

Treatment of TYPE 2 DIABETES MELLITUS

By A. BHATTACHARYYA, DM, MRCP (UK)

The second part of our special feature considers the treatment options in type 2 diabetes mellitus, including new and emerging agents

People with type 2 diabetes mellitus (DM) are characterised by a resistance to insulin and a relative, as opposed to absolute, insulin deficiency. At least initially, and often throughout their lifetime, they do not need exogenous insulin for survival. Thus, although insulin may be required for controlling hyperglycaemia, these patients do not develop diabetic ketoacidosis other than in rare situations.¹

In this article, treatment of chronic hyperglycaemia associated with various organ system dysfunctions will be discussed. The treatment of complications (microvascular [retinopathy, nephropathy, neuropathy] and macrovascular [cardiovascular, cerebrovascular and peripheral vascular diseases]) is beyond the scope of the article.

GOALS OF TREATMENT

The goals of therapy for type 2 DM include:

1. Correction of symptoms such as polyuria, nocturia, blurred vision, tiredness, pruritus vulvae in women and balanoposthitis in men
2. Prevention of macrovascular and microvascular complications
3. Maintenance of a healthy, cheerful life free of the fear of DM

It is worth emphasising that type 2 DM is a complex metabolic disorder, and good diabetic control should include maintaining a normal body mass index, blood pressure (Figure 1) and lipid levels.

The best way of assessing glycaemic control is by estimating the glycosylated haemoglobin (HbA_{1c}) level. Lowering the HbA_{1c} to less than 2 per cent above the upper limit of normal (or less than 7 per cent, as in the Diabetes Control and Complication Trial [DCCT]² standard) should be the goal for which to aim. For some patients, this is difficult and often impractical, such as in the presence of significant co-morbid illness, old age, and in people with a defective state of mind. In routine clinical practice, an HbA_{1c} less than 8 per cent should be acceptable. In certain situations, such as in pregnancy, control should be very strict.

Also, it is important to clarify to readers at the beginning that intensive glycaemic control does not mean multiple insulin injections, the use of insulin pumps or the checking of blood sugar levels 10 times a day. Intensive glycaemic control simply implies that the blood glucose level should be kept as near normal as possible and hypoglycaemia avoided, no matter how simple or complex the treatment regimen is.

GLYCAEMIC CONTROL

Since the publication of the DCCT in patients with type 1 DM, there has been increasing demand for evidence of good glycaemic control in type 2 DM. Before the United Kingdom Prospective Diabetes Study (UKPDS),³ there were some retrospective and prospective studies to assess the microvascular complications in type 2 DM.^{4,5,6} The Kumamoto study⁷ was a randomised, prospective intervention trial like DCCT, although it included 110 patients with type 2 DM.

The UKPDS showed a significant reduction in the development of new diabetic complications such as retinopathy and albuminuria, and a reduction in progression of

Dr Bhattacharyya is specialist registrar in the department of diabetes and endocrinology at Manchester Royal Infirmary

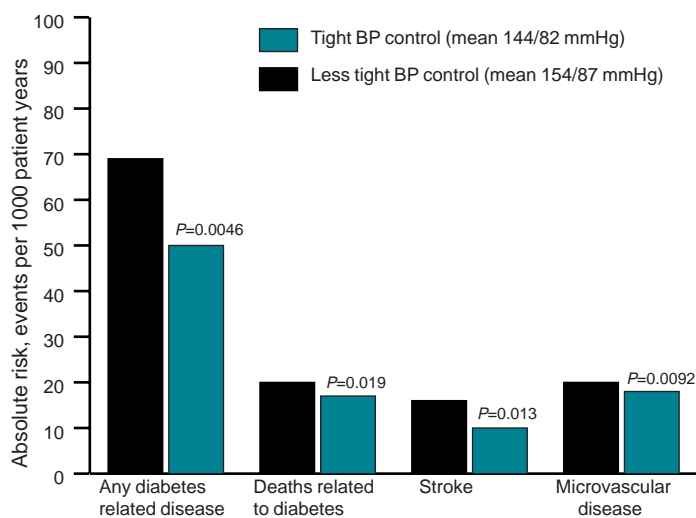


Figure 1: The UKPD study showed that good blood pressure control reduces mortality and morbidity

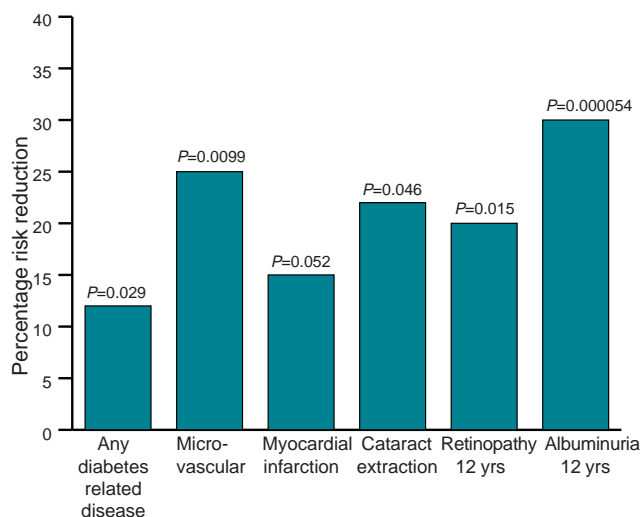


Figure 2: The UKPD study showed that tight glycaemic control reduces complications

established retinopathy and nephropathy with good glycaemic control. UKPDS is the longest and largest study in the history of diabetes mellitus. It showed a 25 per cent reduction of microvascular complications with 0.9 per cent reduction of HbA_{1c} (Figure 2).

