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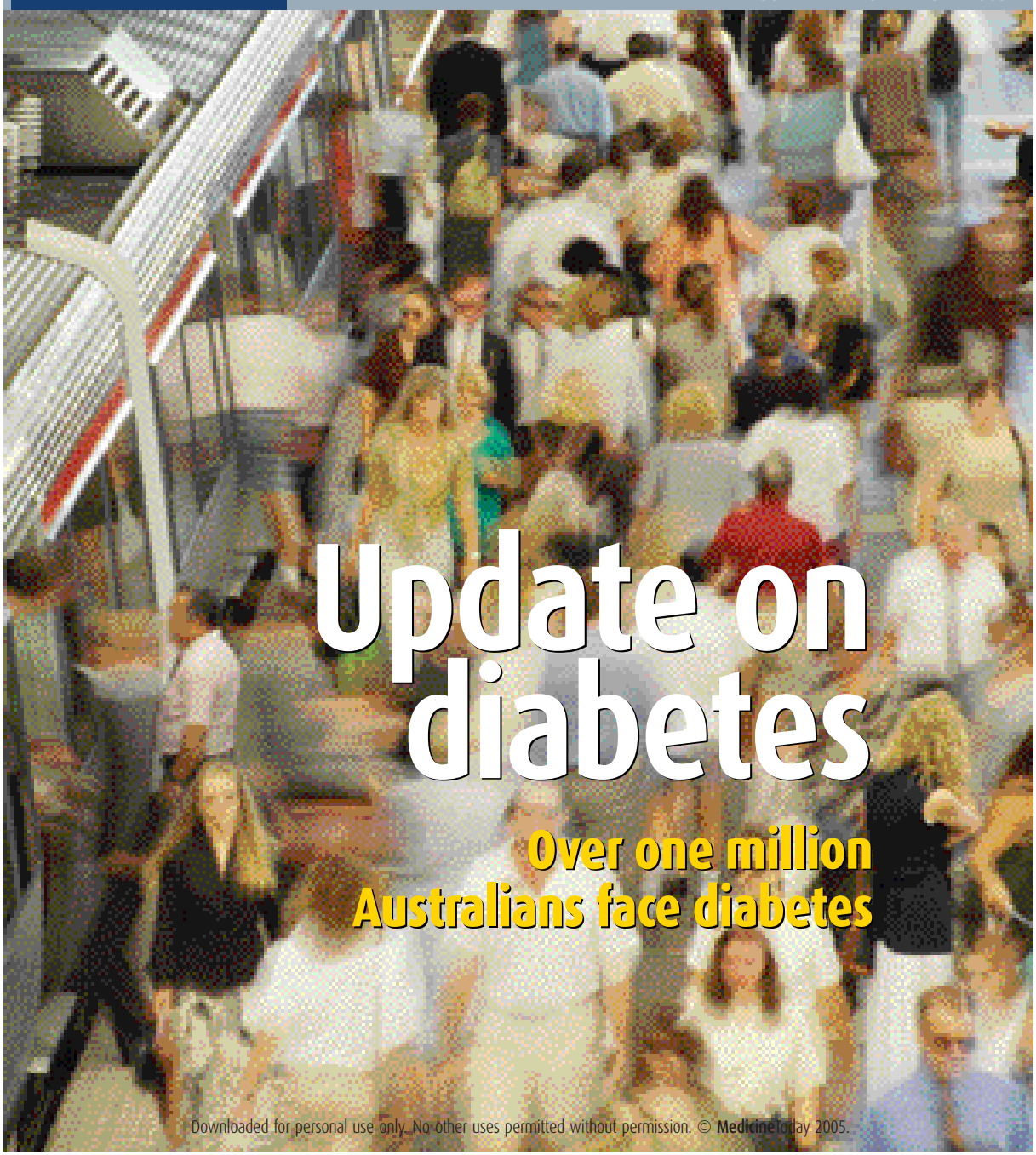
MedicineToday
The Peer Reviewed Journal of Clinical Practice

SUPPLEMENT SEPTEMBER 2005



Update on diabetes

Over one million Australians face diabetes

UPDATE ON DIABETES
September 2005

ISSN 1443-430X

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Opinions expressed are those of the original authors and do not necessarily reflect those of the Editors, the Editorial Board or the Publisher.
Medicine Today is published on the 8th day of each month by Medicine Today Pty Ltd (ACN 089 519 264).

Printed by Hannanprint Victoria,
504 Princes Highway,
Noble Park, VIC 3174.

SUBSCRIPTION RATES
Add 10% GST to all listed prices.
Standard $165.00 per year,
$285.00 for two years
Medical students $70.00 per year,
$120.00 for two years
NZ, PNG, Fiji $198.00
Asia $240.00
Britain, Europe, USA $290.00
Back issues $14.00 each plus postage, prepaid
($7.00 to medical students)

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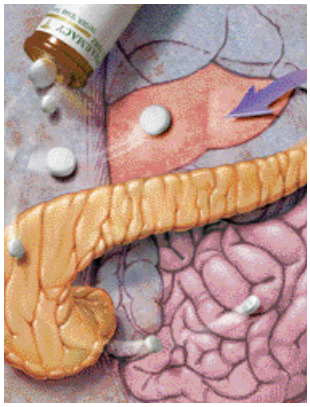

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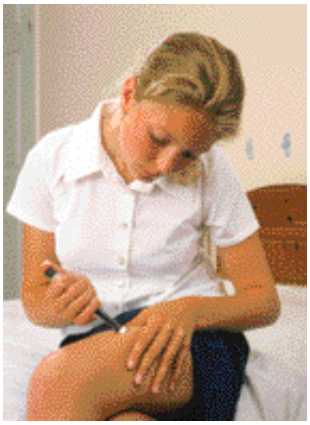

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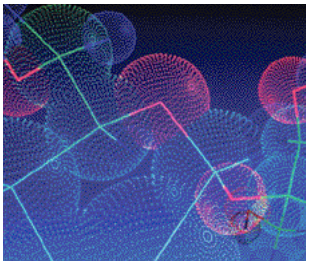

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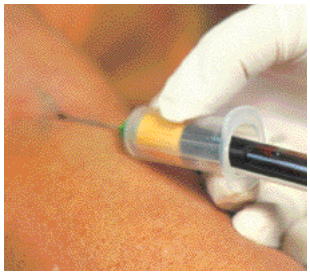

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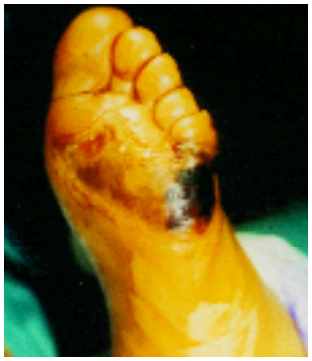

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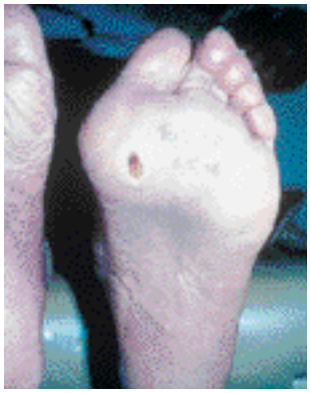

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Diabetes in 2005
what's the scoresheet?

With more than one million Australians estimated to have diabetes, Dr Phillips and Dr Aloizos assess the wins and the losses.

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The wins

Diabetes is on the health agenda in Australia for the Commonwealth and State Governments, the community and the healthcare system. Diabetes is a national health priority, with a national diabetes strategy. There is now greater public awareness that diabetes is not 'just a touch of sugar' but a serious health problem, and the current message being promoted is that diabetes is replacing HIV infection and AIDS as the major threat to world health as we proceed through the 21st century. Start talking about chronic disease, and diabetes will be the lead chronic disease. And we now have specific services available for diabetes through the Chronic Disease Management items and the MedicarePlus Scheme for allied health and nursing services.

We also have new medications and new ways of using old ones to tackle diabetes all along its continuum. Moreover, there is the promise of curing type 1 diabetes with islet substitutes and designing magic pills to target the basic metabolic abnormality of type 2 diabetes. This is pretty good so far.

The losses

Diabetes is still a 'big ticket' item for the economy, the healthcare system and individuals living with diabetes. The direct healthcare costs for someone with diabetes are three times higher, and are on the rise. Think of the costs of end-stage renal failure programs, the costs of cardiovascular intervention, the costs of foot problems (the theme this year of World Diabetes Day on 14 November). The daily management of diabetes isn't cheap either – the costs of self-monitoring, medication, devices and insulin quickly add up.

If these direct costs are of concern to the accountants, the indirect costs are often a nightmare for affected individuals. Quality of life starts declining before diabetes is diagnosed, and keeps on going down. Anxiety and depression are much more common in people with diabetes, even before complications set in. Many people still die prematurely, or lose their sight and/or their limbs, finish up on dialysis or are incapacitated by heart failure or strokes. The 'Big D' can be pretty nasty.

What's the balance?

Are you an optimist – a glass-half-full person? We are making progress, and the immediate future offers exciting promise. The pessimist – the glass-half-empty person – will point out that every year we get fatter and less fit, and that we are getting fatter faster. The baby boomers of 1946 to 1964 are hitting prime time for diabetes. How can we tackle diabetes when we can't control the 'F word' drivers – Forty, Fat and Family history?

You decide. This Medicine Today supplement provides a tempting smorgasbord on the 'Big D', but don't overindulge! MT

Individualising initial therapy for hyperglycaemia in type 2 diabetes

The clinical scenarios in which type 2 diabetes may be diagnosed vary markedly. Tailoring initial therapy for glycaemic control to each individual forms an essential part of clinical practice.

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Glycaemic control in patients with newly diagnosed type 2 diabetes is an important issue. Initial therapy is usually dictated by clinical presentation, which can be broadly divided into three types:

- nonketotic hyperosmolar coma (rare), a medical emergency caused by severe hyperglycaemia
- symptomatic hyperglycaemia (much more common), which can be quite marked and needs to be treated promptly
- asymptomatic hyperglycaemia (increasingly common), for which there is now clear evidence that glycaemic control helps prevent long term diabetes-related complications.

This article describes an approach to managing hyperglycaemia in type 2 diabetes in the early days, weeks and months after initial diagnosis. A summary is presented in Table 1.

Hyperosmolar coma at diagnosis

A patient who is not known to have type 2 diabetes may present in hyperosmolar coma, with progressive obtundation, polyuria and dehydration. Information from a family member usually helps in making the diagnosis because symptoms are generally present in the preceding days and weeks. A precipitating factor is usually present, such as urinary tract infection, recent myocardial infarct or (occasionally) recent commencement of anti-inflammatory therapy such as supraphysiological doses of corticosteroids. Recent excess intake of sugary liquid may also be a contributor to the

IN SUMMARY

- **Australian surveys have shown that 50% of people with type 2 diabetes are undiagnosed.**
- **Patients who are not known to have type 2 diabetes but present in hyperosmolar coma require hospitalisation with rehydration and insulin therapy, usually by a controlled intravenous infusion.**
- **The oral hypoglycaemic agent generally recommended for type 2 diabetes is metformin, which has been shown to improve total and cardiovascular mortality in people who are overweight or obese.**
- **Approaches to initial therapy in type 2 diabetes to achieve control of hyperglycaemia – lifestyle intervention and medication – are complementary. Most people with type 2 diabetes are overweight or obese at diagnosis, and aiming for 7% of bodyweight loss can result in major improvements in glycaemic control.**
- **In patients who are diagnosed with diabetes but are asymptomatic, prevention of long term complications of diabetes is the goal.**

hyperglycaemia. Formal plasma glucose testing usually shows a level between 40 and 70 mmol/L, and significant ketonuria is absent.

These patients require rehydration and insulin therapy, usually by a controlled intravenous infusion in a hospital setting. Very close inpatient monitoring is needed to reduce the plasma glucose in a controlled manner and thus help to avoid cerebral oedema that may occur if serum osmolality changes and fluid shifts are too rapid. It is reasonable to aim for a maximum rate of glucose reduction of 4 to 5 mmol/L per hour. Potassium replacement is commonly necessary, along with treatment for the precipitating condition. It may be possible to switch the patient from insulin therapy to oral hypoglycaemic agents prior to discharge.

All patients with hyperosmolar coma at diagnosis will need comprehensive education about diabetes, preferably from an accredited diabetes educator, and advice from a dietitian. This is generally best arranged in an outpatient ambulatory setting after the patient has returned home and is more likely to be able to absorb the information.

Symptomatic hyperglycaemia at diagnosis

Typical symptoms of hyperglycaemia include polyuria, polydipsia and polyphagia. Recent weight loss may be reported – even in overweight or obese patients – and vaginal candidiasis, fungal and bacterial skin infections or blurred vision may be present. Less commonly, new or increasing urinary incontinence occurs in elderly patients and is associated with an underlying bladder abnormality and urinary tract sepsis. Cutaneous wounds, if present, may heal poorly.

Symptom control

For patients with symptomatic hyperglycaemia, there is considerable debate about whether oral medication or insulin should be commenced at the time of diagnosis or whether lifestyle intervention alone is sufficient. I recommend both lifestyle changes and oral hypoglycaemic therapy, particularly when random blood glucose levels are higher than 10 mmol/L, because such combined treatment will result in more rapid resolution of symptoms.

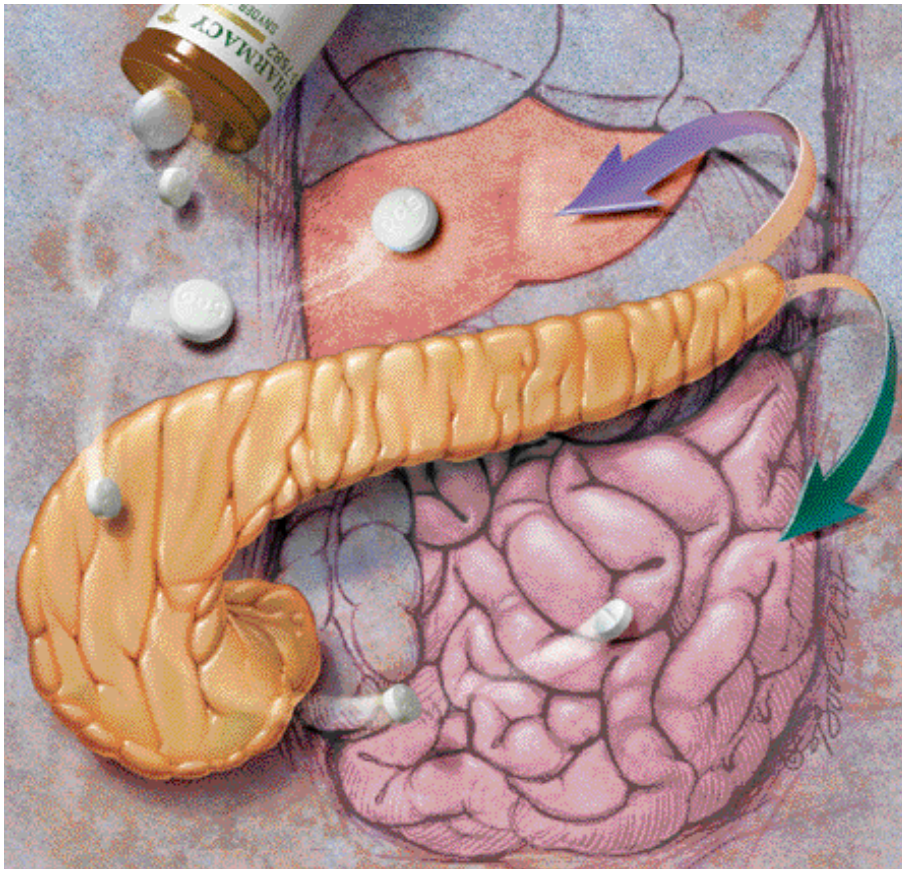

Figure. Oral medications in diabetes have different time courses of action and different side effect profiles, which help to optimise their application to individual patients with type 2 diabetes.

Table 1. A general approach to selecting initial therapy in patients with type 2 diabetes

Initial therapy	Presentation at diagnosis of type 2 diabetes		
	Hyperosmolar coma	Symptomatic hyperglycaemia†	Asymptomatic hyperglycaemia
Insulin therapy	Yes	Not usually	No
Oral hypoglycaemic therapy	Not initially, but possibly after acute treatment	Yes, usually metformin and commonly with a sulfonylurea	Yes, usually metformin as monotherapy if lifestyle improvements alone are inadequate
Lifestyle modification	Not initially, but after acute treatment completed	Yes	Yes

* Actual management will depend on the degree of hyperglycaemia when diabetes is diagnosed. † Nonemergency hyperglycaemia.

Table 2. Oral medication options in symptomatic hyperglycaemia*

Metformin
- Medication with the best evidence base for preventing macrovascular complications in diabetes
- Dose needs to be titrated upwards slowly, so it is not the most useful agent for patients presenting with marked hyperglycaemia

Sulfonylureas
- Most efficient class of oral therapies for promptly reducing hyperglycaemia and related symptoms
- Hypoglycaemia is most common with agents in this class and needs to be prevented and managed

Thiazolidinediones
- Best class of agents for improving blood glucose levels and reducing insulin resistance in combination
- A significant period of time is required for maximal hypoglycaemic effect (usually 6 to 8 weeks)
- Weight gain and lower limb oedema are the major side effects
- Contraindicated in heart failure
- Not available on the PBS as monotherapy

Acarbose
- A relatively weak hypoglycaemic agent, but as monotherapy does not cause hypoglycaemia
- The need to titrate up the dose slowly limits its use in treating patients with symptomatic hyperglycaemia

Glitinides
- Can be used in place of sulfonylureas, although somewhat less potent
- Hypoglycaemia is common with agents in this class and needs to be prevented and managed
- Expensive, not available on the PBS

Orlistat
- Useful for reducing weight in obese and overweight patients, and thus improving glycaemia
- Most useful in people who consume excess dietary fat
- Gastrointestinal side effects may limit tolerability
- Not registered for treating type 2 diabetes
- Expensive, not available on the PBS

Sibutramine
- Useful for reducing weight in obese and overweight patients, and thus improving glycaemia
- Most useful in people who consume excess dietary carbohydrate
- Hypertension exacerbation side effects may limit usefulness
- Not registered for treating type 2 diabetes
- Expensive, not available on the PBS

* Nonemergency hyperglycaemia.

Oral hypoglycaemic therapy

The oral hypoglycaemic agent generally recommended for type 2 diabetes is metformin, as monotherapy, which has been shown to improve total and cardiovascular mortality in people who are overweight or obese. In the acute setting, however, metformin can cause gastrointestinal effects that limit the starting dose that can be used, even with food. A useful alternative is a mid-range dose of a sulfonylurea (alone or with low dose metformin), such as:
- gliclazide, modified release (Diamicron MR), 30 or 60 mg once daily, or gliclazide (Diamicron, Glyade, Mellihexal, Nidem), 40 to 80 mg twice daily
- glimepiride (Amaryl, Dimirel), 2 mg once daily
- glipizide (Melizide, Minidiab), 10 mg twice daily
- glibenclamide (Daonil, Glimel), 5 mg twice daily.

In a patient who is overweight with type 2 diabetes, I generally simultaneously commence low dose metformin therapy, such as 250 mg twice daily initially and increasing to 500 mg twice daily in the second week.

Symptoms of hyperglycaemia usually abate over subsequent days and weeks. During this time, patients should receive education about diabetes and the benefits of tailored dietary modifications and structured physical activity. They should also learn to use a blood glucose meter and to focus particularly on the pre-breakfast reading, which is less affected by meals and provides a useful indication of changes in basal overnight glucose levels.

Although there are other oral hypoglycaemic agents that can be used instead of metformin to treat type 2 diabetes, each has properties that make it less desirable as primary treatment in the setting of symptomatic hyperglycaemia (Table 2). Glitinides such as repaglinide (NovoNorm) act like sulfonylureas and could be used in place of those agents, but their high cost is often limiting and they are often reserved for patients with sulfonylurea allergy.

Titrating therapy

The dose of oral hypoglycaemic medication should be titrated according to symptoms and blood glucose levels on a weekly basis. Commonly, the pre-breakfast blood glucose level begins to fall under 10 mmol/L over succeeding days and particularly weeks, and the patient begins to feel better and less lethargic. In these cases, I usually increase the dose of metformin to a total daily dose of 2.0 to 2.5 g (if tolerated) because this amount has been shown to prevent mortality in patients with type 2 diabetes, and reduce the dose of sulfonylurea by, say, 50%. When symptomatic hyperglycaemia is resolving, it is appropriate to set longer term glycaemic targets.

Nonresponding cases

Occasionally, symptomatic hyperglycaemia in patients with newly diagnosed type 2 diabetes persists and may even worsen, and hyperglycaemia may not settle. In this case, the main options are to:

- maximise the dose of sulfonylurea and monitor response for 1 to 2 weeks, or
- commence insulin therapy.

Particularly close patient monitoring is necessary, and urinary tract infection or other forms of sepsis or inflammation should carefully be excluded. I usually commence twice daily, premixed insulin therapy because insulin deficiency is the primary reason a response is not occurring to the sulfonylurea. The starting dose is affected by the patient's current blood glucose readings, bodyweight and degree of liver dysfunction, which reflect fatty liver and insulin resistance. Commonly used preparations are:

- Humulin 30/70 (neutral insulin 30%, isophane insulin suspension 70%)
- Mixtard 30/70 (neutral insulin 30%, isophane insulin suspension 70%)
- NovoMix 30 (insulin aspart 30%, insulin aspart in protamine suspension 70%)
- Humalog Mix25 (insulin lispro 25%, insulin lispro in protamine suspension 75%).

