinide, metformin

Key: * = a thiazolidinedione can be used with either metformin or a sulphonylurea if a metformin-sulphonylurea combination is inappropriate. Based on current licensing in Europe

Insulin

When oral agents are unable to achieve or sustain adequate glycaemic control, or symptoms become severe, it is customary to switch to insulin. The need for insulin indicates that the natural history of the disease has progressed to severe beta-cell failure (figure 2). Some of these patients may, in fact, have a very slowly developing form of type 1 diabetes. Around 5–10% of patients on one or more oral therapies will require insulin each year, and the potential advantages of insulin at this stage mitigate against any delay in making the switch.

Insulin acts on the liver to reduce hepatic glucose output, and on peripheral tissues, especially skeletal muscle, to increase glucose uptake and metabolism. The choice of insulin regimen, and the procedure for initiation and titration are still vigorously debated.[35] Popular options are twice-daily injection of an intermediate-acting insulin or a mixture of a short-acting insulin with an intermediate-acting insulin (table 9). Basal insulin replacement with a single-daily injection of a long-acting insulin is often insufficient to achieve good glycaemic control due to the 'dome' profile of circulating insulin. A single-daily injection of the newly available soluble long-acting analogue, glargine, produces fairly constant circulating insulin concentrations for most of a 24-hour period. A long-acting insulin at bedtime with an oral agent during the daytime is successful and convenient for many patients.[36] Metformin, for example, can improve glycaemic control and reduce insulin requirement in insulin-treated patients, while reducing the weight gain induced by insulin.[37] Where lifestyle is irregular and/or a particularly intensive regimen is required, multiple daily injections of a rapid acting insulin analogue can be given with meals, supported with a long-acting insulin given in the evening. Pen injection devices, pre-mixed insulins and routine self-monitoring of blood glucose are valuable aids for the patient to take day-to-day responsibility and make adjustments to their regimen.

Large doses of insulin can be required to overcome the insulin resistance of type 2 diabetes, and disharmony between the dose regimen and lifestyle carries a risk of serious hypoglycaemia.[24] Although insulin can directly accentuate insulin resistance, this is usually offset in the long term through reduced glucotoxicity.

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Table 9. Synopsis of insulin preparations*

Category	Rapid	Short	Short–intermediate	Intermediate	Long	Very long
Type		Soluble	Soluble-isophane mixture	Isophane	Crystalline Zinc suspensions	Soluble
Examples	Aspart, Lispro	Actrapid, Humulin S	Mixtard, Humulin M2/3/5	Insulatard, Humulin I	Ultratard, Lente	Glargine
Onset of action (mins)	< 15	15–60	15–60	60–120	120–240	60–120
Duration of action (hours)	1–4	4–8	8–16	8–16	16–30	> 24 hours

Key: * = times for onset and duration of action are approximate ranges that vary between individuals, with dose and site of subcutaneous injection and pathophysiological state

Since human insulins may be absorbed faster than their porcine or bovine equivalents, this may cause complaints of rapid onset of episodes of hypoglycaemia with little or no warning. Adjusting the regimen is then indicated.

Although the switch to insulin is often perceived with horror by the patient, most adapt quickly. Remember with the advent of glargine (which is soluble, i.e. clear) the old characterisation of insulins into clear (short-acting) and cloudy (long-acting) is now redundant. The possibility of a non-injection delivery method, such as an aerosol, is particularly appealing, but this is still in the trial stages.