As opposed to microvascular complications, macrovascular complications, such as cardiovascular or cerebrovascular disease, are the predominant cause of morbidity and mortality in type 2 DM. The available literature evaluating the relationships between glycaemic control and macrovascular disease suggest an ever-important role for good glycaemic control. In fact, any reduction is beneficial.^{8,9}

DIET AND EXERCISE

Dietary regulation, with the goal of reducing the total body fat, is the first line therapy for controlling type 2 DM. As little as a 5 per cent reduction in fat may be associated with a significant improvement in glycaemic control. The success rate of diet alone in the treatment of DM, however, may not be in excess of 10 to 15 per cent.¹⁰ Even then, diet should not be ignored.

Dietary modification smoothes the glycaemic control, improves efficacy of oral or insulin treatment, and helps in reducing dyslipidaemia and cardiovascular risks. Dietary exchange regimens, where one exchange of carbohydrate is approximately 50 calories, one of fat is 110 calories and one of protein is 70 calories, fell out of favour in some centres but have a role in clinical practice. In particular, it becomes easier to talk to patients about dietary modification when they are aware of the exchanges. This approach is extremely helpful in managing diabetic pregnancies and patients on multiple subcutaneous insulin injections.

A successful diet programme should include a combination of sensible caloric reduction, behaviour modification and

patient education. The goal should be clear and acceptable to the patient. Due respect should be given to the religious, cultural and financial constraints. Patients should be encouraged to take more frequent, smaller meals and to be vigilant about any changes in routine that may precipitate hypoglycaemia (eg, unexpected exercise, missed meals) if a hypoglycaemic agent is currently being used. Patients should be encouraged to consume a well-balanced diet with 10 to 20 per cent of the caloric intake from protein, 60 to 70 per cent from unrefined carbohydrate and less than 10 per cent from saturated fat. Vitamin and mineral supplements should not be necessary if a balanced diet is consumed. However, if the patient takes a diet containing less than 1200 calories, iron and folate supplementation may be necessary.

It is becoming increasingly clear that the increased incidence of type 2 DM around the world is associated with a decreasing level of activity and an increasing prevalence of obesity. Thus, promoting exercise as a vital component of the prevention, as well as the management, of type 2 DM must be viewed as a high priority. It must also be recognised that the benefit of exercise in improving the metabolic abnormalities of type 2 DM is probably greatest when it is used early in the progression from insulin resistance to impaired glucose tolerance to overt hyperglycaemia requiring treatment with oral agents and insulin.¹¹

ORAL HYPOGLYCAEMICS

Figure 3 outlines the sites of action of the oral hypoglycaemic agents commonly used in the treatment of type 2 DM.

Sulphonylureas Sulphonylureas, which include chlorpropamide, glibenclamide, glizalide and tolbutamide, act mainly by augmenting insulin secretion and are effective only when residual pancreatic β-cell

function is present. They are not the drugs of choice for obese type 2 DM, since they can cause weight gain. The main concern with their use is hypoglycaemia. Sulphonylurea-induced hypoglycaemia can persist for several hours and such patients should always be admitted to hospital. The dangers of prolonged hypoglycaemia are most frequently seen with chlorpropamide which, as a rule, is avoided in the elderly.

Approximately 20 to 25 per cent of patients with type 2 DM encounter primary failure of sulphonylurea therapy (that is, glycaemic control not improved on initiation of the therapy). The usual causes of primary failure are dietary discordance, wrongly selected patients (eg, cases of type 1 DM) and severely impaired β-cell function (advanced type 2 DM). Among those who achieve initial control, 5 to 10 per cent develop secondary failure every year. Patients should be given this information clearly at the beginning to avoid the "sense of guilt" some patients suffer on development of secondary failure.

The cardiovascular effects of sulphonylurea treatment have been the subject of extensive debate since the University Group Diabetes Program (UGDP) was published in 1970. This showed an increased mortality from myocardial infarction in tolbutamide-treated patients.¹² Although the validity of the UGDP observation remains unclear, sulphonylureas should be used with caution in patients with increased cardiovascular risks. Sulphonylureas are primarily metabolised in the liver and should be used with caution in patients with hepatic dysfunction.

Biguanides Biguanides have been used in the treatment of DM since mediaeval times. French lilac, rich in guanidine, has a hypoglycaemic effect, but guanidine is too hepatotoxic for clinical use. Guanidine derivatives gained popularity in the 1950s when sulphonylureas became available for

treatment. Phenformin and metformin were introduced in 1957, but the former was withdrawn in the 1970s, due to its tendency to cause lactic acidosis. Metformin has much less risk of lactic acidosis. Metformin has a different mode of action from the sulphonylureas. It inhibits hepatic gluconeogenesis and also increases peripheral utilisation of glucose.