Late onset autoimmune diabetes

Occasionally, adults present with clinical features that are more suggestive of type 1 diabetes than the usual type 2. Such patients are commonly not overweight (and may be underweight) and often have symptomatic hyperglycaemia with asthenic body habitus. Ketones may be elevated on urine or blood testing. Autoantibody testing for glutamic acid decarboxylase and islet cell antibody is frequently positive.

This type of diabetes is due to insulin deficiency, and insulin therapy is usually needed from the outset. Oral agents will generally not be effective. The main therapeutic options are a twice daily, double mix regimen (e.g. a combined fixed ratio of rapid acting and intermediate acting insulin) or a basal bolus regimen (e.g. intermediate acting basal insulin, once or twice daily, in combination with rapid acting insulin at each main meal). The latter schedule provides the greatest flexibility in self-management in the longer term, but it is somewhat more demanding.

Secondary diabetes

Insulin therapy may be indicated soon after diagnosis in patients who have developed diabetes because of chronic pancreatic insufficiency or cystic fibrosis. The primary problem is major insulin deficiency and can only be addressed by insulin therapy.

Insulin is often required soon after diagnosis in patients who have developed diabetes after commencing supraphysiological doses of corticosteroids for an inflammatory condition. In these cases, blood glucose is prone to become elevated late in the day, and an insulin schedule targeting this time is needed. Oral agents do not generally provide adequate control.

Antipsychotic therapy and diabetes

Early insulin therapy may be necessary in a patient taking antipsychotic therapy. The atypical antipsychotic agents ending in 'ine' are especially likely to cause weight gain and diabetes. The rate of weight gain tends to be problematic, and patients taking such medication frequently have schizophrenia, which is likely to create challenges in modifying lifestyle as part of diabetes management. Oral hypoglycaemic agents are often inadequate in managing symptomatic hyperglycaemia, and insulin therapy is often the only effective way to achieve some control.

Asymptomatic hyperglycaemia at diagnosis

With the increasing use of screening tests, many patients who are being diagnosed with diabetes are asymptomatic. In such cases, prevention of long term complications of diabetes is the goal. Prospective studies indicate that for each 1% decrease in glycosylated haemoglobin (HbA_{1c}), there is an average 37% reduction in the risk of microvascular complications (e.g. diabetic neuropathy, nephropathy, retinopathy) and a lesser reduction in macrovascular complications (such as a 16% reduction for myocardial infarct). It takes more than five years (and more like 8 to 15 years) for most patients to derive such benefit from tight glycaemic control.

Glycaemic targets

Commonly described longer term glycaemic targets in patients who have type 2 diabetes are a HbA_{1c} of less than 7.0%, with an average fasting blood glucose level under 6.5 mmol/L and 2-hour postprandial level under 10 mmol/L. However, these targets should be individualised. For example, a middle-aged person with recently diagnosed asymptomatic hyperglycaemia who is otherwise well should have a tight glycaemic target as close to normal as possible, including a HbA_{1c} of 6.0 to 6.5%. However, for an institutionalised elderly person who is doubly incontinent with dementia, it may be quite proper to not have a HbA_{1c} target and to aim for a broader range blood glucose level, between 5 and 15 mmol/L, to help avoid symptoms or hyper- and hypoglycaemia.

Some patients become highly motivated to modify their lifestyle when their diabetes is diagnosed. In those who make such changes, oral hypoglycaemic therapy may not be required – indeed, up to a 2% reduction in HbA_{1c} can be achieved with weight loss and appropriate exercise. In those who need to make major lifestyle changes but are unable or unprepared to do so, oral hypoglycaemic therapy is appropriate – even in those who are asymptomatic of hyperglycaemia. In patients who already have an appropriate diet and exercise program, oral hypoglycaemic therapy may also be required.

Lifestyle intervention

Most people with type 2 diabetes are overweight or obese at diagnosis. Aiming for bodyweight loss of 7% can result in major improvements in glycaemic control. To help achieve this, reduced total caloric intake and regular physical activity are both desirable.

It is important to focus on reducing the total number of calories consumed, rather than being overly concerned about the type of food, such as fat, protein or carbohydrate. Very low carbohydrate diets are associated with more rapid weight loss over initial months, but they are difficult to sustain and no more effective than low-fat equicaloric diets over a 12-month period. Weight loss agents such as orlistat (Xenical) and sibutramine (Reductil) may be of use in helping patients achieve and maintain weight loss.

Ideally, the duration and frequency of moderate exercise should be gradually increased to at least 60 minutes on most days, rather than the recommended 30 to 40 minutes three to four times per week for cardiovascular fitness. The former amount of physical activity, in combination with vigilance in caloric intake, will be of greater help in achieving and maintaining weight loss.

In patients who are able to lose weight, it is important to be aware that physiological and psychological factors act against maintaining the reduced weight. About 95% of people who deliberately lose weight regain it within two years. It is useful to remind patients who have achieved weight loss that some is commonly regained after four months and that they will need to work hard to avoid weight gain. Oral agents may be needed to help achieve blood glucose targets.

Oral hypoglycaemic therapy

There are many therapeutic classes of agents used to achieve glycaemic targets in asymptomatic patients with type 2 diabetes. I prefer to use metformin in overweight or obese patients because data from the United Kingdom Prospective Diabetes Study (UKPDS) showed higher dose metformin can reduce mortality in such patients.[1] My preference is to progressively increase the dose to a maximal or near-maximal amount of 2 to 2.5 g daily, and to commence a second oral agent only if glycaemic targets are not being achieved.

In patients with type 2 diabetes who have normal weight, any agent as monotherapy can be used to help achieve the glycaemic target, such as a sulfonylurea, acarbose (Glucobay), pioglitazone (Actos) or rosiglitazone (Avandia), but PBS restrictions on thiazolidinediones limit their use. There is some early evidence that a thiazolidinedione may help preserve pancreatic beta cell function (thus potentially delaying the need for insulin) and most effectively target the insulin resistance/metabolic syndrome, but the lack of hard endpoint and longer term data means that these reasons cannot currently be used to justify these agents as the preferred monotherapy.

I commence dual oral hypoglycaemic therapy only when one agent alone has not been adequate in achieving glycaemic targets in combination with optimal lifestyle intervention. When dual therapy is commenced, one option is to use a combined preparation, such as metformin and glibenclamide (Glucovance), which will potentially reduce a patient's required number of tablets. This is important because patients with type 2 diabetes usually require many other medications.

Insulin therapy

The majority of patients with type 2 diabetes who are asymptomatic at the time of diagnosis will require insulin within 10 years because their pancreatic beta cell function will continue to fail. When this occurs, maintaining the oral hypoglycaemic therapy and commencing a longer acting insulin before bed is usually an adequate regimen.

Debate is ongoing about the value of home blood glucose monitoring in patients with type 2 diabetes. For patients taking insulin, this is clearly desirable. I recommend home monitoring in people with type 2 diabetes taking oral hypoglycaemic agents because it can help in determining the response and in maintaining a closer real-time watch on blood glucose than the HbA_{1c} (which, by definition, is a 'hindsight' test). If the blood glucose levels are near target, checking it only a few times each week prior to breakfast is desirable.

Avoiding hypoglycaemia

For patients who are taking hypoglycaemic medication, regular consumption of three main meals daily, each with some carbohydrate, is optimal to help prevent hypoglycaemia. In general, episodes of hypoglycaemia in patients with type 2 diabetes are mild and can be readily self-treated. Rarely, more severe cases with unconsciousness occur in patients treated with insulin and in those with acutely deteriorating renal impairment who are taking sulfonylureas excreted by the renal route (e.g. glibenclamide and glimepiride, which are also more prone to cause mild and severe hypoglycaemia than modified-release gliclazide). In comparison with sulfonylurea therapy, metformin and thiazolidinediones are much less likely as monotherapy to cause hypoglycaemia, but other side effects may limit their usefulness (e.g. gastrointestinal intolerance for metformin, and weight gain for

thiazolidinediones). The hypoglycaemic effects of thiazolidinediones take six weeks or more for full effectiveness in patients taking sulfonylureas, so hypoglycaemia may be delayed. If it occurs, reducing the sulfonylurea dose is most appropriate.

Diabetes complications

It is important to be aware that end-organ complications may be present at diagnosis, regardless of the severity of hyperglycaemia at presentation. Therefore, patients diagnosed with type 2 diabetes should be promptly screened for diabetic retinopathy, diabetic renal disease, and diabetic neuropathy, which, if detected, should be managed appropriately. A low threshold to investigate for ischaemic heart disease is also important, especially in patients with any suggestive symptoms or in those planning to increase physical activity from a sedentary base.

Final comments

The clinical context and severity of the hyperglycaemia at presentation of patients with type 2 diabetes will help guide appropriate therapy. Through combined use of lifestyle intervention and hypoglycaemic medication, symptoms of hyperglycaemia will be promptly resolved and long term glycaemic targets can be established and, in many cases, realised. MT

Reference

1. United Kingdom Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854-865.

DECLARATION OF INTEREST: Dr Twigg delivers lectures for the following companies on an ad-hoc basis: Alphapharm, GlaxoSmithKline, Novo Nordisk, Sanofi Aventis and Servier. He is a member of the national Advisory Board for Pfizer for Olmetec, and for GlaxoSmithKline, and is on an international advisory Board for Sanofi Aventis in the IDMPS clinical diabetes audit study.

When and how to start insulin therapy in type 2 diabetes

The initiation of insulin therapy is often one of the most difficult treatment decisions that patients with type 2 diabetes mellitus and their clinicians have to make. However, a delay in the initiation of this therapy, as well as a failure to recognise the chronic nature of type 2 diabetes, contribute to the excess morbidity and mortality of this disorder.

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In developed nations the prevalence of type 2 diabetes and disorders of impaired glucose tolerance continues to rise. The causes of this rise are largely related to lifestyle changes associated with decreased physical activity, increased obesity and increases in energy consumption. At a public health level, the great concern is the impact that this rise is having on the development of microvascular and macrovascular complications. Multiple strategies are needed to lessen the impact of this disorder on our health systems, including better:

- attempts at primary prevention
- identification of the disorder at earlier stages
- clinical management of the disorder in patients with established disease.

Several strategies have been used to improve the clinical management of diabetes, including the standardisation of clinical guidelines, the use of financial incentives to improve GP clinical behaviour and subsidies for diabetic patients, and the development of National Service Improvement Frameworks. Despite these measures, poor patterns of care persist and can be directly related to the development of complications of the disorder.[1]

Pathogenesis of type 2 diabetes

The pathogenesis of type 2 diabetes is reviewed elsewhere, but, briefly, the disorder reflects a combination of insulin resistance at the level of muscle and liver and impaired insulin secretion. In patients with type 2 diabetes, there is unequivocal evidence of hepatic resistance to insulin, verified by an

IN SUMMARY

- **Type 2 diabetes mellitus is a chronic and progressive disorder.**
- **Effective blood glucose control prevents or delays the development of complications of diabetes.**
- **Many patients with type 2 diabetes will need insulin therapy.**
- **Patients should have clear timelines set as they approach the need for insulin therapy.**
- **There are several simple ways to start insulin therapy as an outpatient, all of which are equally effective. The choice depends on multiple factors, including patient preference, cost, convenience, and response to therapy. Patients should receive education on how to administer insulin.**
- **Oral agents for diabetes are often used in combination with insulin therapy for patients with type 2 diabetes.**

impaired ability of insulin to suppress hepatic glucose production. This accounts for the increase in the fasting plasma glucose levels secondary to the accelerated gluconeogenesis. In response to a meal, the ability of endogenously secreted insulin to augment muscle glucose uptake is also markedly impaired, and muscle insulin resistance and impaired suppression of hepatic glucose production contribute about equally to the excessive postprandial increase in the plasma glucose level. Impaired insulin secretion also has a major role in the pathogenesis of glucose intolerance in type 2 diabetes.

Glycaemic control and complications

The reduction of blood glucose levels in patients with type 2 diabetes to close to normal while avoiding hypoglycaemia is one of the main therapeutic goals. Evidence indicates that tight metabolic control prevents the risk of microvascular complications and may contribute to a risk reduction of macrovascular complications.

The Diabetes Control and Complications Trial (DCCT) established that in type 1 diabetes mellitus, maintaining near-normal blood glucose levels with intensive insulin therapy could reduce the risk of microvascular complications. No glycaemic threshold for the development of long term microvascular complications was observed in this trial. Several other trials, including the United Kingdom Prospective Diabetes Study (UKPDS), have shown that the results of the DCCT can be extrapolated to patients with type 2 diabetes.[2-6]

The main findings of the UKPDS are summarised in the box on this page. Importantly, this study showed that:

- type 2 diabetes is a progressive disorder that can be treated initially with oral monotherapy but will eventually require the addition of other oral agents
- in many patients, insulin therapy will be needed to achieve targeted glycaemic levels.

The finding that improved glycaemic control, irrespective of the agent used, decreased the incidence of microvascular complications emphasises the need for constant reassessment of diabetic patients and appropriate adjustment of therapeutic regimens to maintain desired levels of glycaemic control.

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Therapeutic goals

Diabetes is a chronic, progressive metabolic disorder requiring the patient and clinician to work in partnership to achieve therapeutic targets.

The patient should adhere to instructions on:

- nutrition
- physical activity
- regular self-monitoring of blood glucose
- regular attendance to health professionals for assessment of glycaemic control and investigations to detect early signs of complications.

United Kingdom Prospective Diabetes Study: main findings[2,3]

- The development of microvascular complications was similarly reduced in patients with type 2 diabetes treated with sulfonylureas, insulin or metformin.
- There was no threshold for the reduction in HbA_{1c} and the development of microvascular complications (retinopathy, nephropathy and neuropathy).
- In patients with type 2 diabetes assigned to intensive therapy with sulfonylureas or insulin, the incidence of macrovascular complications (heart attacks, stroke and peripheral vascular disease) was not increased compared with that in the group assigned to conventional therapy.
- A decrease in macrovascular complications was seen only in patients with type 2 diabetes assigned to intensive therapy with metformin.
- Type 2 diabetes is a progressive disorder that can be treated initially with oral monotherapy but will eventually require the addition of other oral agents.
- In many patients with type 2 diabetes, insulin therapy will be needed to achieve targeted glycaemic levels.

Table 1. Therapeutic glucose targets for type 2 diabetes

Indicator	Ideal target	Acceptable target
Fasting blood glucose	<5.5	<7.0 mmol/L
Postprandial blood glucose	<7.0	<10.0 mmol/L
HbA_{1c}	<7.0%	<8.0%

These requirements are complex, and clinicians should not underestimate their burden on individuals.

Clinicians need to establish a system to provide:

- education
- regular surveillance for complications
- appropriate and timely advice on goals of therapy and changes to therapeutic regimens.

The main aim of therapy is to maintain blood glucose within a normal range (Table 1). The degree of blood glucose lowering is influenced by many factors, including patient age, the stage of the disorder, patient preference, and side effects of treatment, including hypoglycaemic risk.

Table 2. Treatment strategies for type 2 diabetes

First line

- Biguanides (metformin)

Second line

- Sulfonylureas (glibenclamide [Daonil, Glimel], gliclazide [Diamicron, Glyade, Mellihexal, Nidem], glimepiride [Amaryl, Dimirel], glipizide [Melizide, Minidiab])
- Meglitinide (repaglinide [NovoNorm])

Third line

- Thiazolidinediones (pioglitazone [Actos], rosiglitazone [Avandia])
- Acarbose (Glucobay)
- Insulin and insulin analogues
- Appetite suppressants

Treatment strategy

General approach

Although there are alternative approaches, the general consensus for patients with type 2 diabetes is to start medical treatment with an insulin sensitising agent such as metformin (first line; Table 2). If therapeutic goals are not achieved, this is followed by the addition of a sulfonylurea or meglitinide (second line). Second line agents may also be used alone if side effects or contraindications limit the use of metformin. Third line therapy is more complicated, and requires factors such as cost, complexity of the therapeutic regimen, and adverse effects to be taken into account when making decisions about the choice of drug. This choice includes the use of thiazolidinediones (glitazones), acarbose, appetite suppressants and insulin.

Generally, treatment to target is the aim of therapy, and doses should be titrated to achieve the targets listed in Table 1. If marked hyperglycaemia is present, two drugs may be needed at the outset; one may then be tapered and withdrawn as insulin sensitivity improves. Rarely, insulin may be needed at the outset if hyperglycaemia is complicated by a serious illness such as sepsis, coma or myocardial infarction.

Difficulties in starting insulin therapy

Initiation of insulin therapy is often one of the most difficult treatment decisions that patients with diabetes and clinicians have to make. For the patient the difficulty reflects a combination of factors, including the following:

- requirements for technical capability
- fear of injections
- longstanding misconceptions that complications will worsen
- a sense of failure and self-blame.

Often clinicians also feel uneasy about the decision to start a patient on insulin, usually because of inadequate knowledge and competence in starting and adjusting insulin therapy.

An important point to stress to patients at the time of diagnosis is that insulin may be needed, particularly if weight loss and increased physical activity cannot be achieved. However, the threat of insulin therapy should not be used as a motivator to improve adherence, given that many patients will ultimately need this therapy.

Clear timelines to start insulin should be established with patients if maximum doses of oral agents have been reached and metabolic targets not achieved. This will avoid protracted negotiations between doctors and patients, often delaying the inevitable. This timeline should not exceed three to six months. Referral of patients to a diabetes centre for education on the task of starting insulin should be considered.

Indications for starting insulin therapy

A general guide to the indications for starting insulin is given in Table 3. These indications should be adjusted for the elderly and patients with other disorders such as renal, hepatic or cardiac failure.[7,8] Specifically, in those with impaired renal failure (GFR <25 mL/min), the risk of lactic acidosis due to metformin is increased and the duration of action of sulfonylureas is prolonged.

In patients with poorer control (i.e. a greater degree of hyperglycaemia), the decision to start insulin therapy is easier and the benefits, particularly alleviation of symptoms such as thirst and polyuria, more easily demonstrable. Conversely, in those with HbA_{1c} values between 8 and 9%, the benefits are less apparent and thus the decision to start insulin more

Table 3. Indications for starting insulin therapy

- Fasting blood glucose level >10 mmol/L
- HbA_{1c} >9%
- Progressive weight loss
- Acute medical complications – e.g. sepsis, surgery, myocardial infarction
- Prepregnancy planning
- Intolerance of oral hypoglycaemic agents

difficult. Hayward and coworkers examined insulin therapy prescribed by general practice physicians.[9] In 1738 insulin-treated patients with type 2 diabetes, the mean decrease in HbA_{1c} at one year was 0.9%, but 60% of patients had a HbA_{1c} value that exceeded 8.0% at two years. However, patients whose baseline HbA_{1c} was 13% had a threefold greater decline in HbA_{1c} than those whose baseline HbA_{1c} was 9%. In other words, patients with the poorest baseline glycaemic control achieved greater HbA_{1c} reductions than those with moderate control.

Insulin therapy

For patients starting insulin treatment, two objectives need to be achieved:

- they must develop adequate skills and confidence to administer and adjust insulin doses
- their blood glucose levels need to be improved.

There is usually no urgency to reduce the blood glucose level rapidly, unless the patient has an acute medical complication such as sepsis or myocardial infarction. Generally, the adage start low and go slow is appropriate.

There are several approaches to starting insulin therapy in patients in whom oral therapy has failed. Essentially, three main regimens are used, as shown in Table 4 and discussed below, with variations on a theme. Oral agents are always continued in patients taking the basal-only insulin regimen, and often continued in those taking the two other regimens. The aim of this is to lessen the weight gain effect of insulin and reduce the total daily dose of insulin required to normalise blood glucose levels.

Weight gain and hypoglycaemia are common side effects of insulin therapy. Weight gain results from increased truncal fat and is closely related to the mean day-long plasma insulin level and daily insulin dose. In the UKPDS, insulin-treated obese patients with type 2 diabetes gained 4 kg more after 10 years than did patients assigned to diet therapy.

Basal insulin plus oral agent therapy

The effectiveness of bedtime insulin therapy in patients with type 2 diabetes in whom acceptable glycaemic control has not occurred with oral agents is well documented. In such patients, the elevated fasting plasma glucose level is caused by incomplete suppression of basal hepatic glucose production by sulfonylurea or

Table 4. Examples of insulin regimens for patients with type 2 diabetes

Regimen	Examples of insulin used	Timing of insulin dose
Basal	Intermediate acting • Isophane insulin (NPH: Humulin NPH, Hypurin Isophane, Protaphane) Long acting • Insulin detemir (Levemir) • Insulin glargine (Lantus)	Before bed
Mixed-split	Rapid or short acting plus intermediate acting • Insulin aspart 30%, insulin aspart protamine suspension 70% (NovoMix 30) • Insulin lispro 25%, insulin lispro protamine suspension 75% (Humalog Mix25) • Neutral insulin 30%, isophane insulin suspension 70% (Humulin 30/70, Mixtard 30/70)	Before evening meal and, if needed, before breakfast and lunch
Basal bolus	Rapid acting • Insulin aspart (NovoRapid) • Insulin lispro (Humalog) Short acting • Neutral insulin (Actrapid, Humulin R, Hypurin Neutral) Intermediate acting • Isophane insulin (NPH: Humulin NPH, Hypurin Isophane, Protaphane) Long acting • Insulin detemir (Levemir) • Insulin glargine (Lantus)	Rapid or short acting insulin before each major meal and long or intermediate acting insulin before bed

metformin; these agents are still working, but not producing the desired hypoglycaemic effect.

Bedtime insulin takes advantage of the differential sensitivity of hepatic compared with peripheral tissues to insulin.[10] Low doses of insulin effectively suppress hepatic glucose production and have a much smaller effect on stimulating muscle glucose uptake. By giving a modest dose of an intermediate acting or long acting insulin at bedtime, the elevated basal rate of hepatic glucose production can be reduced to normal.