Anti-obesity agents

Reducing the adiposity in obese type 2 diabetes is a well-recognised (if difficult to achieve) route to ameliorate insulin resistance and improve glycaemic control. Weight reduction also benefits other associated cardiovascular risk factors such as dyslipidaemia and hypertension, and justifies the persistent reinforcement of diet and lifestyle messages to diabetic patients.[38]

To facilitate weight loss, the intestinal lipase inhibitor orlistat can reduce fat absorption by up to 30%.[39] Although steatorrhoea and associated bowel problems can be limiting, orlistat has been shown to improve weight loss in conjunction with a low calorie diet by around 10% (compared with about 6% on placebo). Obese type 2 diabetic patients who achieved this weight loss showed an improved HbA_{1C} by about 0.5%.[40] Similar success has been achieved with sibutramine, a satiety-inducing serotonin-noradrenaline re-uptake inhibitor.[41]

Cardiovascular issues about antidiabetic drugs

Several controversial issues regarding the cardiovascular effects of antidiabetic drugs remain unresolved. Potential benefits of the acute vasodilatatory response to insulin are well recognised, and use of insulin-glucose infusion has been shown to improve survival after a myocardial infarction, especially in type 2 diabetes (Diabetes mellitus Insulin-Glucose infusion in Acute Myocardial Infarction [DIGAMI] study). It is still unclear whether chronic hyperinsulinaemia can promote extra growth of vascular smooth muscle to aggravate the clinical course of atherosclerosis. The balance of evidence suggests that therapeutic concentrations of insulin probably do not adversely affect the vascular wall in diabetes.[42]

Key messages

- Type 2 diabetes is a progressive disease
- Intensive treatment reduces complications
- Most patients eventually need a combination of two differently acting oral agents and/or insulin

Cardiac and vascular smooth muscles express K-ATP channels, and high concentrations of some sulphonylureas have been reported to close these channels during periods of myocardial ischaemia. In theory this could reduce arrhythmia during mild ischaemia, but increase myocardial damage during more severe ischaemia. Recent studies have noted that the sulphonylurea receptors of K-ATP channels in cardiac and vascular smooth muscle (SUR-2A/B) lack the high affinity sulphonylurea binding site of SUR-1. However, SUR-2A/B retain the benzamido site. Thus, sulphonylureas that have a benzamido moiety (glibenclamide, glipizide, glimepiride) and meglitinides can bind to SUR-2A/B. Nevertheless lower affinity and shorter duration of binding at the benzamido site suggest that therapeutic concentrations of these agents are unlikely to exert a clinically significant impact. Several studies, including the UKPDS, have not shown a detrimental effect of sulphonylureas on cardiac events. Concern that tolbutamide adversely affected cardiac events in type 2 diabetic patients during the controversial American University Group Diabetes Program (UGDP) cannot be attributed to an effect on SUR-2A/B since tolbutamide does not possess a benzamido moiety.

As mentioned earlier, initiation of oral antidiabetic drug therapy with metformin reduced macrovascular events in overweight type 2 diabetic patients during the UKPDS to a greater extent than explained by glycaemic control alone.[9,23] This could be related to reduced insulin resistance, although metformin may have independent effects on vascular function and thrombolysis, as well as reducing cardiovascular risk from effects on blood lipids and obesity. Whether the TZDs, which also reduce insulin resistance, will offer a similar protective effect is now under investigation in several long-term trials with hard end points. Various

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markers and risk factors for cardiovascular disease show potentially beneficial changes during TZD therapy, including reductions of C-reactive protein, homocysteine, vascular smooth muscle proliferation and platelet aggregation. Different changes to the lipid profiles during treatment with rosiglitazone and pioglitazone have been suggested as a potential influence to vary cardiovascular outcomes with these agents, but head-to head trials have not been undertaken.

Conclusions

The consequences of glycation and other vascular risks associated with hyperglycaemia, such as hypertension, dyslipidaemia and obesity, render type 2 diabetes a complex multifaceted condition to treat. Insulin resistance, initially provoking hyperinsulinaemia but leading to progressive beta-cell failure, presents an ever-shifting natural history. Consequently different therapies are required at different stages of the disease process. Intensive use of available therapies directed against different pathogenic aspects of the disease is strongly encouraged to return blood glucose and attendant vascular risk factors to as near normal as reasonably possible.

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