Contraindications to the use of metformin include renal failure, hepatic impairment, alcohol abuse, cardiac disease and intercurrent illness. Age has not been proven to be an independent risk factor for its use. In routine clinical practice, the drug is usually discontinued when serum creatinine is above 150 to 160 micromol/L. Acute renal failure, due to transient hypotension (which may be due to investigation with radiographic contrast materials), may lead to lactic acidosis in metformin-treated patients. Nowadays, metformin is stopped during the 48 hours prior to, and 72 hours after, such a procedure.

Metformin is the drug of choice in obese type 2 DM as it enhances weight loss, while controlling hyperglycaemia. The UKPDS showed a reduction in macrovascular complications and mortality with the use of metformin in obese type 2 DM (Figure 4).¹³ It is effective as monotherapy and can also be used in combination with sulphonylureas and insulin. Used alone, it reduces fasting blood glucose by 22 to 26 per cent and HbA_{1c} by 12 to 17 per cent.¹⁴ Around 20 to 30 per cent of patients experience abdominal discomfort, nausea, anorexia and a metallic taste in the mouth. However, a significant proportion of these patients go on to tolerate metformin quite well.

Metformin should always be started slowly, and the dose built up in a matter of weeks, rather than days. Approximately 30 per cent show evidence of malabsorption of vitamin B₁₂, although low vitamin B₁₂ levels develop only rarely in clinical practice. Again, secondary failure develops at the rate of 5 to 10 per cent per year.

Acarbose Acarbose inhibits the α -glucosidase enzyme in the intestine and prevents the absorption of starch and sucrose. If tolerated, the drug is often useful in obese type 2 DM. The main benefit of acarbose is its reduction of postprandial blood glucose, but it does not have much effect on fasting glucose. Treatment with acarbose may reduce the insulin demand by decreasing postprandial hyperglycaemia.

Flatulence and diarrhoea are the common side effects. Again, like metformin, these symptoms get better with continued use and treatment should be started with a small dose.

Repaglinide Repaglinide is a novel enantiomeric benzoic acid derivative. It promotes the secretion of insulin by closing ATP-sen-

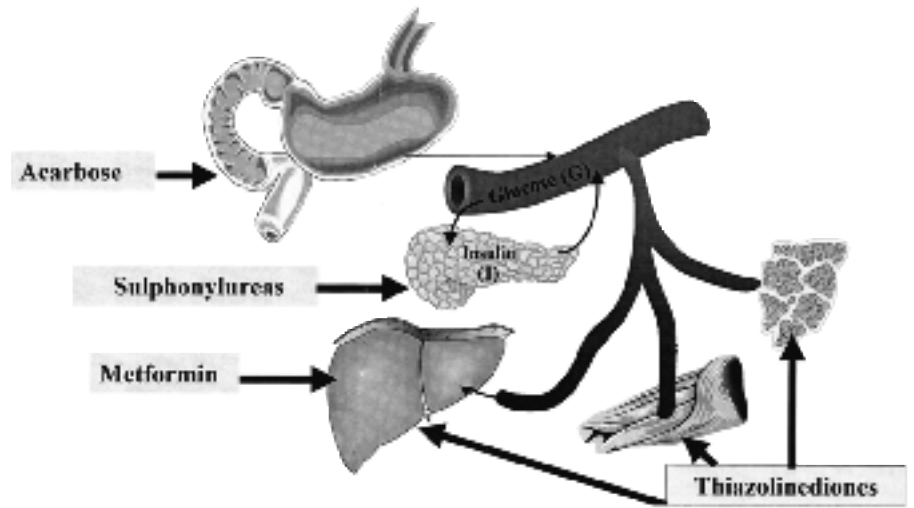


Figure 3: Sites of action of oral hypoglycaemic agents

sitive potassium channels in the β -cell membrane. Although sulphonylureas stimulate the same secretory mechanism, studies *in vitro* indicate that repaglinide has a distinct β -cell binding site.

Repaglinide, unlike glibenclamide, does not stimulate insulin secretion in the absence of glucose. A single dose (0.5 - 4mg) taken before breakfast has been shown to be effective in reducing postprandial hyperglycaemia in a manner which is dose-dependent.¹⁵

Thiazolidinediones Thiazolidinediones include troglitazone, rosiglitazone, pioglitazone and ciglitazone. Thiazolidinediones directly enhance insulin sensitivity, thereby reducing insulin resistance, the major defect in type 2 DM. Troglitazone was licensed in the UK in 1998 and had a remarkable response from diabetologists all over the country. However, because of its life-threatening side effect (hepatic failure), it was withdrawn from the market after only a few weeks.