In practice, this approach usually is achieved by administering either isophane insulin (NPH; Humulin NPH, Hypurin Isophane, Protaphane) or the new analogue insulin glargine (Lantus) just before bed at about 9 pm to 10 pm. Insulin glargine has a longer duration of action and a flatter time-action profile than insulin isophane. It reduces nocturnal hypoglycaemia by 58% in insulin-naive patients and 22% in patients previously treated with insulin.[7, 11-13] Insulin detemir (Levemir) is another long acting insulin analogue that has similar benefits to insulin glargine.[14,15] Neither of these long acting insulins is currently available on the PBS.

Insulin is usually administered via a pen delivery device. The starting dose is usually 10 to 12 units, but this should be adjusted downwards for those who are elderly, have renal failure or are of small body build. The dose is increased every three to four days and titrated to achieve a fasting blood sugar level in the acceptable range (see Table 1). Oral hypoglycaemic agents are maintained at previous doses at the outset, but as blood glucose levels fall, their frequency of administration should be reduced to twice daily, and the dose of sulfonylurea may be reduced.[16]

The addition of bedtime insulin to a sulfonylurea or metformin monotherapy is a safe and effective way to normalise the day-long glycaemic profile while minimising weight gain and reducing the insulin dose by 50 to 60% compared with a multiple-injection insulin regimen.

Mixed insulin and basal bolus regimens

Recent evidence has shown that postprandial hyperglycaemia is an important contributor to overall hyperglycaemia in patients with moderately controlled diabetes, whereas the contribution of fasting hyperglycaemia increases with worsening diabetes.[17] These findings have renewed interest in the use of mixed insulin regimens in the management of type 2 diabetes. This interest has been further stimulated with the availability of

rapid or short acting insulin analogues such as insulin lispro (Humalog) and insulin aspart (NovoRapid). Biphasic analogue insulin mixes have an advantage over basal insulin alone because they provide the rapid or short acting insulin analogue as the soluble component covering mealtime glycaemic needs.

Raskin and colleagues recently found that biphasic insulin aspart 70/30 appeared to be more effective than insulin glargine and a reasonable choice to initiate insulin therapy in insulin-naive subjects with type 2 diabetes who were not optimally controlled on oral therapy.[18] This applied particularly to subjects whose HbA_{1c} before insulin initiation was greater than 8.5%.

Similar principles to the commencement of bedtime basal insulin therapy apply to mixed insulin regimens. Start with a small amount, say 10 to 15 units, before the evening meal and increase the dose by 4 units every three to four days. Subsequently, a morning and sometimes a lunchtime dose may be required. The use of oral agents should be managed as discussed in the basal insulin section.

Not all authors agree that this approach is better than bedtime basal insulin. Janka and colleagues found that basal therapy with insulin glargine was slightly more efficacious than a fixed dose, mixed insulin regimen.[19] The difference between the Raskin and Janka studies is probably explained by the continued use of oral agents in the former study.

Basal bolus approaches are used less often but are certainly an option to consider in younger people with type 2 diabetes.[7]

In the future, inhaled insulin may also offer some benefit for these patients.[20]

As Davidson recently summarised, commenting on the Raskin and Janka studies, it probably does not matter what regimen is used as long as blood glucose levels are normalised while the risk of hypoglycaemia and patient inconvenience are minimised.[21]

Conclusion

The effective management of diabetes can significantly alter the course of long term microvascular and, to some extent, macrovascular complications, thus reducing morbidity and mortality. Clinical experience with intensive therapy for type 2 diabetes offers convincing evidence of the benefits of early insulin use in a regimen providing strict 24-hour control of blood glucose levels.

New insulin analogues offer significant advantages in terms of pharmacokinetics, resulting in improved postprandial glycaemic control (with insulin lispro and insulin aspart) and enhanced control of nocturnal hypoglycaemia (with insulin glargine and insulin detemir). MT

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DECLARATION OF INTEREST: None.

Insulin delivery devices
which one is best for your patient?

The range of insulin delivery devices may appear so varied as to mirror the range of insulins, but it is possible to navigate through the maze.

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Remember when there was only a handful of insulins and only syringes to administer them with? Life for those involved in diabetes management may have seemed easier then, but insulin pens and other delivery devices have revolutionised the way health professionals prescribe and patients administer insulin. The Diabetes Control and Complications Trial (DCCT) has shown that a basal bolus schedule can achieve glycaemic targets in type 1 diabetes,[1] and the United Kingdom Prospective Diabetes Study (UKPDS) has highlighted that insulin therapy is inevitable for most people with type 2 diabetes.[2] The availability of insulin pens allows health professionals to apply recommendations based on these studies in a practical manner. Commercial preparations of insulin that are currently available for use in pens are listed in Table 1.

There is no clear right or wrong choice of insulin delivery device; rather, appropriate selection requires consideration of the features of each pen (including the types of insulin that can be used with it) and individual patient needs. Do not discount the old fashioned syringe – it remains one of the most common methods for children to administer a combination of rapid and intermediate acting insulins because it provides dosing flexibility that cannot be equally attained using a twice daily premixed schedule. Elderly people living at home or in low care residential facilities may find one week's supply of insulin, predrawn into syringes and stored in their refrigerator, easier to administer. Not uncommonly, people with long-standing type 1 diabetes keep using syringes, a preference that often stems from negative experiences with earlier insulin pen models.

Insulin pens

Insulin pens can be divided into two categories: disposable and nondisposable. These are described in Tables 2 and 3, respectively.

Disposable pens have the immediate benefits of no assembly requirement (other than attachment and removal of a needle) and portability that often allows patients to store them at home, work or school, thus reducing the chance of missing doses. However, disposable pens are available for use with only a few types of insulin.

Nondisposable pens require a similar degree of assembly as fountain writing pens. They are

IN SUMMARY

- **The availability of insulin pens allows health professionals to apply recommendations based on the DCCT and UKPDS in a practical manner.**
- **Appropriate selection of an insulin pen (or pens) requires consideration of the features of each device and individual patient needs.**
- **Patients using insulin pens need to be aware of some important procedures, such as how to resuspend cloudy insulin before use and how to perform an 'air shot' to remove air bubbles and check needle placement.**
- **All patients with diabetes need to know how to treat hypoglycaemia initially with oral glucose.**

Table 1. Commercial insulin preparations for use in pens

Insulin analogues

Rapid acting

Humalog (insulin lispro) – cartridges

NovoRapid (insulin aspart) – cartridges, FlexPen

Long acting

Lantus (insulin glargine) – cartridges

Levemir (insulin detemir) – FlexPen

Biphasic

Humalog Mix25 (insulin lispro 25%, insulin lispro protamine suspension 75%) – cartridges

NovoMix 30 (insulin aspart 30%, insulin aspart protamine suspension 70%) – cartridges, FlexPen

Human insulins

Short acting

Actrapid (neutral insulin) – cartridges

Humulin R (neutral insulin) – cartridges

Intermediate acting

Humulin NPH (isophane insulin suspension) – cartridges

Protaphane (isophane insulin suspension) – cartridges, InnoLet, NovoLet

Biphasic

Humulin 30/70 (neutral insulin 30%, isophane insulin suspension 70%) – cartridges

Mixtard 20/80 (neutral insulin 20%, isophane insulin suspension 80%) – cartridges

Mixtard 30/70 (neutral insulin 30%, isophane insulin suspension 70%) – cartridges, InnoLet

Mixtard 50/50 (neutral insulin 50%, isophane insulin suspension 50%) – cartridges

available in a variety of colours, which can provide useful visual differentiation for an individual who is taking two or more types of insulin. For some patients, nondisposable pens appear more discreet in appearance. They are generally available free of charge from diabetes educators, endocrinologists and Diabetes Australia (an exception is Innovo, which costs around $70).

It is not uncommon for an individual administering multiple types of insulin to use a disposable pen for one and a nondisposable pen or syringe for another. Flexibility is important, and it may be necessary to change the delivery device if it becomes difficult or inappropriate for the individual to use.

Some insulin pen devices lend themselves to particular categories of patients. For example:

- Elderly or disabled patients are often better suited to the InnoLet device, which has a 'clock timer' appearance, appears familiar and requires minimal strength and dexterity to operate. This device is often more accepted by patients with type 2 diabetes commencing insulin therapy.
- Younger children and some adults who are highly sensitive to rapid or fast acting insulin and therefore require very precise dosing are suited to the NovoPen 3 Demi, which enables adjustment in increments of 0.5 unit. This pen may also be useful for people starting the new Dose Adjustment For Normal Eating (DAFNE) program, which involves intensive carbohydrate counting and may lead some patients to want to adjust their insulin doses in increments of 0.5 unit.
- Patients starting two different types of insulin may be suited to a nondisposable pen that may be used with both types so that they need to learn how to operate only one device.

Educating patients about insulin

When starting any patient on insulin or changing an insulin prescription, patient education is required. Those who administer insulin need specific information about the onset, peak and duration of their insulin if optimal glycaemic control is to be achieved. This is vital when considering the timing of insulin administration and eating, activity and blood glucose tests.

All patients with diabetes need to know how to treat hypoglycaemia initially with glucose. Carbohydrate foods that contain sucrose, fructose or lactose can take a considerable time to be digested into glucose and absorbed. Drinking 150 mL of Lucozade, which is formulated with glucose syrup, is one of the most rapid ways to raise the blood glucose level and reduces the need to overeat, which can cause profound hyperglycaemia.

Using insulin pens

Patient education does not stop when the device is selected. Education should include discussion about injection technique, administration sites, insulin storage and safe sharps disposable.

Preparation

Patients need to be aware of some important procedures that are required for disposable and nondisposable insulin pens. Cloudy insulin needs to be resuspended by upward and downward movement of the pen at least 10 times, but must not be shaken vigorously (this can cause frothing and interfere with the accuracy of measurement). Pens loaded with NovoMix 30 need to be rolled between the palms of the hands 10 times (this is similar to the preparation of insulin vials) prior to performing the upward/downward movement.

All pens require that a two-unit 'air shot' be performed before the required dose is dialled up, a precaution that removes any air bubbles and ensures the needle is correctly placed and patent. For nondisposable pens, it may be necessary to repeat this procedure several times when a new cartridge has been inserted – the Autopen 24, for example, requires initial priming of eight units.[3]

Table 2. Features of disposable insulin pens*

Pen (manufacturer)	Insulin preparations	Delivery	Points in prescribing
FlexPen (Novo Nordisk)	Levemir, NovoMix 30, NovoRapid	Dials up to 60 units of insulin, in increments of 1 unit	Popular for patients on a basal bolus schedule and for patients with type 2 diabetes who require a twice daily premixed insulin schedule Pens dispensed with NovoMix 30 and NovoRapid are similar in appearance (both navy in colour) A reasonable degree of dexterity and hand strength is required for operation
InnoLet (Novo Nordisk)	Mixtard 30/70, Protaphane	Dials up to 50 units of insulin, in increments of 1 unit	Suitable for elderly or disabled patients and for patients who have a fear of needles Storage of a complete prescription (five repeats) requires considerable fridge space
NovoLet (Novo Nordisk)	Protaphane	Dials up to 78 units of insulin, in increments of 2 units	Suitable for patients wanting a slim, nonbulky disposable device, especially if smaller doses are required Not suitable for visually impaired patients Errors may occur when larger doses are required because the pen has no indicator of individual units greater than 20; patients are required to keep a mental account of the number of full 20-unit rotations dialled

* All disposable pens contain 300 IU of insulin (100 IU/mL, 3 mL).

Needles for insulin pens are available in several sizes, and the choice will be influenced by the age and weight of the patient. Generally speaking, the following are used:

- for obese patients – 28 gauge (12 mm) and 29 gauge (12.7 mm)
- for most patients – 30 gauge (8 mm) and 31 gauge (8 mm)
- for children and very lean patients – 31 gauge (6 mm) and 31 gauge (5 mm).

Injection technique and sites

Insulin is generally injected into the abdomen, but it may be injected into the thigh if a slower rate of absorption is required – for example, intermediate acting insulin given at bedtime for a patient who experiences overnight hypoglycaemia and wishes to prolong the onset of action. Wiping the site with alcohol or methylated spirits is not required and serves only to toughen the skin. The needle is inserted at a 90° angle into a fold of skin.[5] If a pen is used, it must be kept *in situ* for up to 10 seconds after the insulin has been injected – this will ensure no leakage occurs when the needle is removed.

Storage

As a general rule, insulin yet to be used must be stored at between 2°C and 8°C. However, the vial or cartridge in current use should be kept at room temperature;

Disposable insulin pens

FlexPen

NovoLet

InnoLet

Table 3. Features of nondisposable insulin pens*

Pen (manufacturer)	Insulin preparations	Delivery	Points in prescribing
Autopen 24 (manufactured by Owen Mumford; available from Sanofi Aventis)	Lantus	Green pen: dials up to 21 units, in increments of 1 unit Blue pen: dials up to 42 units, in increments of 2 units	A dose selector adapter and release button extension (clip fitted to administration button) are available for patients with reduced dexterity (the release button extension is commonly used)
HumaPen Ergo (Eli Lilly)	Humalog, Humalog Mix25, Humulin R, Humulin NPH, Humulin 30/70	Dials up to 60 units, in increments of 1 unit	Pens are available in two colours Ergonomic design Light weight
Innovo (Novo Nordisk)	Actrapid, Mixtard 20/80, Mixtard 30/70, Mixtard 50/50, NovoMix 30, NovoRapid, Protaphane	Dials up to 70 units, in increments of 1 unit	Has an electronic display indicating the dose delivered and time elapsed from previous dose, which assists when the patient cannot remember when the last dose was taken Requires additional explanation – quite technical
NovoPen 3 (Novo Nordisk)	Actrapid, Mixtard 20/80, Mixtard 30/70, Mixtard 50/50, NovoMix 30 NovoRapid, Protaphane	Dials up to 70 units of insulin, in increments of 1 unit	Patients like the solid 'feel' Pens are available in different colours There is a distinct 'click' when each unit is dialled (ideal for visually impaired patients) Patients need to learn how to operate only one pen for a variety of insulins A dial magnifier is available for visually impaired patients Pens can be fitted inside a PenMate 3, an automated needle insertion device Dialling back an incorrect dose is not simple – an additional step is required
NovoPen 3 Demi (Novo Nordisk)	Actrapid, Mixtard 20/80, Mixtard 30/70, Mixtard 50/50, NovoMix 30, NovoRapid, Protaphane	Dials up to 35 units of insulin, in increments of 0.5 units	Suitable for patients requiring very small or precise amounts of insulin Similar features to NovoPen 3, except that only one colour is available

* All nondisposable pens contain cartridges of 300 IU of insulin (100 IU/mL, 3 mL).

insulin at this temperature will cause less stinging than very cold insulin. All insulin stored at room temperature must be discarded after four weeks, regardless of expiry date.

Disposal

Needles should be used once only and then discarded. Syringes and pen needles are both available free of charge from the National Diabetes Services Scheme (NDSS); patient registration is free and requires the signature of a medical practitioner or credentialled diabetes educator. Most shire councils and municipalities have policies for safe disposal of sharps, and some may charge for sharps containers. Diabetes Australia sells a variety of disposal containers.

Insulin pumps

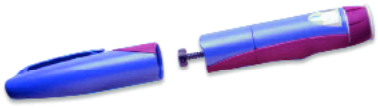
Insulin pumps (continuous subcutaneous insulin infusion devices) are becoming an increasingly viable option for many people with type 1 diabetes. Children, women planning pregnancy and people who have severe diabetes complications such as gastroparesis or are waiting for a transplant are increasingly opting for this system of management.

In short, however, insulin pumps are not suitable for all patients. Units cost between $4000 and $8000 and, although consumables are now available on the NDSS, there have been disturbing reports recently that some private health insurance

continued

Nondisposable insulin pens

Autopen 24



HumaPen Ergo

Innovo

NovoPen 3

NovoPen 3 Demi

funds are refusing to provide coverage for this treatment option. Nor are insulin pumps the answer to poor compliance – carbohydrate counting and frequent capillary blood glucose testing must be performed.

Resources

If you are unsure of the appropriate insulin delivering device for a particular patient, diabetes health professionals can assist. Diabetes educators can demonstrate the use of a wide range of insulin delivery devices, allowing the patient to choose the one that feels most suitable. Suppliers of disposable and nondisposable insulin pens also produce information for both health professionals and patients. MT

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DECLARATION OF INTEREST: Ms Robins has received an ADEA travel grant sponsored by Aventis to attend the annual meeting of the European Association for the Study of Diabetes in September 2005. She has also received honoraria for presentations from Novo Nordisk and Eli Lilly.

Postprandial glucose in diabetes

role of rapid acting insulin analogues

The rapid onset of action of insulins aspart and lispro make them important tools for reducing elevated postprandial glucose, which is now thought to be involved in the development of macrovascular complications in types 1 and 2 diabetes.

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The traditional approach to glycaemic control in diabetes has been to focus on HbA_{1c} as a primary target, as there is good evidence in both type 1 and type 2 diabetes that reduction of HbA_{1c} can prevent microvascular complications.[1,2] The situation with macrovascular disease is less clear, and cardiovascular disease prevention strategies have focused, therefore, on factors such as hypertension and dyslipidaemia.

Recently, researchers have turned their attention to the possibility that postprandial glucose elevations (that is, postprandial hyperglycaemia) play a major role in the genesis of diabetic complications, firstly by contributing to the HbA_{1c} elevation, and secondly by having a direct adverse effect on the vascular system.

Postprandial glucose and elevated HbA_{1c}

In poorly controlled diabetes, the elevation in HbA_{1c} correlates well with fasting blood glucose.[3] As glycaemic control improves, the fasting glucose contributes less to the HbA_{1c}, and the postprandial glucose level becomes more important so that at HbA_{1c} levels under 7.3%, postprandial glucose contributes 70% of the HbA_{1c} elevation (Figure 1).[3] It follows that in patients with HbA_{1c} levels close to 7%, elevated levels of postprandial glucose must be addressed to achieve an improvement in glycaemic control.

Although well-controlled patients are not often studied, there is evidence that the use of a rapid acting insulin analogue (which can reduce postprandial glucose levels more than regular insulin) can improve HbA_{1c} in such patients.[4] In one study, patients with well-controlled type 1 diabetes (HbA_{1c} 6.0 to 7.5%) were randomised to receive either insulin lispro or regular insulin (neutral insulin [human]), with bedtime isophane (NPH) insulin.[5] The mean HbA_{1c} value over one year was lower with lispro (6.34 +/- 0.10% *v.* 6.71

IN SUMMARY

- **Postprandial glucose elevations are the main contributors to elevated HbA_{1c} levels in patients with good glycaemic control.**
- **In patients with diabetes or impaired glucose tolerance there is a strong association between elevated postprandial glucose levels and cardiovascular disease.**
- **The rapid acting insulin analogues lispro (Humalog) and aspart (NovoRapid) reduce postprandial glucose more effectively than regular insulin (neutral insulin [human]; Actrapid, Humulin R).**
- **Early studies using surrogate endpoints suggest that rapid acting insulin analogues may be more effective than regular insulin in reducing diabetes-related vascular damage.**

+/- 0.11% ; p <0.002), and the mean daily blood glucose was also lower. Interestingly, hypoglycaemia occurred less often with insulin aspart (7.4 *v.* 11.5 episodes/patient-month), a further advantage that has been well documented in many studies with short acting insulin analogues.[4]

Postprandial glucose and cardiovascular complications

Several studies have shown a correlation between the glucose level reached after a glucose challenge and the risk of cardiovascular disease.

The Honolulu Heart Program found that the 1-hour postchallenge glucose at study entry predicted risk of cardiovascular death in the next 12 years: men whose postchallenge levels were in the top quintile had almost four times the risk of dying from coronary heart disease than did men in the lowest quintile.[6] Similar findings have come from the Diabetes Intervention Study and the very large Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study, both of which showed that postprandial glucose or postchallenge glucose level, but not fasting glucose, predicted mortality.[7,8]

In the Risk Factors in IGT for Atherosclerosis and Diabetes (RIAD) study, which used intima–media thickness (a marker of atherosclerotic progression in arteries) as an endpoint, the 2-hour postchallenge glucose level predicted increased intima–media thickness, whereas HbA_{1c} and fasting glucose showed no such relation.[9]

Why postprandial glucose peaks are harmful

The endothelium plays a crucial role in vascular health and abnormalities of endothelial function can lead to the development of atherosclerosis. Endothelial function is abnormal in people with diabetes, and it has been shown that in the postprandial state there is a rapid impairment of endothelial function that correlates with the spike in blood glucose.[10,11]

Cellular adhesion molecules are expressed on endothelial cells and mediate the adhesion of leucocytes, one of the earliest stages of the inflammatory process. Inflammation has been shown to be an important part of the atherosclerotic process in people with diabetes. It has also been shown that hyperglycaemia can increase the expression of the adhesion molecule sICAM-1 (soluble intercellular adhesion molecule-1), thus providing a possible link between postprandial hyperglycaemia and atherosclerosis.[12,13]

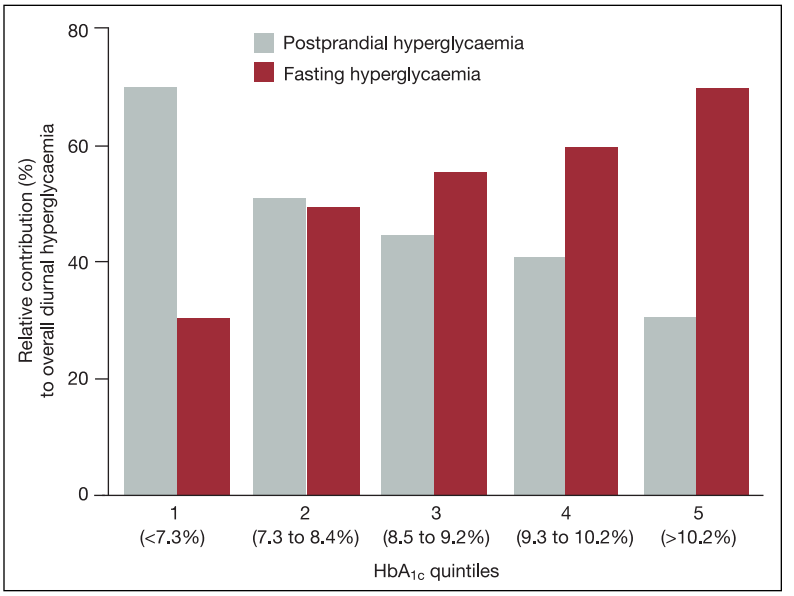

Figure 1. The relative contributions of fasting and postprandial hyperglycaemia to the HbA_{1c} elevation seen in diabetic patients. At high HbA_{1c} levels, fasting hyperglycaemia is the main contributor to HbA_{1c}; as the HbA_{1c} falls towards normal, postprandial hyperglycaemia becomes progressively more important.[3]

There is considerable evidence that the abnormalities of endothelial function in diabetes may be linked to oxidative stress. Our study group found that impairment of endothelial function in young people with type 1 diabetes was highly correlated with the susceptibility of LDL-cholesterol to oxidation.[14] Other investigators have shown that antioxidant defences are reduced in the setting of hyperglycaemia.[15] The oxidative stress induced by hyperglycaemia can cause production of the toxic radical, peroxynitrite, which can react with amino acids in cells to produce nitrotyrosine, a predictor of cardiovascular disease.[16,17] Nitrotyrosine is increased in the plasma of diabetic patients, and correlates with blood glucose but not with HbA_{1c}.[18]

Improving cardiovascular outcomes

Reducing postprandial glucose can improve oxidative stress in people with diabetes. The rapid acting insulin analogue aspart decreases postprandial glucose and reduces nitrotyrosine production,

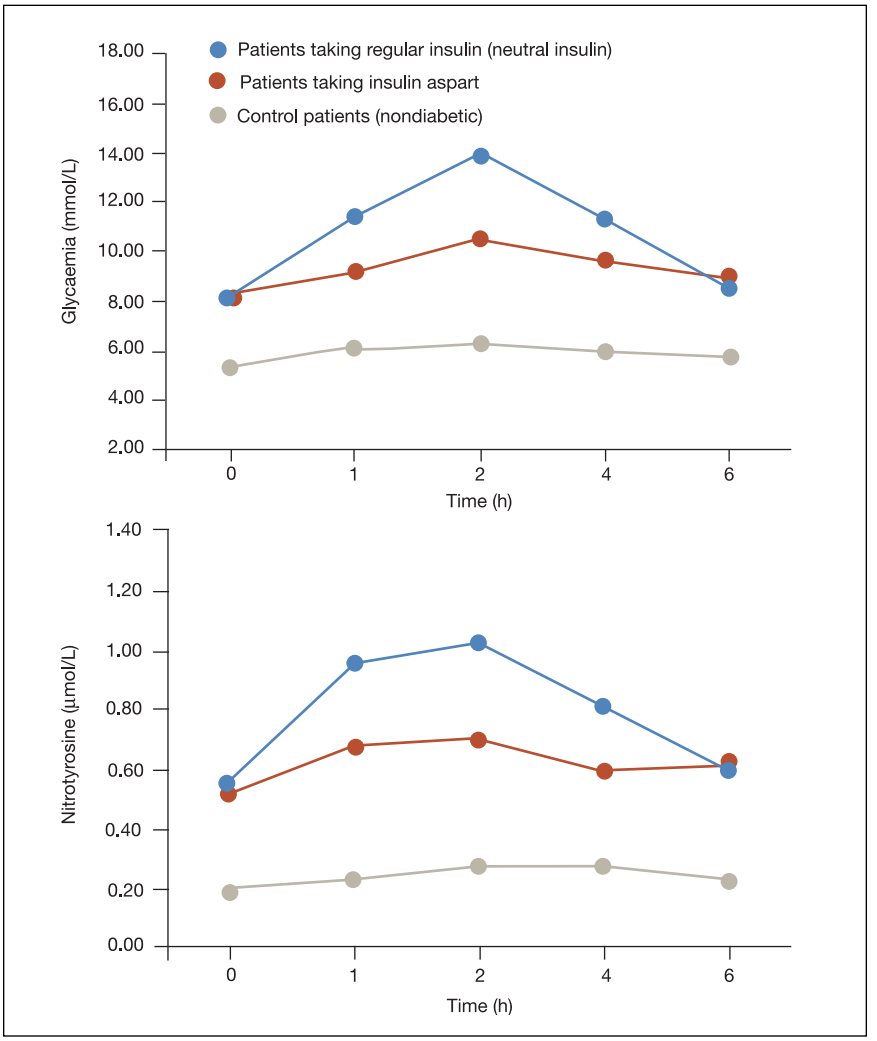

Figure 2. Glycaemia and nitrotyrosine variations during a meal in diabetic patients taking either regular insulin (neutral insulin) or insulin aspart, and in control nondiabetic subjects.[18] Aspart significantly decreased blood glucose and nitrotyrosine levels compared with regular insulin.

compared with regular insulin (Figure 2).[18]

No specific studies have been designed to determine whether reducing postprandial glucose can improve cardiovascular outcomes. However, some interesting suggestive data have come from the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial, which used acarbose to prevent diabetes in patients with impaired glucose tolerance.[19] Acarbose reduces postprandial glucose level, and it was found in this study that subjects taking acarbose had a reduced risk of both myocardial infarction and cardiovascular disease in general.

Another study examined carotid intima–media thickness in a group of patients with type 2 diabetes taking either the short acting oral agent repaglinide or the sulfonylurea glibenclamide over a 12-month period.[20] Postprandial glucose was significantly lower in patients taking repaglinide, and regression of intima–media thickness occurred in 52% of the repaglinide treated group versus 18% of the glibenclamide group, suggesting that control of postprandial glucose can improve vascular health.[20]

Conclusion

Diabetes care has advanced significantly in recent times with the development of new insulins and oral medications and improvements in technologies such as insulin injection pens and home blood glucose monitoring. These all help patients achieve better glycaemic control.

Traditional management has focused on HbA_{1c} as a glycaemic target, but there is accumulating evidence that postprandial glucose peaks are an important therapeutic target, particularly for the prevention of macrovascular complications. Because of their ability to target postprandial glucose, the rapid acting insulin analogues aspart and lispro are important tools to help achieve postprandial glucose targets. MT

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DECLARATION OF INTEREST: Professor O'Brien is a member of advisory boards, has received honoraria for speaking and has conducted research studies for numerous pharmaceutical companies in the field of diabetes.

MedicineToday PEER REVIEWED ARTICLE MedicineToday 2003; 4(4): 64-72

Unstable type 1 diabetes in adolescence

Improving glucose control in a patient who has chronically unstable type 1 diabetes is an extremely intensive exercise for both patient and physician. Lessons learned in managing type 1 diabetes in adolescents generally apply also to the disorder in children and adults.

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Type 1 diabetes differs from other diseases in that patients are required to make multiple daily biochemical assessments of their disease and then make decisions on the dosage of their medication, insulin, which has a therapeutic ratio (toxic dose/therapeutic dose) narrower than almost any other drug. Chronically unstable type 1 diabetes is characterised by either chronic hyperglycaemia or swings from normoglycaemia to both hyperglycaemia and hypoglycaemia. These instabilities increase the risks of long term complications.

This article focuses on chronically unstable diabetes in adolescence but the lessons learned in this age group apply, with variations, to the disorder in both childhood and later adult life.

What the doctor knows about type 1 diabetes

Type 1 diabetes is a state of insulin deficiency following destruction of pancreatic beta cells by an autoimmune process that is polygenic and, possibly, partly environmental in origin. The plasma glucose concentration is determined by the difference between the rate of glucose entry into the blood, from gut absorption from food and liver glucose release, and the rate of glucose exit from the blood into muscle, fat and other tissues. Some of these processes are influenced by insulin. Diet, exercise, stress (including emotional state) and sleep all affect glucose metabolism (Figure 1).

The condition can be complicated by retinopathy, nephropathy, neuropathy and macrovascular disease, although multiple daily insulin injections, careful attention to diet and frequent glucose monitoring, in addition to avoidance of tobacco use, have been shown to reduce the risk of these long term complications.

What the adolescent knows about type 1 diabetes

In the eyes of an adolescent, type 1 diabetes is completely different from the pathophysiological

IN SUMMARY

- **The current treatment methods for type 1 diabetes are far from perfect; acknowledging this with the patient will aid compliance in the treatment of chronically unstable disease.**
- **Agreement should be reached between the patient and doctor about the need for regular measurement and recording of blood glucose levels.**
- **A list of management and lifestyle difficulties should be compiled by the patient and doctor together, and the problems then addressed individually.**
- **Using the 'pattern recognition' approach to insulin choice and dosing should achieve fewer fluctuations in blood glucose levels than using the 'top-up' approach.**
- **Emotional, stress and educational problems are common causes of chronically unstable type 1 diabetes and should be identified and treated.**
- **The treating doctor's skills and attention to detail will be sharpened if he or she has experience of the devastating long term complications of diabetes.**

situation described above. It is an uncool problem in which parents and doctors expect at least three but usually four insulin injections each day plus adherence to a diet lacking in spontaneity (to be eaten at six strict times during the day) and excluding the fun foods of adolescence.

As an adolescent with diabetes, you are also expected to prick your finger between two and six times a day, and then record the test results in a diary – revealing your daily deviations in diet to both your parents and your doctor. Even worse, your friends may see you injecting or finger pricking! The final humiliation is a coma, convulsion or a state of incoherence from hypoglycaemia in front of your friends. You therefore run high sugars even though you tend to feel tired and crabby, but this is certainly better than looking stupid in front of the guys.

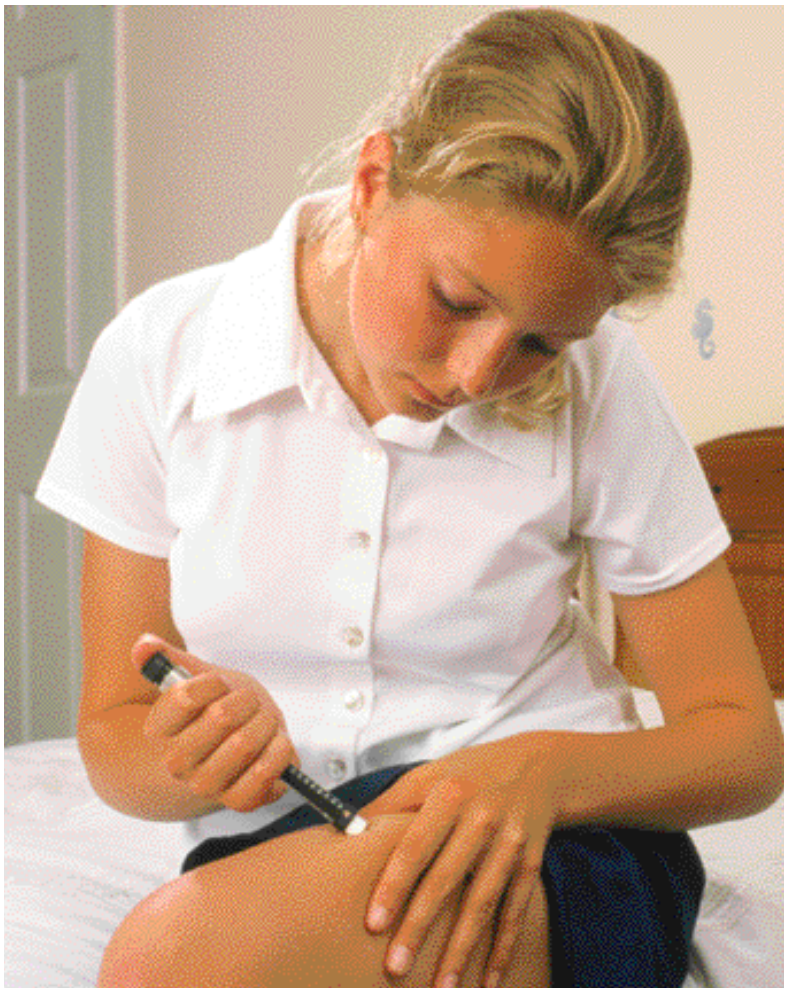
And then you are told that if you don't jump through the diabetes management hoops perfectly, you may go blind or lose a leg. Plus, you may have difficulties in having healthy babies or, if you are a guy, lose your sexual performance.

Finally, unlike asthma or epilepsy, diabetes does not give you a holiday. It is there 24 hours each day, 365 days each year. If you miss just one insulin injection, you may end up in hospital with ketoacidosis, missing yet more time from school or work.

Compliance

Realising the attitudes of normal adolescents, compliance with the expectations of doctors and dietitians in the management of diabetes must be regarded as a psychologically abnormal response. Compliance should probably be discarded as a concept, and certainly as an expectation of health professionals. The request for compliance should be replaced by an approach that identifies and improves, one at a time, the various obstacles and hurdles in the achievement of reasonable blood glucose control that are faced by a person of any age with type 1 diabetes.

The patient will only identify the obstacles to reasonable glucose control if the doctor acknowledges that the current treatment for type 1 diabetes is grossly imperfect and unphysiological. The label 'brittle diabetes' is an admission of failure by the doctor and a prescription of despair for the patient and, if improvement in control is desired, should never be used.



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The emotion of guilt

Most people with type 1 diabetes experience guilt when they break the unrealistic regimen imposed upon them by their physician to minimise the risks of hypoglycaemia and long term complications. The experience of guilt is often followed by an overwhelming compulsion to repeat the behaviour.

People with type 1 diabetes should be educated that the treatment regimen, while designed for their own good, is severe and that breaking it simply confirms their psychological normality. The guilt–compulsion cycle of repetition must be explained and they should be encouraged to record aberrations in the treatment regimen, such as eating chocolate. The frequency of indiscretions will usually diminish if they do this, provided that the physician is nonjudgemental.

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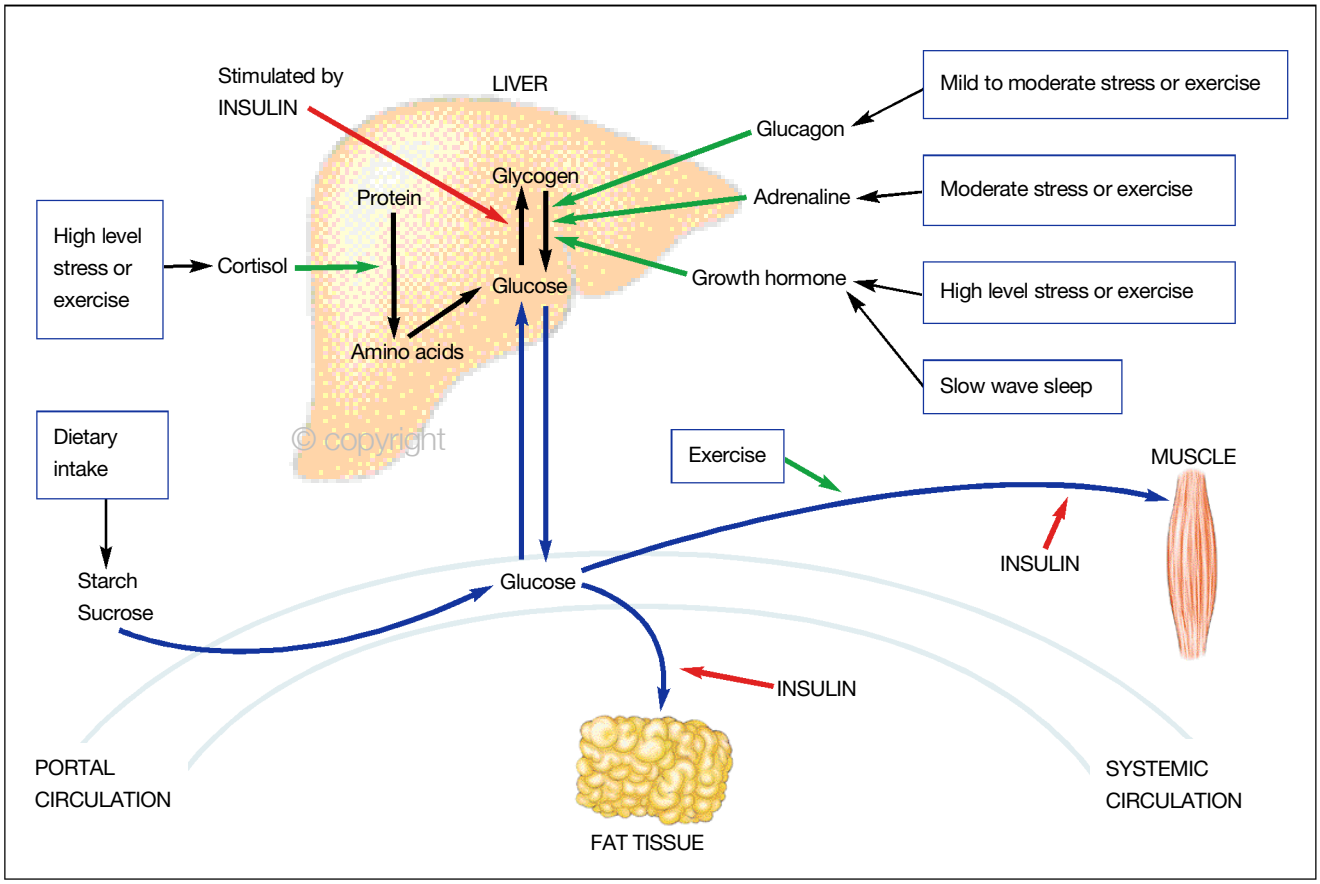


Figure 1. Glucose metabolism.

Diabetes record keeping

The recording of blood glucose test results, insulin doses, hypoglycaemic episodes, variations in diet, intercurrent infections and stressful life events in a diabetes diary is an absolute prerequisite in the assessment and improvement of unstable diabetes. It is, however, one of the most odious duties for the patient. The patient and doctor must come to an agreement about the importance of the diary and the fact that it will be maintained, because improvement in control is unlikely to occur otherwise.

An electronic diary in a glucose monitor is not a satisfactory alternative for three reasons:

- an electronic diary rarely records life events such as infections, dietary indiscretions, stresses and menstruation
- by visually scanning across and down the manually kept glucose test results columns, the physician can see daily patterns and their relation to insulin doses, periods of increased or reduced exercise (such as at weekends) or menstruation, for example, that would never become obvious in an electronic record
- a manual spreadsheet record also allows the person with diabetes to detect patterns in glucose fluctuations that may be related to diet or to life events, providing valuable feedback.

Management factors in unstable diabetes

Diet

The concept of the optimal diet for people with type 1 diabetes has changed dramatically over the past decade. We are now aware that starch in different foods is digested and absorbed as glucose at greatly differing rates.

Glycaemic index

The measure of a starchy food's rate of absorption as glucose is called its glycaemic index (GI), with glucose having a value of 100. Many previously 'forbidden foods', some sweets and many desserts have been found to have a relatively low GI and can now be included in the diabetic diet without causing deterioration in glycaemic control, thereby breaking some of the monotony and restriction of the diet. Others, such as potato, can cause a marked rise in plasma glucose and contribute to poor glycaemic control.