Thiazolidinediones bind to peroxisome proliferator-activated receptor, a molecule implicated in the transcription of insulin responsive genes. Troglitazone has been shown, in the presence of glucose, to increase both basal and insulin-stimulated glucose uptake in muscle and adipose tissue, and to enhance the expression of glucose transporter receptors in the cell wall. It has also been shown to protect the β -cell from exhaustion.¹⁶ The development of thiazolidinediones is probably the biggest breakthrough in the treatment of diabetes since the discovery of insulin. Rosiglitazone and pioglitazone were licensed in the UK in 2000. The three agents troglitazone (on a named-patient basis only), rosiglitazone and pioglitazone) are available in the United States. No major data are available comparing the efficacy of the three agents. King reported his experience of 101 cases (35 on troglitazone, 36 on rosiglitazone and 30 on pioglitazone).¹⁷ HbA_{1c} was decreased similarly using the three agents. The beneficial effects on dyslipidaemia were more pronounced with pioglitazone in the four months observational study, while the group that received pioglitazone had the greatest weight gain. Only in one case, using rosiglitazone, was abnormal liver function a problem. Larger and longer-term studies, however, are warranted to compare the effects of these three agents.

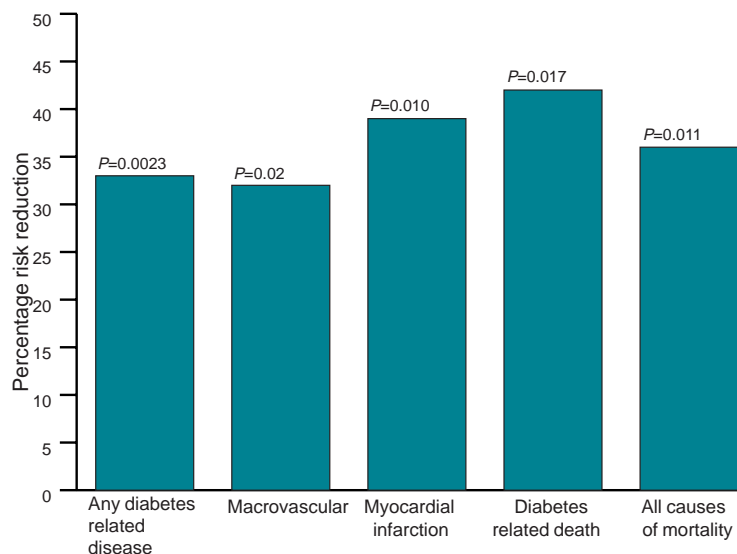


Figure 4: The UKPDS study showed that metformin reduces the risk of macrovascular complications

INSULIN THERAPY

Most patients with type 2 DM secrete enough insulin to be treated with diet, exercise and oral agents, at least initially. As the disease progresses (and it almost always does), insulin secretory capacity declines to a level requiring exogenous insulin. Common indications for insulin are listed in the Panel. When insulin is used in the newly diagnosed patient with type 2 DM, the usual reasons are a very high fasting glucose (more than 17 mmol/L) and primary sulphonylurea failure.

Insulin preparations are classified according to the duration of action (long, intermediate, short or ultra-short acting), source (porcine, bovine or human) and purity (conventional, purified and highly purified). The currently available preparations are highly purified and the human insulins are prepared by DNA recombinant technology. One unit of insulin is the same regardless of the duration, source or purity. (One unit of insulin is defined as the amount of insulin required to reduce blood sugar by 50 per cent in 45 minutes in a rabbit weighing five pounds.)

Theoretically, all patients with type 2 DM can be controlled by insulin. In most of the cases of uncontrolled DM, the reasons for failure are poor regimen selection, dietary discordance and inappropriate help from the specialist. The two main problems of insulin use are hypoglycaemia and weight gain. Concomitant medical conditions such as hypothyroidism, Addison's disease and liver and renal disease can contribute to hypoglycaemia. The most common reason for hypoglycaemia in insulin-treated patients, however, remains the mismatch between food and insulin injection (dose and/or timing). Coeliac disease can be associated with diabetes and can be responsible for unexplained hypoglycaemia.¹⁸ Other side effects of insulin use are lipodatrophy, lipohypertrophy and, rarely, insulin allergy. Hypoglycaemic unawareness to human insulin is, at best, debatable.

Designing an appropriate insulin regimen is the most important aspect of prescribing insulin. Due consideration should be given to the age of the patient, the patient's wishes,

Panel: Indications for insulin therapy in type 2 DM

- Non-ketotic hyperosmolar coma
- Pregnancy
- Failure of oral treatment
- Acute myocardial infarction
- During and after major surgery
- Ill health, any condition precluding the use of the oral route
- Fasting blood sugar greater than 17 mmol/L on presentation

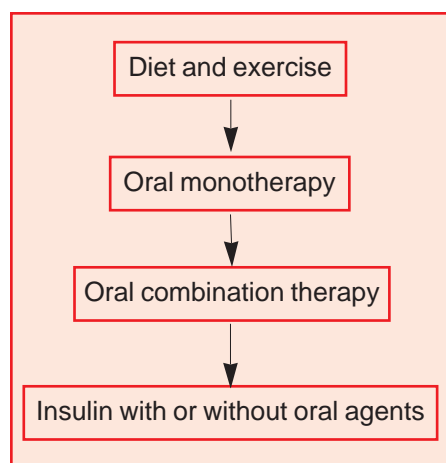


Figure 5: Stepwise approach to managing type 2 diabetes mellitus

co-morbid diseases and glycaemic profile. The various options available include once-daily, long-acting insulin (really a choice for elderly patients only); twice-daily, intermediate-acting insulin; and twice-daily, pre-mixed insulin (mixture of short and intermediate-acting insulin in various combinations from 10 to 50 per cent).