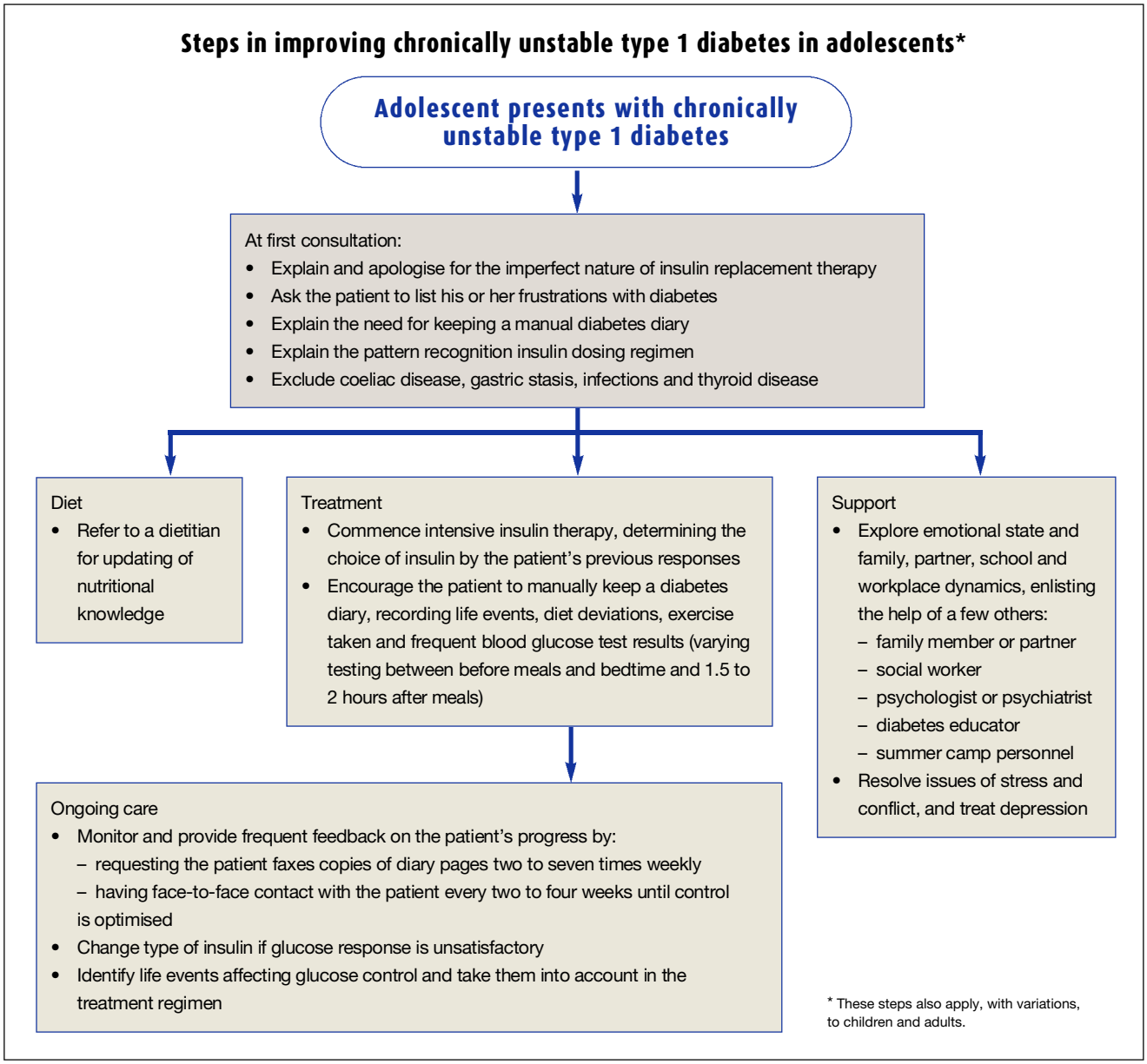
All patients with unstable diabetes should have their nutritional knowledge updated by a professional dietitian. Patients should also be encouraged to purchase one of Professor Jennie Brand-Miller's books on the glycaemic index, such as *The New Glucose Revolution* (written with Kaye Foster-Powell and Stephen Colagiuri) or the accompanying pocket guides (all published by Hodder Headline, Sydney).

Exercise

Moderate physical exercise produces a moderate increase in the secretion of the stress hormones glucagon, adrenaline and growth hormone, all of which act on the liver to increase liver glucose production by stimulating hepatic glycogen breakdown to glucose (see Figure 1). The rise in liver glucose release is less than the increase in muscle glucose uptake and the plasma glucose therefore falls and hypoglycaemia may ensue if additional food is not eaten.

More severe exercise, above 90% of maximal exercise capacity, stimulates a greater outpouring of glucagon, adrenaline and growth hormone and also increases cortisol secretion. Liver glucose production is increased by a greater extent than muscle glucose uptake and the plasma glucose will rise.

Paradoxically, exercise on waking



before administration of insulin and before breakfast will also cause the plasma glucose to rise because liver glucose production is accelerated pre-dawn by the physiological mid-sleep surge in growth hormone secretion.

Explanation of these phenomena to the person with type 1 diabetes will cause a glow of enlightenment to spread across his or her face and acceptance that some of the common frustrating experiences are now explicable and all is not hopeless.

Insulin dosing: top-up or pattern recognition approach?

One of the common causes of glycaemic fluctuations in type 1 diabetes is the use of the 'top-up' or 'tail chasing' approach to insulin dosing, whereby an insulin dose is determined by the pre-dose blood glucose level. This approach seems intuitive to many patients and doctors.

Fewer fluctuations in plasma glucose levels will be achieved with a change to the 'pattern recognition' approach to insulin dosing. In this approach, a particular insulin dose is determined by the efficacy of that dose during the time period of action of that dose over the preceding four to seven days.

For example, if a person with type 1 diabetes woke with an elevated glucose of 16 mmol/L, the pattern recognition approach would suggest that, if this was a regular event, the pre-bedtime dose should be increased or a slower and longer acting insulin should be used at bedtime. In the same situation, the top-up approach would increase the breakfast insulin dose, causing a fall in glucose before lunch; the lunch insulin dose would then be decreased, causing a rise in glucose late afternoon and an increase in the dinner dose of insulin; the pre-bed glucose level would then most likely fall, tempting a reduction in the bedtime dose so that the pre-breakfast glucose level would be just as high or higher than the previous morning.

Some people with longstanding type 1 diabetes have great difficulty in overcoming their compulsion to adjust an insulin dose on the basis of the pre-dose glucose level. The top-up approach is only appropriate when hyperglycaemia is the result of an acute infection, an operative procedure or acute stress.

Reducing food intake to control hyperglycaemia – a common error

It is common and understandable that people with type 1 diabetes attempt to control hyperglycaemia by restricting food intake. This, however, leads to a further increase in fat breakdown and a further increase in ketone formation that can antagonise insulin action and cause nausea. Patients with diabetes should be educated that their food intake should be determined by their daily bodily requirements, including energy expenditure and growth, and not by their glucose levels.

Fasting hyperglycaemia

Overnight blood glucose homeostasis is achieved in nondiabetic individuals by the secretion of growth hormone during levels 3 and 4 sleep (slow wave or non-REM sleep), accelerating the breakdown of liver glycogen to glucose, causing a pre-dawn rise in blood glucose.

In type 1 diabetes, the difficulty is to achieve overnight blood insulin concentrations that do not cause hypoglycaemia between 12.00 a.m. and 2.00 a.m. but which control the pre-dawn surge in liver glucose production. A pre-bed supper is almost always essential in the achievement of this aim. If sleep is disturbed, slow wave sleep is not achieved, little growth hormone is secreted and hypoglycaemia ensues.

Research has shown that fasting hyperglycaemia is not due to counter-regulatory rebound from hypoglycaemia, the so called 'Somogyi effect'. Nocturnal hypoglycaemia stimulates secretion of counter-regulatory stress hormones that almost always cause the blood glucose to rise only to low-normal or normal levels.

Table 1. Choice of pre-meal insulin type

Insulin type	Trade name	Duration of action	Advantages	Disadvantages
Aspart	NovoRapid	Very short acting	Rapid onset of action Little day-to-day variation in effect Action 1 hour longer than lispro	Duration of action short, so blood glucose levels may rise before the next meal
Lispro	Humalog	Very short acting	Rapid onset of action Little day-to-day variation in effect	Duration of action very short, so blood glucose levels may rise before the next meal
Neutral (human)	Actrapid, Humulin R	Short acting	Action long enough to cover lunch to dinner period	A 20- to 30-minute gap between injection and eating preferable Some day-to-day variation in effect May overlap with bedtime insulin, increasing risk of nocturnal hypoglycaemia

Choice of insulin type and regimen

Glycaemic control and fluctuations can rarely be improved on twice daily insulin therapy. Most people with type 1 diabetes will only achieve significant improvement in glucose control with intensive insulin therapy comprising a short acting insulin before each main meal and a longer acting insulin usually before bed, but occasionally with the evening meal and rarely with breakfast.

The main criteria in the choice of insulin are onset and duration of action and variability in efficacy from dose to dose or from day to day. The most common insulin-induced cause of glucose instability is variability in action or in duration of action of the evening longer acting insulin. The properties, advantages and disadvantages of short acting and long acting insulins are outlined in Tables 1 and 2.

Pump infusion of insulin subcutaneously will solve almost all insulin problems but requires enormous dedication from the patient and is very expensive. Similar results can be achieved more simply and less expensively using insulin glargine or insulin detemir before bed with either lispro or aspart insulins before meals.

The steps to improve chronically unstable type 1 diabetes are outlined in the flowchart on page 31.

Illnesses destabilising type 1 diabetes

Infections that cause fluctuations in glucose levels, such as urinary tract infection (often asymptomatic in the presence of a

Table 2. Choice of pre-bed insulin type

Insulin type	Trade name	Duration of action	Advantages	Disadvantages
Isophane (human)	Humulin NPH, Protaphane	Intermediate	Gives consistent results in most patients	Action may be too strong around 12.00 a.m. to 2.00 a.m. Day-to-day variability in some patients
Detemir	Levemir	Long acting	Less variable time action profile and lower day-to-day variability in fasting plasma glucose than isophane insulin	Not yet available on PBS, very expensive
Glargine	Lantus	Long acting	Very even action over 24 hours	Not yet available on PBS, very expensive

neuropathic bladder) or low-grade cholecystitis, are uncommon causes of unstable diabetes but warrant exclusion.

Coeliac disease, which affects at least 2% of people with type 1 diabetes, and delayed gastric emptying from autonomic neuropathy can lead to erratic absorption of food and poor glucose control.

Stress, conflict and depression

Family, partner, school or work stress and conflict are common causes of chronically unstable diabetes. Elucidation of these problems will often only be achieved once a trusting and nonjudgemental relationship has been established between the doctor and the person with diabetes.

Depression is also very common, and improvement in glycaemic control will only be achieved once the depression has been acknowledged as existing and then treated.

Psychologists, psychiatrists, social workers and family members can be very helpful in improving depression and stress but it can be counter-productive to involve too many people. Summer camps for children and adolescents with diabetes are among the most helpful agencies in improving acceptance of this demanding disease.

Organisational barriers to improved glucose control

The diabetes team

For more than two decades, type 1 diabetes has tended to be managed by teams of health professionals – GPs, endocrinologists, dietitians, diabetes educators, psychologists and social workers, each adding the value of their own unique skills to the patient's management. This approach, however, can lead to an escapist tendency to assume that diabetic instability is due to a problem in the area of another health professional rather than in one's own area.

Every person with type 1 diabetes needs one professional who takes ultimate responsibility. This professional ideally should be an endocrinologist due to the complexities of type 1 diabetes management, particularly in unstable situations. However, the GP is often the key to the detection of the patient's own or his or her family's emotional and stress problems that are a common cause of unstable glucose control. The diabetes educator may occasionally fill this role.

The adolescent to adult transition

Adolescent and childhood diabetes is mostly managed by doctors who never see the devastating results of poor glycaemic control: blindness, dialysis or offspring with severe congenital abnormalities. Adolescent and childhood diabetes physicians then hand over their patients to adult diabetes physicians at an emotionally tempestuous time in the young person's life: around the end of schooling and the beginning of employment or tertiary education.

Adult physicians usually expect a higher degree of patient self-control than childhood physicians – high expectations from a young adult with whom they do not have a long-established relationship, at a time of rebellion and rejection of adult expectations and when complications are likely to first appear. Consequently, despite so called 'hand-over clinics', the patient is often lost to follow up for a number of years, obtaining repeat insulin prescriptions from his or her GP or anonymous medical centres, presenting again in the mid-twenties with ketoacidosis or a retinal haemorrhage and irreversible damage. This system could not be designed to give a worse long term outcome for young people with diabetes.

Preferred time of transition

Preferably, the hand-over from childhood to adult diabetes physician should take place on entry to high school in order that a therapeutic relationship with an adult physician is established before the turmoil of adolescence. The hand-over could, however, take place at around 25 to 26 years of age, a stage of life when even immature young people become cognisant of the future, a fact recognised by the motor vehicle insurance industry. This, in reality, is the time when many young adults adopt adult endocrinologist care after a gap of six to eight years.

In the future

In the longer term, endocrinologists should be trained as 'from diagnosis to the grave' paediatric–adult specialists whose skills and attention to detail will inevitably be sharpened when one of their long term diabetic patients develops retinopathy or renal failure 10 to 20 years after they first met at diagnosis. This change in training is already occurring in the USA.

Conclusion

The improvement of glucose control in patients with chronically unstable type 1 diabetes is an extremely intensive exercise for both the patient and the doctor. However, the effects on wellbeing and performance in the short term and the reduction in complications in the long term make it one of the most worthwhile exercises in medical practice. MT

DECLARATION OF INTEREST: Dr Kidson has been involved in paid clinical trials of repaglinide (Novo Nordisk) and insulin glargine (Sanofi Aventis).

Long acting insulin analogues in type 1 diabetes: do we need them?

PAUL C. BARTLEY MB BS, FRACP

Scientific data indicate the new insulins detemir and glargine are better at controlling blood glucose than isophane insulin. However, currently they are only available on private prescription.

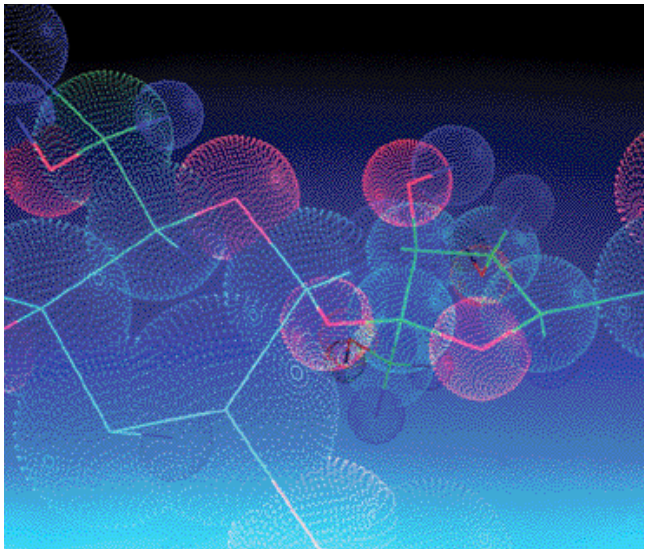


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Figure. Computer graphic of the B-chain of the insulin molecule.

One of the major lessons learned from continuous subcutaneous insulin infusion is the paramount importance of basal insulin. Before 1 August 2005, three types of insulin were available on the Pharmaceutical Benefits Scheme (PBS) for basal therapy: isophane insulin (also known as NPH insulin), insulin lente and insulin ultralente. Now there is only isophane insulin (human: Humulin NPH, Protaphane; bovine [rarely used]: Hypurin Isophane).

So what is wrong with there only being isophane insulin? Like the lente and ultralente insulins, isophane insulin is subject to day-to-day, within-patient variability of the glucose lowering effect and uneven intensity of action over time; isophane insulin, however, seems to give the most consistent results in the majority of patients. These characteristics lead to the risks of overnight hypoglycaemia and morning (fasting) hyperglycaemia, thus limiting the control that can be achieved overnight. Also, isophane insulin often requires administration up to three times daily.

Hence an insulin capable of addressing particularly overnight hypoglycaemia and morning hyperglycaemia is required.

Long acting insulin analogues

Two insulin analogues with very prolonged and even action have been developed, but as yet neither is available on the PBS.

Insulin detemir

Insulin detemir (Levemir) is the first of a new class of long acting insulin analogues that are soluble at neutral pH. Its prolonged duration of action is attributable to a combination of increased self-association (hexamer stabilisation and hexamer–hexamer interaction) and albumin binding (due to acylation of lysine at position B29 with the 14-C fatty acid, myristic acid).

Detemir is highly albumin bound in the interstitial fluid and in plasma,[1] and has been shown to elicit a protracted metabolic action with a slow onset of action and a less pronounced peak of action compared with that observed for isophane insulin.[2,3]

Insulin glargine

Insulin glargine (Lantus), the first long acting insulin analogue to be developed, differs from native human insulin in both the A and B subunits of the protein: the A-chain contains an asparagine to glycine substitution at position 21, and the B-chain is elongated at the C-terminus by the addition of two arginine residues.[4] The modifications to the B-chain shift the isoelectric point of the molecule towards the neutral (that is, to a less acid pH), which gives complete solubility at pH 4 but much less solubility at neutral pH, while the A-chain modification confers stability.[5]

Glargine is soluble in the slightly acidic environment of the solution in which it is presented. On parenteral administration, the neutral pH of the subcutaneous tissue causes a stable hexamer to form and precipitate, which then dissolves slowly and evenly.

Comparing detemir, glargine and isophane insulins

In a short article such as this, it is not possible to discuss fully the literature with respect to these insulins. I will, however, attempt to summarise what makes detemir and glargine superior to isophane

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insulin, and highlight their differences when used in adult patients with type 1 diabetes mellitus.

Advantages of detemir and glargine, compared with isophane insulin

Both detemir and glargine have been shown to:

- reduce overnight hypoglycaemia compared with isophane insulin[6-10]
- lower HbA_{1c} compared with isophane insulin[6,10-12]
- reduce fasting blood glucose level compared with isophane insulin.[6,7,9,13-15]

They both, therefore, address the criticisms against isophane insulin.

Differences between detemir and glargine

Duration of action

Glargine has a duration of action of up to 24 hours and only needs to be used once daily in most patients (Lantus product information). Detemir has a duration of up to 24 hours and is given once or twice daily, depending on the patient; it is best given at bedtime.[6]

Variability

The best study to date of within-patient variability of the glucose lowering effect of these insulins is the glucose clamp study of Heise and colleagues.[16] This study confirms the variability of isophane insulin. While it suggested that detemir is less variable than glargine, this difference was not statistically significant. Other studies support the reduced variability of detemir compared with isophane insulin.[2,6,7,11]

Weight change

Insulin therapy has long been associated with weight gain when control is achieved or improved.

Many studies with detemir suggest less weight gain or weight loss when detemir is used compared with isophane insulin.[6,8,11,13] This is currently the subject of a prospective trial in which weight change is a prespecified primary endpoint. There are no head-to-head data on detemir versus glargine. In fact, there are no comparable data for glargine. Of the three studies in which weight gain was reported for glargine, one showed no change,[10] one showed no significant difference[17] and one showed a statistical difference but patients had type 2 diabetes.[18]

Using detemir and glargine

Detemir and glargine are fully soluble in the environments of the solutions in which they are presented, and hence these are clear solutions. Patients should be educated so that they avoid confusion

between these insulins and the short acting insulins that are often known as 'soluble' insulins. Injecting detemir or glargine into the thigh and the short acting insulin into the abdomen and using different coloured administration devices can help reinforce the different durations and actions of the insulins.

I would suggest starting the long acting analogue at bedtime. Although doses should be individualised, for a patient currently on isophane insulin at bedtime, I would probably change over unit for unit with the isophane dose. Monitoring of the pre-breakfast blood glucose level will be necessary, and perhaps also the 3.00 a.m. level.

The dose should be slowly increased in 2-unit increments once a week until the blood glucose level before breakfast reaches the target of 4 to 7 mmol/L without overnight hypoglycaemia. If this target blood glucose level is not achieved at dinnertime then a second injection of 6 units should be added before breakfast, and increased by 2 units weekly until the target is achieved.

Conclusion

Insulin detemir and insulin glargine are better at controlling blood glucose than isophane insulin. They are more expensive but the scientific data support their superiority. However, they are not as efficacious as continuous subcutaneous insulin infusion. On private prescription, the cost is hard to justify for all patients.

Preliminary data suggest that detemir is less variable than glargine. While the prospective trial is yet to report, detemir appears to be associated with less weight gain or weight loss when compared with isophane insulin. MT

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DECLARATION OF INTEREST: Dr Bartley has no shares in any biomedical company and has not been employed by any pharmaceutical company. He has been a principal investigator in several international trials of insulin detemir sponsored by Novo Nordisk.

Diabetes, doctors and quality of life

Since diabetes is associated with a reduced quality of life and an increased risk of psychological problems, it is important to assess the psychosocial status of people with diabetes and respond to any issues identified.

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Diabetes imposes significant personal burdens on the individual in terms of self and medical care, short and long term complications and the threat of future problems (Figure 1). The person with diabetes is also faced with a continuous and difficult choice between:

- the risk of diabetes complications with worsening metabolic control, and
- the cost of extra self and medical care and the risks of hypoglycaemia and weight gain associated with improved metabolic control (Figure 2).[1]

It comes as no surprise that diabetes not only increases morbidity, premature mortality and the use of health services, but also reduces quality of life[2,3] and increases the risk of depression.[4] There is also evidence that a vicious cycle can develop with psychosocial issues adversely affecting diabetes control and care, and vice versa.[5-7]

Diabetes starts affecting a person's quality of life well before diagnosis, in terms of physical functioning (Figure 3).[2,3] The physical component summary (PCS) score of the 36-Item Short Form Health Survey, a well-validated measure of health-related quality of life, is affected more than the mental health summary (MCS) score. In addition, the quality of life in women is affected more than it is in men.[8]

Attitudes of patients v. health professionals

Health professionals may understand some of the burden borne by people with diabetes but, by necessity, have a different perspective. The individual with diabetes is continuously involved with the condition, and many choices throughout the day are coloured by the questions: Will this affect my diabetes? How can I control this effect?

The cost of self care is considerable. It has been shown that people with diabetes would be willing, if they could, to trade off a significant proportion

IN SUMMARY

- **Psychosocial issues are common in people with diabetes and pre-diabetes and adversely affect quality of life and metabolic control.**
- **Doctors are aware of these problems but may not feel confident in their ability to assess them and provide psychological support to patients.**
- **Psychosocial assessment is important and should at least be part of the annual 'diabetes first' review.**
- **Simple tools are available to assess mental health, e.g. the Kessler Psychological Distress Scale-10 (K10), and access to psychological resources is available through the Enhanced Primary Care program.**
- **The MedicarePlus Scheme provides rebates for allied health and nursing services, including those of psychologists.**

of their remaining life in return for the removal of their diabetes.[9] In reality, people with diabetes have to pay a considerable cost today for a possible benefit in the future. However, we all would rather have a specific benefit today than have to wait for the same benefit in the future (this is the so-called 'time trade-off' and is implicit in the charging of interest for loans). For this reason, people with diabetes are likely to focus on the short term (Table 1).

Health professionals, on the other hand, have a lesser involvement and a lesser, or no, personal cost for the care of their diabetic patients (because of reimbursements). They are likely to adopt a longer term view and urge more investment in the future than they themselves would choose if they had the continuous involvement and costs of living with diabetes. In this regard, the GP's perspective may be closer than that of the specialist's to the patient's perspective.

The DAWN study

The Diabetes Attitudes, Wishes and Needs (DAWN) study assessed the psychosocial impact of diabetes from the perspective of the person with diabetes and his or her health professionals.[10] The study, sponsored by Novo Nordisk, involved more than 5000 people with diabetes and 3000 health professionals in 13 countries. In the Australian arm, 476 people with diabetes, 300 doctors and 100 registered nurses participated.

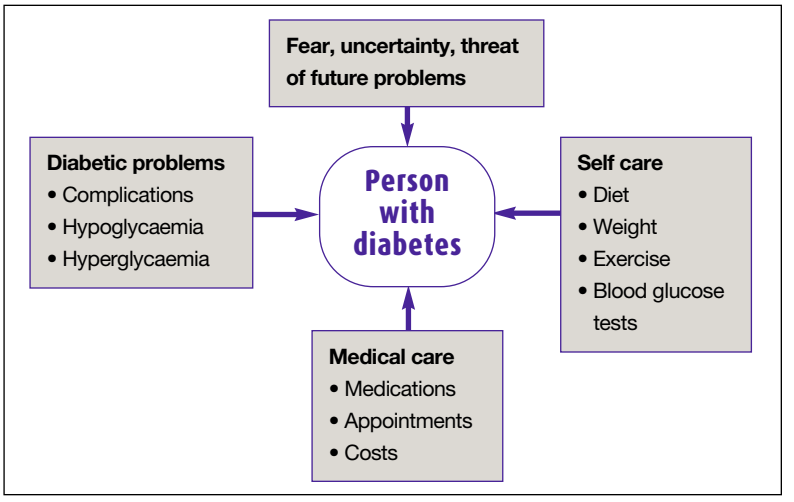

Figure 1. Burdens faced by people with diabetes.

Table 1. Diabetes: involvement, cost and attitudes

Subject	Involvement	Cost of care	Attitude
Patient	Continuous	High	Short term
GP	Intermittent	Low	Mid term
Specialist	Occasional	Very low	Long term

The study found that Australian doctors were aware of psychosocial issues in patients they saw but felt variably able to assess these problems and provide the appropriate psychological support.

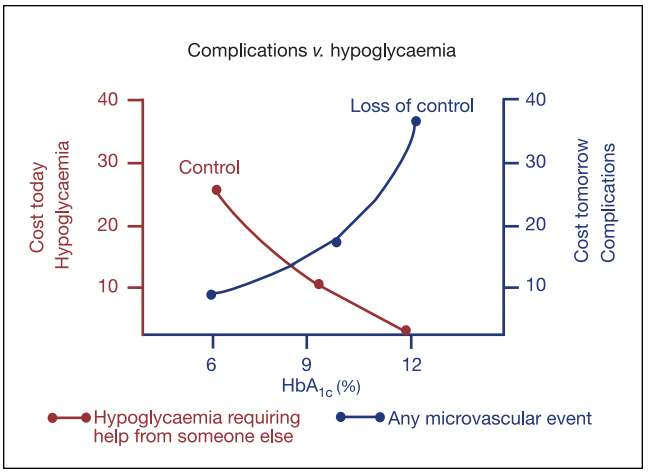

Figure 2. The person with diabetes is faced with a choice between the risk of diabetes complications with worsening control and the cost of extra self and medical care plus the risks of hypoglycaemia and weight gain.

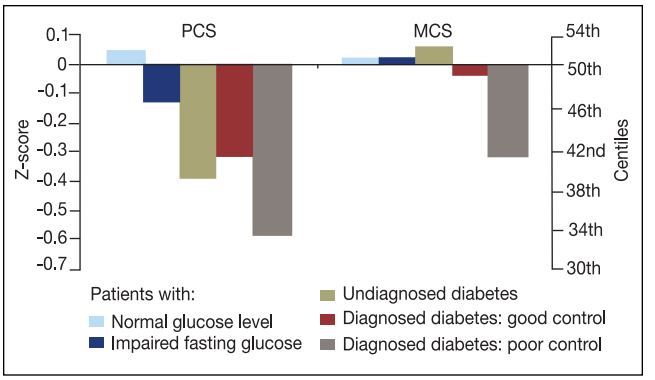

Figure 3. The effect of impaired fasting glucose and diabetes on subjects' quality of life, as measured by the physical component summary (PCS) and mental health summary (MCS) scores of the 36-Item Short Form Health Survey. The 50th centile and a zero z-score represent the general population norm. Values above these represent better health, and those below, poorer health.

Table 2. DAWN study: GPs' attitudes to psychosocial issues in people with diabetes

Perception	% of GPs
Aware of the prevalence of psychosocial issues in patients with diabetes	65%
Feel able to assess psychosocial issues in patients with diabetes	70%
Feel able to support diabetic patients who have psychosocial issues	55%
Have access to experts for referral	62%
Often refer diabetic patients who have psychosocial issues	15%
Would like to improve ability in managing psychosocial issues in diabetic patients	48%
Would like improved access to experts for referral	48%

GPs felt more able to assess and support their patients than did specialists, perhaps because of their greater involvement and longer relationship with patients who have diabetes.

Most GPs felt they had adequate access to outside expertise on emotional and psychological problems if their patients needed it, but only a minority would often refer patients. However, a significant number of GPs felt they needed a better understanding of the psychological consequences of diabetes. In addition, they wanted better access to psychologists and psychiatrists for referral (Table 2).

The Kessler Psychological Distress Scale-10 (K10)

The Kessler Psychological Distress Scale-10 provides a measure of psychological distress. For each of the 10 questions in the table below, ask your patients to circle the number that best describes the amount of time they have been feeling that way in the last 30 days.

Several cut-off points have been used to define the level of psychological distress. The cut-off points used in the 2002 Victorian Population Health Survey were as follows: subjects scoring 10 to 19 are likely to be well; 20 to 24 are likely to have a mild mental disorder; 25 to 29 are likely to have a moderate mental disorder; 30 to 50 are likely to have a severe mental disorder.

Question	None of the time	A little of the time	Some of the time	Most of the time	All of the time
1. In the last 30 days, about how often did you feel tired for no good reason?	1	2	3	4	5
2. In the last 30 days, about how often did you feel nervous?	1	2	3	4	5
3. In the last 30 days, about how often did you feel so nervous that nothing could calm you down?	1	2	3	4	5
4. In the last 30 days, about how often did you feel hopeless?	1	2	3	4	5
5. In the last 30 days, about how often did you feel restless or fidgety?	1	2	3	4	5
6. In the last 30 days, about how often did you feel so restless you could not sit still?	1	2	3	4	5
7. In the last 30 days, about how often did you feel depressed?	1	2	3	4	5
8. In the last 30 days, about how often did you feel that everything was an effort?	1	2	3	4	5
9. In the last 30 days, about how often did you feel so sad that nothing could cheer you up?	1	2	3	4	5
10. In the last 30 days, about how often did you feel worthless?	1	2	3	4	5

Recognition of complex care needs

In July 2004 the Commonwealth Department of Health and Ageing recognised the complex care needs of people with chronic conditions such as diabetes, and made services by several allied health groups available through the Enhanced Primary Care (EPC) Multidisciplinary Care Plan. Such health groups included psychologists, mental health nurses, diabetes educators and some social workers.

In July 2005 new Medicare Chronic Disease Management items replaced the existing EPC items, with the goal to 'make it easier for GPs to manage the healthcare of patients with chronic medical conditions'.

The MedicarePlus Scheme now provides rebates for allied health and nursing services, including psychologists.

Screening tools

Some simple screening tools are available to assess mental health, including the Kessler Psychological Distress Scale-10 (K10), which was used in the 2001 Victorian Population Health Survey (see the box on page 42). The K10 can be completed during a patient's consultation, and scores indicate the likelihood of a patient having psychological distress.

Suggested recommendations

The current Diabetes Australia and RACGP guidelines on the management of diabetes in general practice identify the importance of counselling the person with diabetes,[11] but psychosocial assessment is not included in the recommended review process. Psychosocial assessment is also not recommended in the diabetes annual cycle of care specified by the Health Insurance (General Medical Services Table) Regulations for the MBS component of the diabetes Practice Incentives Program (PIP).

However, it is important to assess psychosocial status and to respond to issues identified. Perhaps the 'ABCss' of diabetes care (A = HbA_{1c} control, B = blood pressure control, C = cholesterol control, s = smoking cessation, and s = taking salicylates) should be expanded to include a third 's' for psychosocial or a 'PS' for psychosocial. Assessment of psychosocial status could become part of the three- to four-monthly 'diabetes first' consultation, and the EPC process could be aimed at addressing any issues identified. MT

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DECLARATION OF INTEREST: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a number of pharmaceutical companies. He does not think that these associations have influenced the content of this article.
Dr Phillips and Dr Aloizos are members of the Australasian DAWN Advisory Committee. They do not think that this membership has influenced the content of this article.

Does your patient have glucose intolerance?

Persons with impaired glucose tolerance are at very high risk of developing type 2 diabetes. Several recent successful interventional studies targeting subjects with impaired glucose tolerance have stimulated enthusiasm for prevention of type 2 diabetes.

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Type 2 diabetes is positioned to be one of the largest epidemics in human history, and it is one of the major threats to human health in the 21st century.[1] The past two decades have seen an explosive increase in the number of people with diabetes globally. It is estimated that the total number of people with diabetes worldwide will rise from 194 million in 2003 to 333 million by 2025.[2] The number of people with diabetes is predicted to increase in virtually every nation in the world, with the greatest increases expected in developing countries and the socially disadvantaged groups in developed nations. In the Australian Diabetes, Obesity and Lifestyle Study (AusDiab), the prevalence of impaired glucose tolerance in adults was 10.6%; this translates to almost 1,300,000 people.[3]

A number of small studies have demonstrated the benefits of lifestyle interventions in delaying progression from impaired glucose tolerance (IGT), a high risk category, to type 2 diabetes. Two recent successful intervention studies targeting subjects with IGT – the Finnish Diabetes Prevention Study and the US Diabetes Prevention Program – have stimulated enthusiasm for efforts to prevent type 2 diabetes.[4,5] In these studies, lifestyle interventions targeted at overweight people with IGT reduced the risk of progression to diabetes by more than 50%. The studies confirm the strategies used in the first major lifestyle intervention, the Da Qing study in China.[1]

What is impaired glucose tolerance?

IGT is defined as a condition in which blood glucose levels are higher than normal but not high

IN SUMMARY

- **In the Australian Diabetes, Obesity and Lifestyle Study (AusDiab), the prevalence of impaired glucose tolerance (IGT) in adults was 10.6%. This translates to almost 1,300,000 people.**
- **If the fasting plasma glucose is between 5.5 and 6.9 mmol/L, or the random blood glucose is between 5.5 and 11.0 mmol/L, an oral glucose tolerance test is recommended.**
- **Detection of IGT, an asymptomatic condition, is unlikely to provide optimal benefit unless it is accompanied by a comprehensive health assessment that includes consideration of obesity, blood pressure and serum lipids.**
- **People with IGT are at very high risk of developing type 2 diabetes, and lifestyle intervention studies into preventing diabetes have targeted these people.**
- **The principles of successful lifestyle interventions for diabetes prevention are weight loss, regular physical activity and a fibre-rich diet in which less than 30% of total energy is fat and less than 10% of total energy is saturated fat.**
- **The use of pharmacological agents for type 2 diabetes prevention is being explored.**
- **Longer term follow up studies are needed to establish whether lifestyle and pharmacological interventions actually prevent type 2 diabetes or merely delay its onset.**

Table 1. Diagnostic criteria for categories of glycaemia

No diabetes
Fasting plasma glucose <6.1 mmol/L and
2h plasma glucose* <7.8 mmol/L (if measured)†

Impaired fasting glucose
Fasting plasma glucose 6.1 to 6.9 mmol/L and
2h plasma glucose <7.8 mmol/L

Impaired glucose tolerance
Fasting plasma glucose <7.0 mmol/L and
2h plasma glucose 7.8 to 11.0 mmol/L

Diabetes
Fasting plasma glucose 7 .0 mmol/L and/or
2h plasma glucose 1 1.0 mmol/L (if measured)

* 2h plasma glucose values measured after an oral glucose tolerance test (OGTT) with 75 g anhydrous glucose.
† OGTT not recommended for fasting plasma glucose values outside the range 5.5 to 6.9 mmol/L.

enough to be classified as diabetes (Table 1). Apart from their high risk of type 2 diabetes, people with IGT also have a heightened risk of macrovascular disease because of the association with other known cardiovascular risk factors, including hypertension, dyslipidaemia and central obesity.[6] Therefore, a diagnosis of IGT, particularly in apparently healthy and ambulatory individuals, has important prognostic implications.

IGT is a stage in the natural history of disordered carbohydrate metabolism. A stage called 'impaired fasting glycaemia' (IFG) was introduced by the World Health Organization in 1999, referring to fasting glucose concentrations that are lower than those required to diagnose diabetes but higher than the normal reference range (Table 1).[7] IGT and IFG are not clinical entities in their own right but are risk categories for future diabetes and cardiovascular disease. They represent impaired glucose regulation, and refer to a metabolic state intermediate between normal glucose homeostasis and diabetes. Both IGT and IFG are often associated with other components of the metabolic syndrome.[1,6] IFG will not be discussed in detail in this article.

An individual with a fasting plasma glucose concentration between 6.1 mmol/L and 6.9 mmol/L is considered to have IFG (Table 1). If an oral glucose tolerance test (OGTT; 75 g anhydrous glucose) is performed, the diagnostic cut-points for IGT are fasting glucose less than 7.0 mmol/L and 2-hour post oral glucose between 7.8 and 11.0 mmol/L.

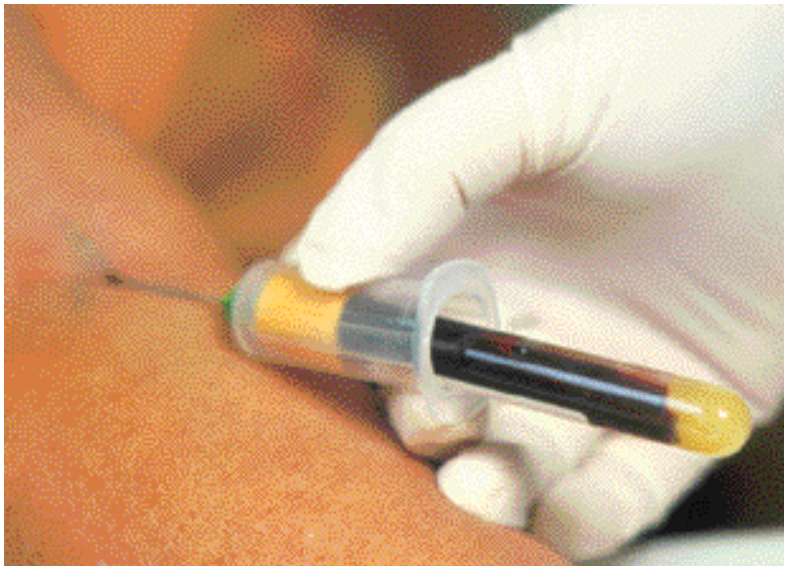
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Figure 1. Laboratory fasting plasma glucose is a recommended screening test for type 2 diabetes.

IGT screening and diagnosis

Evidence-based guidelines endorsed by the National Health and Medical Research Council (NHMRC) help optimise case finding of patients with undiagnosed diabetes in primary care in Australia.[8] These advocate testing for undiagnosed type 2 diabetes in certain high risk groups (see Table 2), and recommend laboratory plasma glucose (preferably fasting) as a screening test (Figure 1). Although the OGTT has the disadvantage that it is labour-intensive and cumbersome for patients and there are concerns about its reproducibility, its use is recommended in Australia in people with blood glucose values in the uncertain range.

According to the guidelines, if the fasting glucose is less than 5.5 mmol/L, then diabetes is unlikely. A fasting glucose of 7.0 mmol/L or more, or a non-fasting glucose of 11.1 mmol/L or more, makes diabetes likely and the diagnosis is confirmed by a repeat abnormal test. If the fasting glucose is between 5.5 and 6.9 mmol/L, or the non-fasting glucose is between 5.5 and 11.0 mmol/L, an OGTT with 75 g anhydrous

glucose is recommended. This strategy was designed for the identification of people who have undiagnosed diabetes, rather than IGT. However, the risk factors are essentially the same.

A cut-off fasting glucose of 5.5 mmol/L for performing the OGTT will result in missing up to 50% of people with IGT. More people would be diagnosed using a lower cut-off fasting glucose, but those in the group that is missed using the cut-off of 5.5 mmol/L are at a lower risk of developing diabetes than those identified,[5] and the missed cases should be picked up with repeat screening in subsequent years before diabetes develops.

Blood glucose testing, therefore, is required only in people with risk factors, and ideally begins with a fasting glucose and progresses to an OGTT where necessary (Table 3).

The purpose of diagnosing IGT is to initiate treatment (lifestyle modification or drug therapy) that will reduce the risk of progression to diabetes, and possibly cardiovascular disease. Detection of IGT, an asymptomatic condition, is unlikely to provide optimal benefit unless other lifestyle-related conditions requiring treatment are also considered. This includes assessment of obesity, blood pressure, serum lipids and physical activity.

IGT and the metabolic syndrome

IGT is often a manifestation of a much broader underlying disorder. The metabolic syndrome (sometimes called syndrome X) is a cluster of cardiovascular risk factors that includes, apart from glucose intolerance (IGT or diabetes), hyperinsulinaemia, dyslipidaemia, hypertension, visceral obesity, hypercoagulability and microalbuminuria (Figure 2). This association also influences contemporary management of IGT. Evidence now exists for a far more aggressive approach to not just the prevention of diabetes but also the treating of other cardiovascular risk factors.

Preventing type 2 diabetes – the reality and the challenge

It does not come as a surprise, given the dramatic increase in type 2 diabetes and its complications and socioeconomic impact, that there is now great interest in primary prevention. People with IGT are at the top of the list of targeted people. Several studies have clearly shown that lifestyle modification (such as weight reduction and increased physical activity) can dramatically reduce the incidence of type 2 diabetes in high risk subjects.[1,4,5] Lifestyle intervention studies have shown that quite modest changes can reduce the progression from IGT to diabetes by 50 to 55%.[4,5]

The principles of the successful lifestyle interventions for diabetes prevention are:

- 5 to 7% weight loss
- moderate intensity physical activity of at least 150 minutes per week
- total fat intake less than 30% of total energy intake
- saturated fat intake less than 10% of total energy intake
- fibre intake more than 15 g per 1000 kcal (4190 J).

An important issue is whether the findings of the two major studies in developed

Table 2. Type 2 diabetes screening: NHMRC recommendations[8]

- People aged 55 years and over
- People aged 45 years and over who have at least one of the following:
  - obesity (BMI ≥ 30 kg/m^2)
  - a first degree relative with diabetes
  - hypertension
- People aged 35 years and over with one of the following ethnicities:
  - Aboriginal or Torres Strait Islander
  - Pacific Islander
  - are from the Indian subcontinent
  - Asian
- People with a history of cardiovascular disease
- People with impaired glucose tolerance or impaired fasting glucose
- Women with a history of gestational diabetes
- Women with polycystic ovary syndrome who are obese

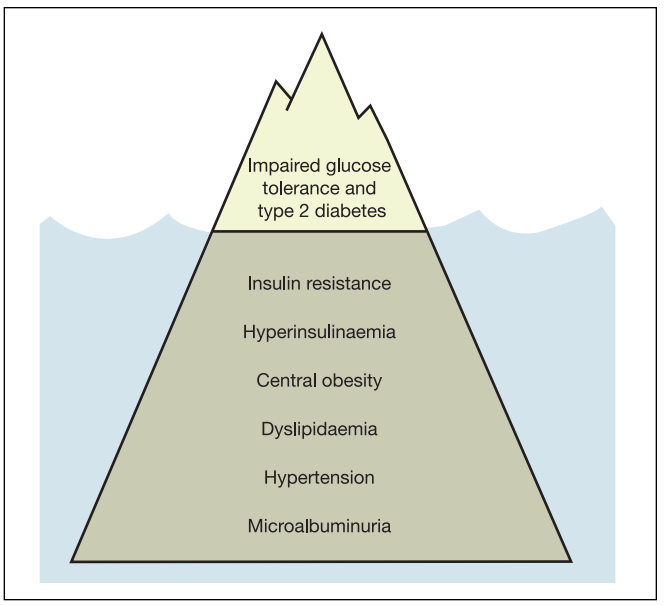

Figure 2. The metabolic syndrome is synonymous to an iceberg with glucose intolerance above the surface but a group of other key cardiovascular risk factors lurking below.

Table 3. Diabetes testing strategy

1. Assess individual for risk factors for undiagnosed diabetes (see Table 2)
2. Measure fasting plasma glucose in those with risk factors
3. Further testing with OGTT depending on result of fasting plasma glucose

countries, the Finnish Diabetes Prevention Study and the Diabetes Prevention Program, can be applied to individual patients. Underpinning the enthusiasm for lifestyle and behavioural modification – clearly the first strategy – there needs to be a realistic approach to interventions with a good understanding of the socioeconomic, cultural and demographic issues and perceptions surrounding chronic diseases such as diabetes. In practice, it is likely that a number of strategies will be needed to complement the lifestyle approach.

The general practitioner needs to assess each person with diabetes not only for glycaemic status but also for other cardiovascular risk factors. Lifestyle advice specific for each person should be provided. People with IGT require follow up, and should be retested annually for progression to diabetes.

The use of pharmacological agents for type 2 diabetes prevention is also being explored. While contrary to an appropriate community-based or individual lifestyle intervention strategy, drugs already used in the management of diabetes may be considered where lifestyle intervention fails or is difficult from a sociocultural perspective.