A more intensive regimen will be free-mixing insulin (again a mixture of short and intermediate-acting insulin). In this case, however, the proportion can be changed depending on the glycaemic profile (unlike the pre-mixed insulin) and the basal bolus regimen (multiple subcutaneous injection, intermediate-acting insulin at bedtime [basal] and short acting insulin before breakfast, lunch and dinner [bolus]). Almost all forms of insulin are now available as pens, making administration easier.

Insulin pumps and continuous subcutaneous insulin infusion are mainly used in cases of type 1 DM but can also be used in young type 2 DM patients. Dosing of insulin totally depends on the glycaemic state and control.

Insulin analogues differ from regular insulin by having changes in the amino acid sequence or composition of the insulin molecule. The rapidly acting analogues reduce the stability of the insulin monomer-monomer interaction, leading to a more rapid sub-unit dissociation and subcutaneous absorption of insulin. Hence, their onset of action is quicker and matches well with postprandial hyperglycaemia. Most patients prefer analogues because it is not necessary to leave any time period between the injection and meals. The first insulin analogue to be licensed in the UK was insulin lispro (produced by changing the sequence of lysine and proline at the 29th and 30th position of the B-chain). It is an ultra-short acting insulin. Later, insulin aspart (proline replaced by aspartic acid at the 28th position of the B-chain) was licensed in 1999. These analogues are associated with less hypoglycaemic episodes, better glycaemic control and less weight gain.¹⁹

COMBINATION THERAPY

Monotherapy with oral agents is often unsuccessful. Combination of a sulphonylurea with metformin or acarbose has long been used successfully. Rosiglitazone and pioglitazone have been licensed for combination use only.

When glycaemic control is not achieved by combining oral agents, insulin can be used along with oral agents (Figures 5 and 6). Insulin is used once daily at night to suppress the hepatic glucose output. Obviously, the injection frequency is increased when acceptable glycaemic control is not achieved.

The properties of different oral hypoglycaemic agents used in the UK are summarised in the table.

PANCREATIC TRANSPLANT

Pancreatic transplantation was first carried out in 1966. According to the international pancreas transplant registry, nearly 10,000 pancreatic transplants had been carried out by 1997, with an overall patient survival rate of 90 per cent and graft survival rate of 82 per cent.²⁰ Selective islet cells transplants are also used but operative/post-operative morbidity and mortality and the need for life-long immunosuppression complicate both procedures.

The role of transplantation has not been addressed in cases of type 2 DM, mainly because of the older age of patients, co-existent vascular problems and the primary difference between the types of DM (insulin lack in type 1 as opposed to insulin resistance in type 2 DM).

NEW TREATMENTS

Nateglinide, a derivative of D-phenylalanine, is a new agent being investigated in the treatment of type 2 DM. It is chemically and pharmacologically distinct from the sulphonylureas, biguanides and repaglinide. Nateglinide raises insulin levels by decreasing pancreatic β -cell potassium-ATPase channels, which results in calcium influx and subsequent insulin release. As plasma glucose rises, β -cell sensitivity to nateglinide increases and insulin release amplifies.²¹

It has been shown recently that combination therapy with metformin is more effective than either treatment alone and these two agents do not have pharmacokinetic interactions.²²

The recently introduced intestinal lipase inhibitor orlistat and the satiety-inducer, sibutramine are weight-reducing agents that may have a beneficial role in glycaemic control in obese type 2 DM.

Azolidinediones inhibit the protein tyrosine phosphatase 1B — a negative regulator of the insulin receptor. Animal studies have

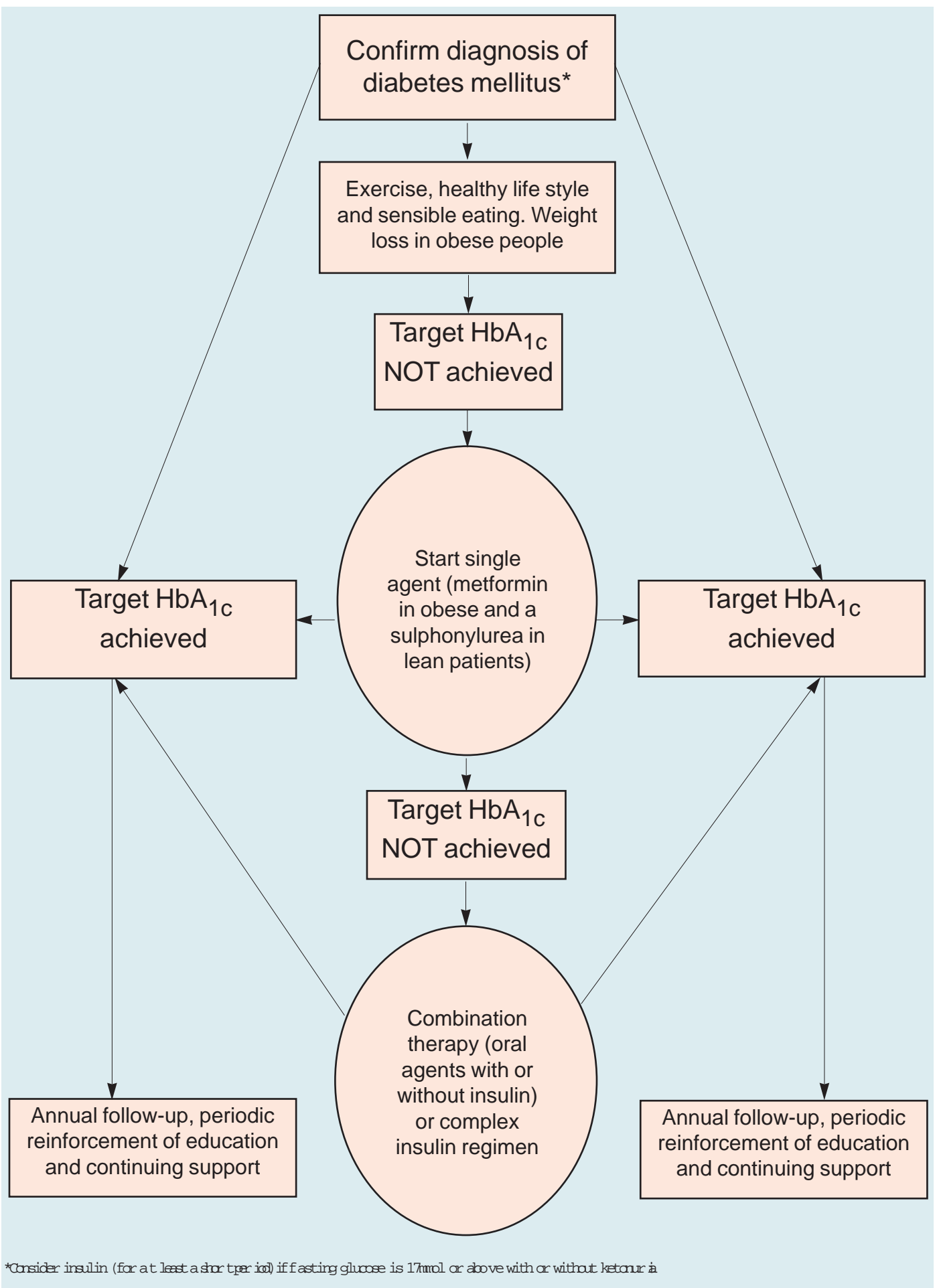


Figure 6: Treatment algorithm for type 2 DM

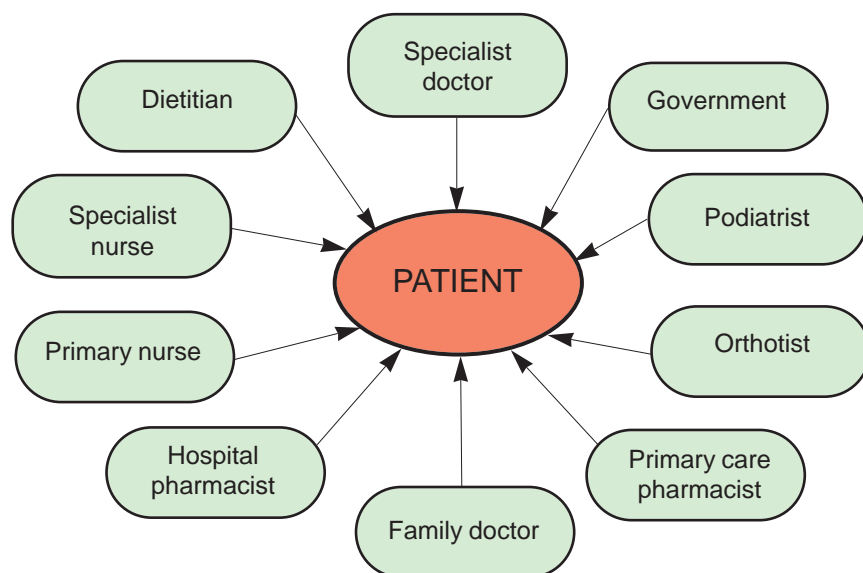


Figure 7: Multidisciplinary approach to care in type 2 DM

shown encouraging results in reducing insulin resistance in the liver.²³

Cholecystokinin-8 is a gut hormone and a neuropeptide which, when infused in normal healthy volunteers, showed insulinotropic action, thus offering some hope for the future.²⁴

Glucagon-like peptide-1 has been shown to regulate transcription factor in insulin-producing cells, which might have a role in the treatment of type 2 DM in the future.²⁵ Continuous subcutaneous infusion in patients with type 2 DM lowered fasting and postprandial glucose and appetite.²⁶

A longer-acting insulin analogue undergoing trial is insulin, glargine (HOE 901). At the 21st position of the A-chain, glycine is replaced by asparagine and two molecules of arginine are attached to the amino terminal of the B chain. This has been claimed to be associated with fewer episodes of hypoglycaemia compared with once or twice daily injections of intermediate-acting human insulin.²⁷ It also has smoother metabolic effects.²⁸

Exogenous insulin inevitably produces peripheral hyperinsulinaemia as its administration is in the systemic circulation as opposed to the endogenous insulin secretion with a high portal versus systemic concentration. To address this issue a new hepatoselective insulin analogue (B₁-T₄-Ins) is being investigated to achieve euglycaemia without peripheral hyperinsulinaemia. This analogue has the capacity to bind to insulin receptors as well as thyroid hormone binding protein.