Benefits, in terms of prevention of diabetes, have been found using metformin, acarbose and the thiazolidinedione troglitazone (withdrawn from the market because of adverse hepatic effects).[9] Large intervention studies are currently in progress with ramipril and rosiglitazone (the Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medications [DREAM] study), and with valsartan and nateglinide (the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research [NAVIGATOR] study). It is unlikely that pharmacological intervention will be recommended for large scale use in IGT until it can be shown that it not only prevents the development of diabetes but also clinical cardiovascular disease.

Conclusion

Although preventive action – lifestyle or pharmacological – will not be easy or cheap, the magnitude of the problem we face with diabetes and its complications demands serious action. Intervention with drugs poses issues such as treating asymptomatic subjects, but the cost of diabetes and its complications to the community may justify this approach. Longer-term follow up studies are needed to establish whether lifestyle and pharmacological interventions actually prevent type 2 diabetes or merely delay its onset.

The person with IGT represents a major challenge for general practitioners. Intervention at an early stage may reduce dramatically the risk of future diabetes and cardiovascular disease.

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DECLARATION OF INTEREST: Professor Zimmet has received support from GlaxoSmithKline, E Merck, Bayer AG, Aventis and Novartis, and is Principal Investigator in Australia for the DREAM study. Dr Shaw has received support from Aventis.

Guessing glycaemia

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How would you check the discrepancy in test results in the following case?

Case history

Julie is 64 years old and has had type 2 diabetes for nine years. You are reviewing her as part of her diabetes care plan.

Over the last two years Julie's HbA_{1c} has increased gradually from 6.8% to the current value of 9.1%; however, her blood glucose values suggest better control. Her blood glucose profile (measured before meals and bed) is as follows:

- breakfast time, 4 to 7 mmol/L
- lunchtime, 3 to 8 mmol/L
- teatime, 4 to 7 mmol/L
- bedtime, 5 to 8 mmol/L.

Julie's current hypoglycaemic medication includes metformin 850 mg twice daily and glipizide (Melizide, Minidiab) 10 mg twice daily. You are reluctant to increase the metformin dosage since previous attempts have resulted in gastrointestinal side effects. You doubt whether increasing the glipizide or changing to another sulfonylurea will help.

In previous discussions Julie has been extremely reluctant to consider insulin treatment. You also have reservations given that she lives alone, has a somewhat erratic lifestyle and is overweight. (Julie's weight is 79 kg and her height, 164 cm; her body mass index is 29.4 kg/m^2.)

You would like to believe that the blood glucose results are correct and wonder if the HbA_{1c} results have been spuriously high.

What should you consider?

To check whether the HbA_{1c} results are spuriously high, consider the following:

- What could explain the apparent discrepancy?
- How would you check the HbA_{1c} results?
- How would you check the blood glucose monitoring results?
- What is the expected relation between the HbA_{1c} and blood glucose results?

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ERICK CAMP, PHOTOLIBRARY/PHOTOTAKE

Explaining the apparent discrepancy

Blood glucose

The blood glucose results may be misleading because of a faulty meter, strip or patient technique. Patients may not be conducting regular quality control checks to ensure that their technique is accurate, and they may be getting systematically high or low readings. Occasionally patients do not record high or low values because they 'know what caused them' and 'it was an unusual event'. Rarely, patients will enter incorrect results or results of nonexistent tests. This may be to give a 'good' report to the doctor because the doctor clearly wants certain tests to be done and certain results to be obtained.

HbA_{1c}

HbA_{1c} is a subfraction of haemoglobin. Its level reflects the integrated effect of blood glucose levels over at least several weeks. The effects of recent blood glucose levels may be overridden by past effects so that the HbA_{1c} may not reflect current blood glucose values.

Furthermore, different laboratories use different assays for measuring HbA_{1c}. Some of these assays may be affected by the presence of abnormal haemoglobin variants and give spuriously low or high HbA_{1c} values.

Checking the accuracy of blood glucose results

By asking patients how they carry out a blood glucose test and watching them perform one, you may be able to identify problems in technique. If you are not confident about your ability to check a patient's technique, you may refer the patient to a diabetes nurse.

To check the reproducibility and accuracy of a patient's technique ask him or her to measure the blood glucose level immediately before and after blood is taken for laboratory blood glucose monitoring. The difference in the patient's blood glucose results before and after venipuncture will indicate the reproducibility of his or her technique, and comparison of the patient's values with the laboratory value will indicate the accuracy of the technique.

By checking the meter's memory, you can identify readings that differ from those entered in the patient's logbook. This can give unexpected information. For example, a study of pregnant women with diabetes whose meters had memories (of which the patients were unaware) showed that even highly motivated patients might enter incorrect values.

Checking the accuracy of HbA_{1c} results

If current blood glucose control is very different from the control achieved in the recent past, repeating the HbA_{1c} measurement in a few weeks' time will give you a better idea of overall blood glucose control.

If there is the possibility of reduced red blood cell survival (e.g. if the patient has experienced blood loss or haemolysis), measurement of the level of another glycosylated protein (e.g. fructosamine) may give a clearer picture of current glycaemic control. Fructosamine is a glycosylated albumin that has a much shorter turnover time than does HbA_{1c}.

Spuriously high HbA_{1c} values caused by the presence of haemoglobin variants can be detected by measuring fructosamine, which will have its usual relation with blood glucose levels despite the presence of variants. Alternatively, you could ask the laboratory if the HbA_{1c} results could be affected by such variants and, if so, how the results could be checked.

Expected blood glucose and HbA_{1c} relation

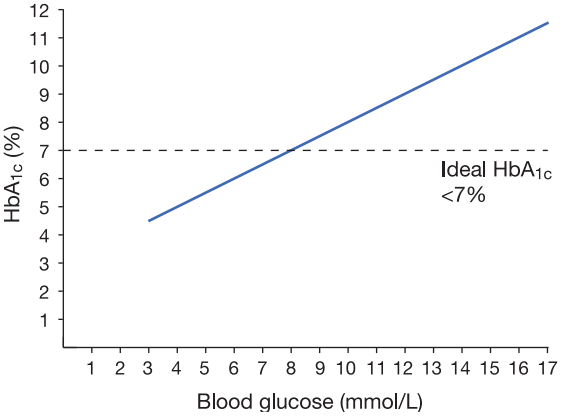
Within the ideal ranges for both HbA_{1c} and blood glucose, values approximate each other. At higher than ideal values, the HbA_{1c} value is lower than the average blood glucose level, with the difference between the two increasing with increasing values (see the graph in the box on this page, which also shows the formal relation between blood glucose and HbA_{1c} values).

Remember that the HbA_{1c} reflects the overall average blood glucose level (24 hours per day over several weeks). If the blood glucose level is measured when it is likely to be low (for example, while fasting), but the level is higher later in the day, HbA_{1c} will be higher than that expected from the fasting value. Conversely, if the blood glucose is measured when it is likely to be high (for example, after meals), but the level is lower before meals and throughout the night, the HbA_{1c} will reflect the overall lower average blood glucose.

Generally, patients are encouraged to measure their blood glucose before meals; this gives a better guide of overall glycaemia than does measurement after meals.

Relation between blood glucose level and HbA_{1c}

HbA_{1c} (%) = (blood glucose level [mmol/L] ÷ 2) + 3



Summary

The key points to check when blood glucose monitoring and HbA_{1c} results seem conflicting are:

- review the blood glucose results over a 24-hour period
- review the patient's blood glucose monitoring technique
- consider checking the patient's blood glucose monitoring values with laboratory values
- ask the laboratory if the HbA_{1c} result could be misleading
- consider checking the HbA_{1c} result by measuring the fructosamine level.

In Julie's case, her blood glucose result was 1.8 mmol/L below the laboratory result. A new meter gave the correct blood glucose results. Julie accepted the need to start insulin and both she and you felt better. MT

DECLARATION OF INTEREST: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think that these associations have influenced the content of this article.

A different approach to the care of the diabetic foot

A traumatic injury requires protection from further trauma if healing is to occur with minimal residual deformity. Diabetic patients often develop ulcerated feet, but continue to walk on them because of reduced pain perception. These people are at risk and need to be alerted early to the dangers involved.

GRACE WARREN
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A different approach

This article provides 'a different approach' in that it has been designed to allow healthcare workers in all situations (including non-ideal) to successfully treat patients with neuropathic feet.

There are many situations in both metropolitan and rural Australia in which there are not enough podiatrists to care for all the neuropathic feet. Hence, GPs need to be able to care for these feet, and to teach patients with diabetes or known neuropathy how to care for their feet.

Recommendations given here do not eliminate the need for podiatrists, but rather address the circumstance when they are not available or serve to supplement their routine care.

The diabetic foot

The basic pathology in the diabetic foot is neuropathy. However, not all diabetic feet are anaesthetic and many diabetic patients have a neuropathy of which they are unaware.

'Of course I can feel. My feet are not numb. I know when my foot hits the floor', says the patient with diabetes. The pressure of foot strike is appreciated by many diabetic patients, but they could be unknowingly walking on a piece of broken glass and driving it in deeper with every step. Pain fibres are often the first fibres destroyed in diabetes, leprosy and many other neuropathies, and it is this impaired pain sensation that is a major problem in the diabetic foot.

It has been estimated that 60 to 70% of diabetes-related ulcers are due to neuropathy. It is likely that this is an underestimate because in the absence of neuropathy, discomfort after even a minor injury would prevent progression to a chronic ulcer.

Testing for neuropathy

In my experience, reduced pain sensation can be detected by testing 'sharp and blunt' perception. Electrophysiological methods can both confirm neuropathy and detect unsuspected neuropathy.

Testing sensation with monofilament nylons provides easily recordable and repeatable measurements. While particularly useful to monitor the progression of a neuropathy, this assesses pressure rather than pain sensation. Moreover, the average GP will not have monofilaments at hand or the time to perform this test.

IN SUMMARY

- **Many diabetic patients have a neuropathy of which they are unaware.**
- **Every diabetic patient should be taught at diagnosis how to care for his or her feet.**
- **Most neuropathic ulcers are not infected and will heal with anything on them except the patient's weight.**
- **Any hot, swollen, painless foot in a diabetic patient should be treated as a neuropathic bone lesion and protected, until proved otherwise.**

A hot, swollen, painless foot

A hot, swollen, painless foot may be the first indication of neuropathy. Doctors often assume this presentation to be osteomyelitis, even when there is no obvious break in the skin. Radiographic examination should be made as soon as possible and preferably before starting any treatment. If x-ray is delayed, the limb should be protected and be non-weight bearing until radiography can be performed.

Some of these patients will have a bone lesion, such as a chip, a fracture (often stress) or localised osteopenia. The last indicates that a fracture or other bone damage has occurred probably within the preceding eight weeks. Osteopenia accompanied by fragmentation or disorganisation of the bone indicates the fracture occurred three to six months previously and needs urgent realignment to prevent permanent deformity and disability. If there is any bone abnormality on x-ray, further views should be taken to clarify the situation.

It is essential that any neuropathic foot with an active bone lesion be adequately immobilised in a total contact cast in a functional position. Figures A to C in the box on this page show progression of a neglected cuneiform fracture.

Diabetic patients may need to use a cast for many months. It is not that these patients' bone takes longer to heal than that of others, but that they are at risk of refracture and formation of deformity during unprotected walking. These patients' reduced pain perception encourages them to abuse the foot and stress the fracture before healing is mature, while early walking may cause deformity of the osteopenic bone.

Charcot foot

The diagnosis of a Charcot joint or Charcot foot strikes terror into many clinicians; however, recent work indicates that these joints will heal but need prolonged protection to prevent refracture. Charcot described a grossly hydroarthropic unstable joint in a patient with syphilis, but the term is now used loosely to describe almost any bone deformity in a neuropathic foot. Due to the fear of the term 'Charcot foot', I prefer to call it neuropathic bone disintegration or disorganisation, and I expect to obtain healing in 100% of compliant patients. Many neuropathic feet with bone lesions become deformed, but it is often possible to reshape the foot before applying the cast, in which case the final shape may be compatible with function. If the foot is grossly deformed, it is often possible to surgically reconstruct the foot so that it returns to a more functional shape.

Neuropathic bone disintegration

A neuropathic foot with a bone lesion needs to be immobilised two to three times longer than a sensate foot with such a lesion. For example, a diabetic patient with a midtarsal fracture or

Cases of bony neglect: progression of untreated fractures

Fractured cuneiforms

Figures A to C show a typical fracture of the cuneiforms that was neglected and progressed to a deformity. It required reconstructive surgery to prevent ulceration over the resultant deformity.

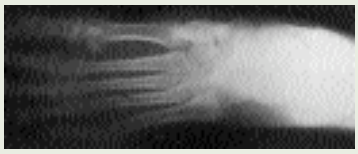


Figure A. X-ray showing a mild cuneiform bone abnormality that was not treated.

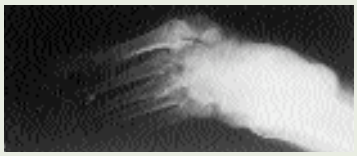


Figure B. X-ray of the same foot 12 months later showing marked deformity of the whole tarsometatarsal joint line (Lisfranc area).

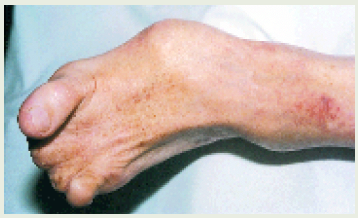


Figure C. External view of the foot at time of the x-ray shown in Figure B.

A fractured navicular

Figures D and E show a fractured navicular in a diabetic patient that on x-ray was reported as a Charcot foot. The patient was told the lesion would not heal and no treatment was given, resulting in marked deformity and ulceration six months later. Subsequent treatment in a total contact plaster cast provided the patient with a functional foot that is still stable years later.

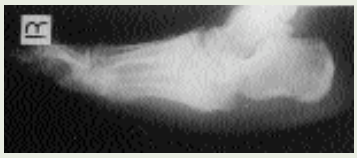


Figure D. X-ray of a fractured navicular that was not treated.

Figure E. X-ray six months later showing disorganisation of midfoot with a boat-shaped foot deformity.

arthrodesis will need eight to 10 months in a total contact walking plaster cast to ensure healing to a degree where walking will not precipitate further damage.

Many diabetic patients who present with a hot, swollen, painless foot have been walking on a fracture that has not been treated adequately (if at all) and so has progressed to deformity and disability. Figures D and E in the box on page 53 show the progression of an untreated 'Charcot foot'. The treatment of any neglected fracture is urgent if the foot is to be saved as a functional unit; hence, any hot, swollen, painless foot should be treated as a neuropathic bone lesion and placed in a cast, until proved otherwise.

If there is an ulcer on the foot, it will heal rapidly while the limb is in the cast. An ulcer does not need frequent dressings unless it is discharging freely – in which case the cause of discharge needs to be ascertained, especially any pathology that necessitates full rest and protection, (e.g. osteomyelitis). Patients should not walk unprotected on a neuropathic foot with osteomyelitis because more bony deformity may occur. All feet with osteomyelitis should be treated in a total contact walking cast as well as with antibiotics. The cast can be modified to allow dressings if needed.

How callus causes ulceration

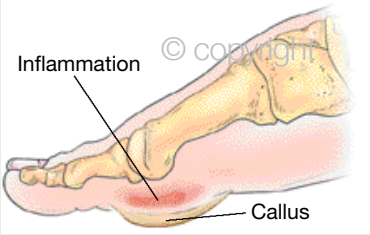


Figure F(i). Pressure during walking forces the callus into the subdermal tissues and traumatises them, causing inflammation and oedema.

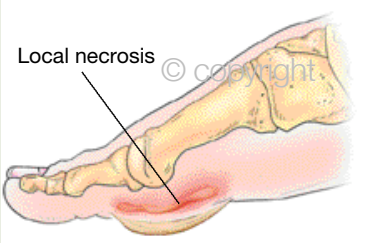


Figure F(ii). The oedema increases the anoxia in the subdermal tissues and causes local necrosis.

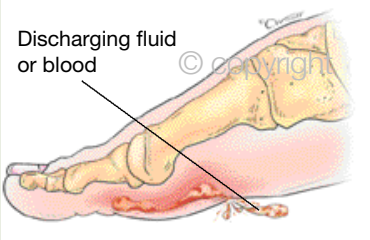


Figure F(iii). When the pressure of the necrotic fluid and/or blood increases, the fluid ruptures out through or beside the callus revealing the ulcer.

ILLUSTRATIONS © CHRIS WIKOFF, 2003

Radiography

Patients with neuropathic feet should have baseline x-rays taken of the feet at the time of diagnosis of the neuropathy. Recommended views are anterio-posterio-oblique (APO) with 15 degrees of obliquity, and standing lateral to show the whole length of the foot and the ankle joint. If there are suspicions of ankle problems, include an AP view of the ankle. The APO view shows the Lisfranc area, which is often fractured and displaced in diabetes, much better than a true oblique or AP view. The standing lateral view should show any prominent bone that may predispose to ulceration when standing or walking. The extent and nature of any abnormal findings should be determined.

Vascular problem?

Many diabetic patients are told they have a 'poor blood supply' and are referred to a vascular surgeon, especially if they have developed dry gangrene. Dry gangrene may certainly result from anoxia such as occurs with a 'poor blood supply', but it can also be caused by anything that produces local anoxia or hypoxia in a limb with a normal blood supply.

We are all familiar with bedsores, in which tissue death results from anoxia. In the same way, gangrene may occur in diabetic patients when a bandage is wrapped around a foot that is then jammed into the patient's usual shoe (Figure 1). The altered pain perception makes a neuropathic limb vulnerable to anoxic tissue injury and necrosis. Diabetic patients hence need to be taught not to use garters or tight bandages, and never to use elastic bandages.

A cold, dry foot

Before jumping to the conclusion that the cold dry foot's blood supply is inadequate, check carefully for local factors that may have caused the anoxia and then rectify the situation to obtain and maintain healing. In my experience, if capillary return in the toe tips is normal, there is

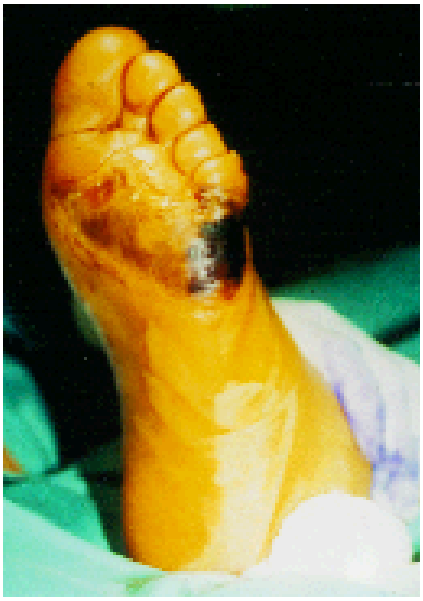


Figure 1. Typical area of gangrene caused by wrapping a bandage around an ulcer on the sole and jamming the foot into a fitted shoe.

probably adequate blood supply for conservative treatment of ulceration and maintenance of a functional foot, eliminating the need of amputation.

It has been shown that the feet of many diabetic patients have up to five times the blood flow of normal nondiabetic feet, yet the feet feel cold. This results from arteriovenous shunting and failure of capillaries to dilate secondary to autonomic neuropathy. However, when the same foot is traumatised it will respond with capillary dilatation and so the patient may present with a hot, swollen, painless foot, reflecting that it is not avascular and that the blood supply is adequate for healing.

Eventually, the autonomic neuropathy causes alteration of sweat and sebum production so that the neuropathic limb is often excessively dry. It is accepted that a cold, dry foot is one at risk of undetected trauma because of the likelihood of accompanying sensory neuropathy.

Characteristics of suitable shoes for diabetic feet

- Easily available and socially acceptable.
- Sufficiently large.
- Reliable means of fixation firmly to the foot – by laces, buckles or velcro – to prevent falling off or excessive slipping during walking.
- Resilient insoles – not soft (see Figure G); preferably also a resilient sole that is thick enough to protect from stones and the like during walking.
- Smooth internal linings with no roughness. Shoes should be stitched or glued, not nailed or tacked.
- Able to be worn all the time – patients should be instructed not to take one step without shoes (or slippers, which need to have similar characteristics).

Figure G. The diabetic patient can check the resilience of shoe insoles by squeezing the insole between the pulps of the index finger and thumb. If the insole compresses to less than half its original thickness, it is too soft; but if it does not compress to near half, it is too hard.

Today's callus is tomorrow's ulcer

The natural response of skin to stress and excessive pressure is the production of hard skin or callus to protect the softer, more vulnerable, tissues underneath. In normally sensate skin, the mass of callus causes discomfort so that the patient acts to alleviate the stress or removes the callus. In the patient with sensory neuropathy the callus builds up until a mass is formed. Local hypoxia and anoxia caused by walking on this mass result in death of the underlying tissues and ulcer formation (see the box on page 54).

A well-hydrated callus is soft, supple and resilient and less likely to cause pressure problems than a dry callus, such as occurs in autonomic neuropathy. The hard callus may become like a pebble and split, with the hard edges of the resulting crack acting as a splint, which tear the split apart and make the ulcer deeper with every movement. Blood or fluid escaping from under a callus indicates that an ulcer is present.