The size of the basal complex confers relative hepato-selectivity compared with insulin by inhibiting access to the peripheral tissue but not to the more exposed hepatocytes. The initial results of the investigation are encouraging.²⁹

SPECIFIC SITUATIONS

Two specific situations in which a strict glycaemic control with the use of insulin is beneficial are acute myocardial infarction and pregnancy.

The landmark DiGAMi trial (Diabetes mellitus insulin glucose infusion in acute myocardial infarction) has shown a clear benefit: only nine patients need to be treated using the DiGAMi protocol with insulin to prevent one death. This is by far the most attractive way to save life in patients with acute myocardial infarction.³⁰

This study has changed our practice significantly, although cost is an important consideration in implementing the protocol. In an audit carried out by us, when compared with pre-DiGAMi management, although a reduction in mortality has not been observed, the rate of re-admissions with unstable angina and of cardiac interventions were reduced.³¹

In patients with type 2 DM planning a pregnancy, insulin should be started before conception to achieve good control at the time of conception. The preferred insulin regimen is basal bolus insulin. The dose needs frequent increments, particularly in the third trimester of the pregnancy. Concerns were raised about the safety of using insulin lispro in pregnancy after two case reports of congenital anomalies.³² Following this, in some centres, patients were advised to stop this insulin before or at confirmation of pregnancy. Again, in our survey involving a large number of patients using insulin lispro in pregnancy this was shown not to be the case.³³ Also, it is clear now that the type of insulin used is unrelated to the progression of retinopathy during pregnancy.³⁴

MULTIDISCIPLINARY CARE

Probably no other disease in modern medicine needs more of a multidisciplinary approach than DM. Teamwork is the key for success in achieving good control and in the follow-up of the patients (see Figure 7). Each and every team member is equally important.

Also, there should be a designated team leader who can communicate well with the members of the team and the patients and

Table: Oral hypoglycaemic agents available in the United Kingdom

Group	Name	Maximum daily dose (mg)	Frequency per day	Primary route of elimination
Sulphonylureas	Chlorpropamide	500	1	Renal
	Glibenclamide	15	1	Renal/faecal
	Gliclazide	360	2	Renal
	Glimepiride	6	1	Renal/faecal
	Glipizide	20	1-2	Renal
	Gliquidone	60	2-3	Renal
	Tolbutamide	2000	2-4	Renal
	Biguanides	Metformin	3000	2-3
Thiazolidinediones	Rosiglitazone	8	2	Renal
	Pioglitazone	30	1	Renal/faecal
α-glucosidase inhibitor	Acarbose	600	2-3	Faecal

take a comprehensive decision. Usually, this role is performed by the diabetic physician.

CONCLUSION

Correction of hyperglycaemia is a vital objective in patients with type 2 DM, but therapy should also be directed at reducing obesity, hypertension³⁵ and dyslipidaemia. In those with obese type 2 DM, weight reduction can potentiate improvement of all the metabolic complications. Unfortunately, one of the most frustrating challenges in clinical medicine is the often futile attempt to change the lifestyle of people in affluent societies. As a result, most patients are prescribed drugs for high blood sugar, hyperlipidaemia and blood pressure, despite the persistence of dietary indiscretion, sedentary lifestyles and obesity. As expected, the therapeutic effect of conventional treatment becomes unsatisfactory and at times dismal. For this reason, a systematic and careful approach is needed in patients with type 2 DM. Most importantly, patients should be at the centre of decision-making and medicines should be prescribed in concordance with the patients.

REFERENCES

1. Sharma SC, Bhattacharyya A. Diabetes ketoacidosis in non-insulin dependent diabetes mellitus. *J R Soc Med* 1998;91:34-5.
2. The Diabetes Control and Complication Trial (DCCT) research group. Effect of intensive diabetes management on macrovascular events and risk factors in the diabetes control and complications trial. *Am J Cardiol* 1995;75:894-903.
3. UK Prospective Diabetic Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.
4. Davidson MB. Importance of control of type 2 diabetes mellitus. *Endocr Pract* 1997;3:145-52.
5. Klein R, Klein BE, Moss SE. Is obesity related to microvascular and macrovascular complications in diabetes? The Wisconsin epidemiologic study of diabetic retinopathy. *Arch Intern Med* 1997;157:650-6.
6. Morisaki N, Watanabe S, Kobayashi J, Kanzaki T, Takahashi K, Yokote K et al. Diabetic control and progression of retinopathy in elderly patients: five-year follow up study. *J Am Geriatr Soc* 1994;42:142-5.
7. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with noninsulin-dependent diabetes mellitus: a randomised prospective 6-year study. *Diabetes Res Clin Pract* 1995;28:103-17.
8. Anderson DK. Long-term glycaemic control related to mortality in type 2 DM. *Diabetes Care* 1995;18:1534-43.
9. Brown DF, Jackson TW. Diabetes "tight control" in a comprehensive treatment plan. *Geriatrics* 1994;49:24-9.
10. Albu J, Konnarides C, Pi-Sunyer FX. Weight control: metabolic and cardiovascular effects. *Diabetes Rev* 1995;3:335-47.
11. Schneider SH, Ruderman NB. Exercise and NIDDM. *Diabetes Care* 1990;13:785-9.
12. University Group Diabetes Program. Effects of hypoglycaemic agents on vascular complications in patients with diabetes: 2. Mortality results. *Diabetes* 1970;19(suppl 2):785 - 830.
13. UK Prospective Diabetes Study. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854-65.
14. Davidson MB, Peters AL. An overview of metformin in the treatment of type 2 DM. *Am J Med* 1997;102:99-109.
15. Owens DR, Ismail I, Luzio SD, Bayer T. Increased prandial insulin secretion after administration of a single preprandial oral dose of repaglinide in patients with type 2 diabetes. *Diabetes Care* 2000;23:518-23.
16. Spencer CM, Markham A. Troglitazone. *Drugs* 1997;54:89-101.
17. King AB. A comparison in a clinical setting of the efficacy and side effects of three thiazolidinediones. *Diabetes Care* 2000;23:557.
18. Bhattacharyya A, Tymms DJ. Life-threatening hypoglycaemia in a patient with type I diabetes mellitus. *Practical Diabetes Int* 1999;16:90-2.
19. Raskin P, Guthrie RA, Leiter L, Riis A, Joranovic L. Use of insulin aspart, a fast-acting insulin analogue, as the meal time insulin in the management of patients with type I diabetes. *Diabetes Care* 2000;23:583-8.
20. Gruessner A, Sutherland DER. Pancreas transplants for United States (US) and non-US cases reported to the International Pancreas Transplant Registry and to the United Network for Organ Sharing (UNOS). In *Clinical Transplants*. Cecka M, Terasak P, editors. Los Angeles: UCLA Tissue Typing Laboratory; 1998.
21. Ikenoue T, Akiyoshi M, Fujitani S, Okazaki K, Kondo N, Maki T. Hypoglycaemic and insulinotropic effects of a novel oral antidiabetic agent, (-)-N-(trans-4-isopropyl cyclohexanecarbonyl)-D-phenylalanine (A-4166). *Br J Pharmacol* 1997;120:137-45.
22. Hirschberg Y, Karara AH, Pietri AO, McLeod JF. Improved control of mealtime glucose excursion with co-administration of nateglinide and metformin. *Diabetes Care* 2000;23:349-53.
23. Malamas MS, Sredy J, Gunawan I, Mihan B, Sawicki DR, Seestaller L et al. New azolidinediones as inhibitors of protein tyrosine phosphatase 1B with antihyperglycaemic properties. *J Med Chem* 2000;43:995-1010.
24. Ahren B, Holst JJ, Efendic S. Antidiabetogenic action of cholecystokinin-8 in type 2 diabetes. *J Clin Endocrinol Metab* 2000;85:1043-8.
25. Wang X, Cahill CM, Pineyro MA, Zhou J, Doyle ME, Egan JM. Glucagon-like peptide-1 regulates the beta cell transcription factor, PDX-1, in insulinoma cells. *Endocrinology* 1999;140:4904-7.
26. Toft-Nielsen MB, Madsbad S, Holst JJ. Continuous subcutaneous infusion of glucagon-like peptide-1 lowers plasma glucose and reduces appetite in type 2 diabetic patients. *Diabetes Care* 1999;22:1137-43.
27. Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycaemia with insulin glargine in intensive insulin therapy for type 1 diabetes. *Diabetes Care* 2000;23:639-43.
28. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analogue insulin glargine (HOE 901) in comparison with those of NPH insulin and placebo. *Diabetes Care* 2000;23:644-9.
29. Shojaee-Moradie F, Powrie JK, Sundermann E, Spring MW, Schuttler A, Brandenburg D et al. Novel hepatoselective insulin analogue. *Diabetes Care* 2000;23:1124-9.
30. Malmberg K. Prospective randomised study of intensive insulin treatment on long-term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ* 1997;314:1512-5.
31. Bhattacharyya A, Vice PA. DIGAMI in a district general hospital in the UK: influence, implementation and outcome. *Diabetes Today* 2000;3:120-3.
32. Diamond TD, Korman N. Possible foetal effect of insulin lispro. *N Engl J Med* 1997;337:1009-10.
33. Bhattacharyya A, Brown S, Hughes SM, Vice PA. Lispro and regular insulin in pregnancy: a comparison. *Diabetes* 2000;49:P1869.
34. Bhattacharyya A, Vice PA. Insulin lispro, pregnancy and retinopathy. *Diabetes Care* 1999;22:2101-2.
35. UK Prospective Diabetes Study. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). *BMJ* 1998;317:703-13.