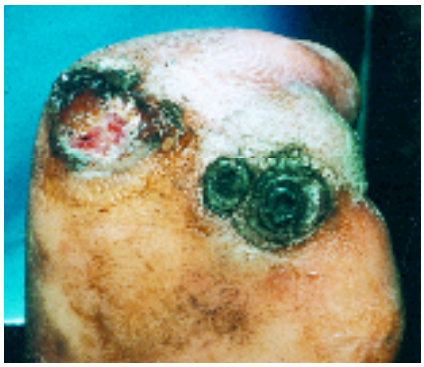
In practice

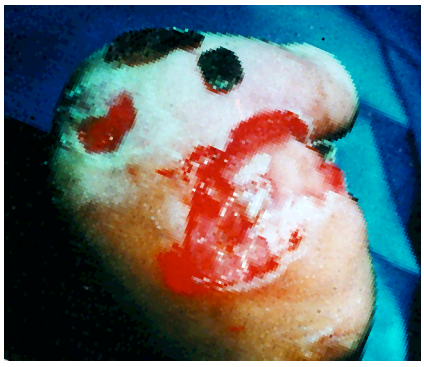
The management and care of neuropathic ulcers is the same irrespective of the cause; however, it is desirable that the underlying cause (e.g. diabetes) be diagnosed so that it can be correctly treated or controlled.

Initial assessment

A patient walks into your surgery on an ulcerated foot without any obvious discomfort. You must assume that the ulcerated area has absent or reduced pain perception. What is the underlying diagnosis? What will you do to help?

- **Assess severity.** Examine the lesion and the foot – is sensation reduced on all or only part of the foot? Check the history, including any previous episodes or accidents and, if available, previous x-rays.
- **Try and establish the immediate cause of the ulcer.** Is it due to direct trauma, such as a cut, blister or foreign body or jumping onto a sharp object? Is there excessive pressure in the shoe due to a tight bandage or stocking, a foreign body or build up of callus? Is any urgent care needed to compensate for this cause?
- **Check the patient's shoes.** Do they fit without excessive pressure? Most diabetic patients do not need special shoes if the foot is still basically anatomically normal, but resilient insoles are important (see the box on this page).
- **Local treatment of the ulcer.** Most neuropathic ulcers are not infected and affected patients do not need antibiotics. These ulcers will heal if kept clean and protected from further trauma, such as walking. However, if there is evidence of inflammation around the ulcer take swabs for culture and sensitivity, and in the diabetic patient prescribe antibiotics. A deep tissue or bone biopsy is generally not indicated and will produce further trauma and risk spread of infection. Do not assume heat and swelling are due to osteomyelitis, but arrange an x-ray as soon as possible. If in doubt, treat at once for the worst possible scenario – i.e. a disintegrating bone lesion – until proved otherwise.





Figures 2a and b. The severity of the lesion cannot be established until callus is removed. a (left). A neglected forefoot – note the loss of most toes with large masses of callus and an apparently small ulcer. b (right). After a thorough soak and scrape. The two thick plugs of callus are laid on the forefoot skin to show their size and allow comparison with the size of the ulcers beneath.

Modified total contact cast

A specially modified total contact plaster cast has been devised that can be bivalved and removed, and then reapplied with velcro straps. This allows access to any acute lesion for debridement and dressings.

These casts are also useful for trial walking, when a patient is returning to walking without a cast. The duration of walking without the cast is gradually increased until the patient can walk all day without any signs of inflammation developing on the affected foot.

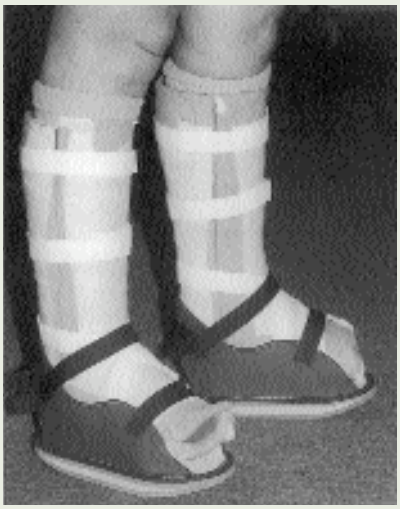


Figure H. A patient standing in reapplied bivalved total contact casts. Football socks are worn inside as liners; they are ideal for filling any dead space and protecting the toes.

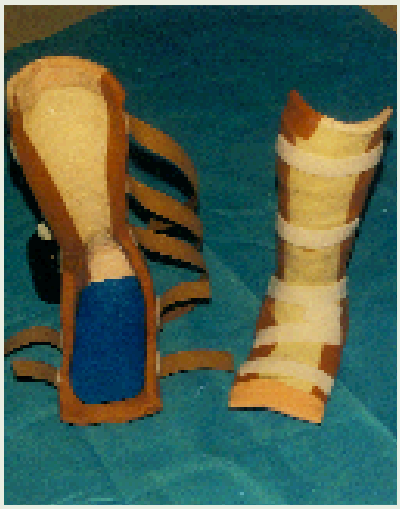


Figure I. The two sections of the cast opened – an optional, suitable insole has been added in the sole.

Allowing the ulcer to heal

Neuropathic ulcers will heal with anything on them except the patient's weight. The sooner the ulcer heals, the better the quality of the scar and the less likely that it will break down again. If the ulcer is a minor break in the epithelium it will probably heal with a simple dressing, provided that the dressing is not thick enough to cause pressure on the ulcer when the patient walks. Many people use donuts around ulcers or extra double thickness insoles with a sink cut in the lower layer beneath the ulcer, which relieves the local pressure without allowing the healing tissue to protrude into the sink like a mushroom. However, the extra insole may increase pressures inside the shoe, producing more problems unless a larger shoe is used. The use of postoperative shoes is not recommended unless they have very resilient insoles added, because the soles are usually not resilient and this may cause additional problems.

An important method of reducing anoxia in the affected tissues and encouraging healing is the removal of callus, (see the box on page 58 and 59). This should be done as soon as possible, preferably before the patient leaves the doctor's surgery. (If the patient waits to see a podiatrist, it may mean walking on the callus for six to eight weeks while waiting for an appointment.) Every doctor who treats patients with neuropathy should be able to remove callus or employ someone who can, because correct treatment cannot be started until the callus is removed and the severity of the lesion is established (Figures 2a and b). Unfortunately, it is a time consuming procedure and may take half an hour or longer.

Chronic ulcers

Chronic ulcers, often claimed to be non-healing, should be treated in a total contact walking cast for at least six to eight weeks before considering surgical intervention. Most neuropathic ulcers will

heal with adequate rest and protection.

A correctly made total contact plaster cast spreads the patient's body weight over the whole of the inside of the cast. Up to 40% of the patient's weight is taken by the leg piece, and the sole's rigidity eliminates the high pressure points that occur during walking. Hence, there are no patches of anoxia, and traumatised areas do not move so are rested, even during walking.

A specially modified total contact plaster cast has been devised that can be bivalved and removed for debridement and dressings, and then reapplied with velcro straps (see the box on page 56). Wearing such a cast day and night – not one step without the cast – will do much to hasten healing. Some doctors are afraid of applying a plaster cast to a neuropathic limb; the bivalving enables checking for fit, pressure and rubbing each time the foot is dressed.

For a seriously infected ulcer, bed rest with a splint to eliminate limb movement is needed until the gross swelling has subsided. The patient can then be treated in a total contact cast at home. Bivalved casts minimise hospitalisation and its complications. However, they are not suitable for the long term treatment of neuropathic bone disorganisation because the damaged bone's position can be compromised during removal and reapplication. Also, the patient may remove the cast at home and walk on the unprotected limb. Once the ulcer is relatively dry and swelling has decreased in the limb with a bone lesion, the bivalved cast can be fixed on (with thick socks worn to fill any gap) or a new total cast can be applied. This allows the position of the healing bones to be undisturbed for the next three to six months.

Long term daily care of the neuropathic foot

Every diabetic patient should be taught how to care for his or her feet, at diagnosis and at repeated refresher sessions. They need to inspect their feet daily, soak the limbs in water at room temperature, remove any forming callus and then oil the skin. Patients with cold feet should wear suitable socks and avoid extreme temperatures from radiators and hot water bottles. All diabetic patients need to know how to select suitable shoes. Socks and shoes should be worn at all times.

Inspection

Inspection for rubs, blisters, cuts or red areas is preferable in the evening. Any break in the skin needs immediate treatment, and the patient should try to assess what caused the lesion to prevent recurrence. A foot that is hot and swollen at the end of the day needs to be checked in the morning. Normal travel heat and swelling should settle overnight. If the symptoms do not subside overnight, pathology of deeper tissues must be suspected, e.g. a bone lesion, and the limb should be rested and protected to allow healing.

Soaking

Soaking compensates for the autonomic neuropathy and consequent reduction in sweat and sebum production. It is not clear how much water permeates beyond the epidermis, but superficial hydration will prevent water loss from the subepidermis where hydration is most needed. Patients who have diabetes should be specifically warned not to use hot water as they are at risk of burning themselves.

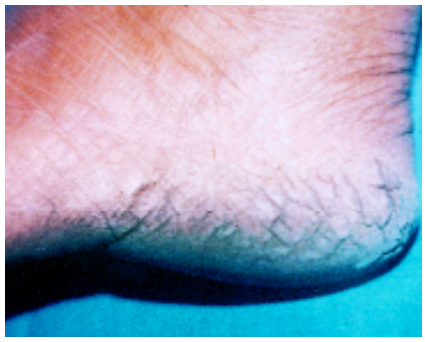


Figure 3. Typical dry callused heel that will tend to split and crack. This is easy to prevent by regular soaking and scraping.

Oiling

Moisturising creams are usually based on mineral oils, which are not absorbed to any appreciable degree by the skin. Vegetable oils are absorbed a little, animal oils and fish oils are absorbed more, and regular applications of these improves the skin's texture and suppleness. After soaking, applying any oil will prevent evaporation by forming a film with the surface keratin. Urea containing creams reduce the production of callus where applied, as well as serving as the oil.

Callus removal

A once weekly podiatry visit is the minimum needed for keeping callus controlled.

Consultant's comment

Dr Warren has written an excellent article containing many very practical tips for the management of the diabetic foot. Her experience in the surgical management of neuropathic feet is derived from many years working in Asia and, in short, relies on a dorsal approach to the foot rather than an approach through the plantar aspect with consequent development of scarring. Dr Warren's surgical approach has been adopted by many foot surgeons and is clearly of major benefit in the management of diabetic foot disease.

Professor Bruce Robinson
Professor of Medicine (Endocrinology)
University of Sydney, Royal North Shore Hospital, Sydney, NSW

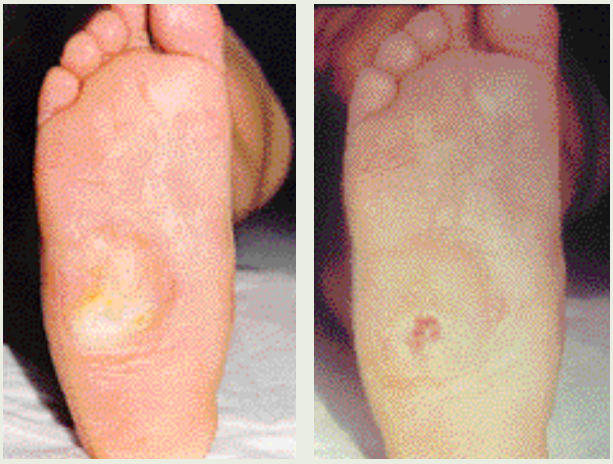
Controlling callus: a daily routine

The feet of diabetic patients and others with sensory neuropathy are particularly at risk and teaching callus removal should be routine.

Daily care

Ideally, the patient with sensory neuropathy or his or her carer should remove some callus every day. A podiatrist, doctor or nurse should remove it initially in order to determine the severity and presence of any complications that need treatment. Not until the callus is removed can the doctor know the extent of any ulceration (Figures J and K). The patient should learn self-care and maintain the feet, with regular podiatry and/or doctor's review to check the efficiency of the patient's care, and to attend to additional needs such as care of the nails.

The method given here has enabled dozens of patients with neuropathic feet and no pain perception to remain ulcer free for many years.



Figures J and K. Removal of callus. J (left). A large callus with a broken surface. K (right). The foot after scraping. Note that there is evidence of a now dry haematoma.

Soaking

Maintain hydration by soaking the feet in plain water at room temperature for 15 to 20 minutes. There is no need to add any medication to the water, but this can be done if there are complicating conditions. Do not advise warm or hot water for fear of burns. In dry climates the legs also need protection from dehydration, which can be achieved by oiling the leg up to the knee and wearing long socks to minimise evaporation.

Callus removal

The callus is removed while the skin is still wet, the restored suppleness making the callus easier to remove. Only withdraw one foot at a time from the water to scrape it. If the callus is very thick, remove some callus and then resoak that foot while starting to scrape the callus off the other foot.

Trim callus located around ulcers right down, to prevent excessive pressure by the callus on the epithelial tissue trying to heal. Such pressure causes local hypoxia and anoxia, and accepted teaching is that anoxia causes ulcers.

Tools to remove callus

There are many implements that can be used to remove callus.

Pumice stone is often recommended and may be adequate if used every day but after a few months the stone needs to be roughened again in order to be effective. Many Asian countries make pottery callus scrapers, and some patients use suitable stones, such as ironstone, or pieces of broken baked brick, with a rough edge. Sandstone should not be used because the sand grains may become imbedded in any ulcer.

Metal 'foot scrapers' can be bought, but are usually not recommended for diabetic patients because they may be too rough and damage the skin.

Green nylon pot scourers (e.g. Scotchbrite) prove effective, easily available worldwide and cheap. If kept on the bath edge and used dry when the foot is still wet, a scourer will remove some callus each day, preventing build up. It is easy to use the flexible nylon pad to get round toes and along cracks. The patient must be taught not to scrub excessively because it is possible to traumatise the epithelium and create an ulcer on insensate skin. This happens rarely, and most patients or their carers rapidly learn how to reduce the callus and keep it down.

Using a scalpel or knife

The most efficient implement for callus removal is a surgical scalpel blade size 10. The clinician holds the knife so that the bevel of the blade is almost parallel to the skin and the blade is used as a razor would be used (Figures L and M). Small swift strokes remove the callus in flakes. No force should be needed with a sharp blade. If the little finger of the hand holding the knife rests on the sole of the foot, it will enable the operator to maintain a regular thickness. Do not cut as if carving meat nor use scissors as these usually leave a rough irregular surface – the aim is to eliminate all roughness and irregularity. Any small bladed knife that can be well sharpened can be used, and I know of many patients who use a pocketknife or penknife, or even pencil sharpener, with excellent results. Also a standard safety razor will keep the sole smooth but is difficult to

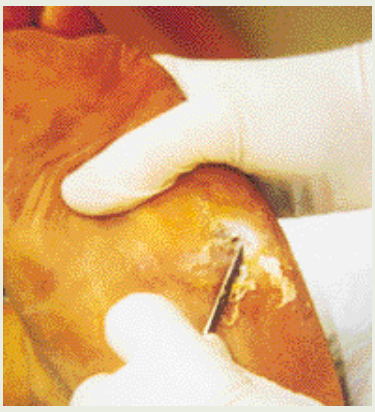
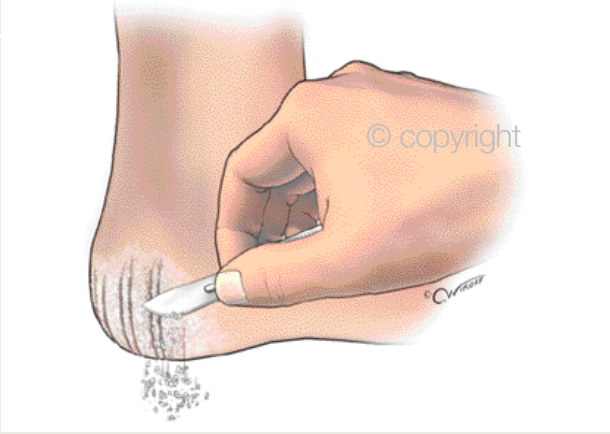
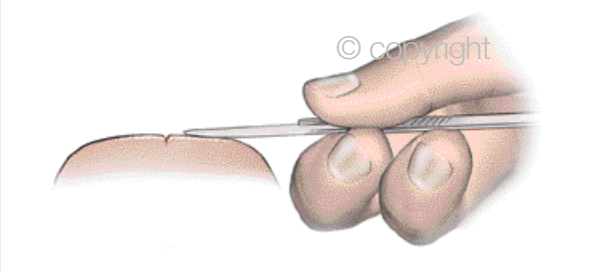


Figure L. Removing callus with a scalpel.





ILLUSTRATIONS © CHRIS WIKOFF, 2003

Figures M(i) and M(ii). A scalpel or other bevelled short knife can be used to shave off callus. i (top). Hold the instrument so that the bevel is almost parallel to the skin. ii (bottom). Scrape along the lines of cracks, not into them.

use around the toes and in cracks.

Although many clinicians may fear patients using scalpels, a clinician skilled and confident in using a scalpel him- or herself can teach selected patients to do the same. The physician less certain of his or her patient's abilities should initially reduce the callus as much as possible (a scalpel providing the most efficient and quickest method), and teach the patient other techniques, such as using a scourer or stone after soaking.

Oiling

After scraping, oil the skin to prevent dehydration. Any oil will form a coat with the keratin and reduce evaporation. Pure lanoline is best to improve skin quality because, being an animal fat, it is absorbed into the skin. Urea containing creams are often advised (e.g. Eulactol Heel Balm) because these reduce the production of the callus where applied and serve as the oil, preventing dehydration.

Footwear

The neuropathic foot often has reduced padding on the sole and this needs to be compensated for if callus and ulcers are to be prevented. The Scholl's Shoe Comfort Comfort Line insoles are an almost ideal

Warren G. Controlling callus. Medicine Today 2003; 4(4): 95-97.

insole that can be bought from the chemist.

This is rarely available and, when it is, can become quite costly. Hence, the patient should maintain his or her own feet, and the podiatrist can check the feet and attend to nail care at regular visits.

All patients who do not have ulceration should be taught some simple method of callus removal (see the box on this and the previous page). I teach all my patients to do this for themselves and have literally hundreds of patients who have learnt to reduce callus using a surgical scalpel or a safety razor. Many clinicians are afraid of suggesting that a blade of any sort be used; however, it is a matter of how well the patient is taught. For the sight impaired and those who cannot reach their feet, a relative or carer should be taught to remove callus for them. A preferably dry, green nylon pot-scraper can also remove the flakes of callus that soften and loosen when the limb is soaked in water. If a little callus is removed every day, a mass should never build up sufficiently to cause problems. Figure 3 shows a typical callused heel, easily improved by soaking and scraping.

When ulceration is present

Ulcers should be covered with any suitable dressing to keep the area clean and encourage healing. 'High-tech' dressings are usually not necessary; advise something simple, affordable and easily available. Magnesium sulphate and glycerol paste (Magnoplasm) is very effective for ulcers and infected wounds. Ensure adequate protection of any ulcerated area for two to three weeks after any lesion is fully healed, and remember that a bulky dressing and a postoperative shoe do not provide the best protection.

Conclusion

Neuropathy should be considered to be present in the feet of all diabetic patients, even those who are unaware of any sensory loss, and all patients should be taught to care for and monitor their feet. In the event of ulceration, the mainstay of treatment is rest and protection from further trauma, noting that most neuropathic ulcers are not infected.

A hot, swollen, painless foot in a diabetic patient should be treated as a neuropathic bone lesion until proved otherwise. MT

Acknowledgement

Chris Wikoff's illustrations are based on original line drawings by Ron Dawes.

Further reading

1. Warren G, Nade S. The care of neuropathic limbs: a practical manual. London: Parthenon, 1999.

DECLARATION OF INTEREST: None.

Priorities in diabetes care

The number one priority in caring for patients with diabetes is the prevention of cardiovascular events by the control of blood pressure and cholesterol. Glycaemic control, smoking cessation and aspirin taking are the next priorities.

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Diabetes and cardiovascular disease

In the last 10 years it has become clear that cardiovascular disease is the major challenge in diabetes care. No matter how you look at it, diabetes and cardiovascular disease are closely linked:

- those individuals with diabetes and no coronary history have the same coronary risk as those with coronary disease but no diabetes, and the combination of coronary history and diabetes is truly 'double trouble' (Figure 1)[1]
- most patients (around 70%) with the acute coronary syndrome have some form of abnormal glucose metabolism if they are tested
- the cost of cardiovascular disease in diabetes is seven times that of the next health issue, which is foot problems, mainly associated with neuropathy (Figure 2)[2]
- mortality associated with the acute coronary syndrome in diabetes is high – 80% of affected patients die within seven years, 45% from the initial presentation and the remainder from a later event.[3]

The big ticket risk factors

Now we have recognised that managing cardiovascular disease is the first priority in the care of patients with diabetes, we are learning to focus beyond glycaemia alone and to concentrate on the ABCss of diabetes care (Table 1):

- control of HbA_{1c}
- control of Blood pressure
- control of Cholesterol
- quitting smoking
- taking salicylates.

The lesson has yet to be fully incorporated into clinical thinking: some doctors still believe that glycaemia is the most important risk factor for cardiovascular disease and have not appreciated that controlling blood pressure and cholesterol gives much more 'bang for your buck' (Figure 3).[4]

We have also learnt that microalbuminuria signals a very high cardiovascular risk (50% eight-year coronary risk), and the Steno-2 Study showed that multifactorial, multidisciplinary interventions can halve this risk.

IN SUMMARY

- **Preventing cardiovascular events is the first priority in diabetes care.**
- **Controlling blood pressure and reducing cholesterol are the first and second priorities, respectively, in this prevention.**
- **Most patients will require multiple antihypertensive agents to control their blood pressure.**
- **Statins are used effectively in controlling LDL-cholesterol. Ezetimibe (Ezetrol) can be used to potentiate their action.**
- **Attention should also be paid to the other ABCss of diabetes care – control of HbA_{1c}, quitting smoking and taking salicylates.**

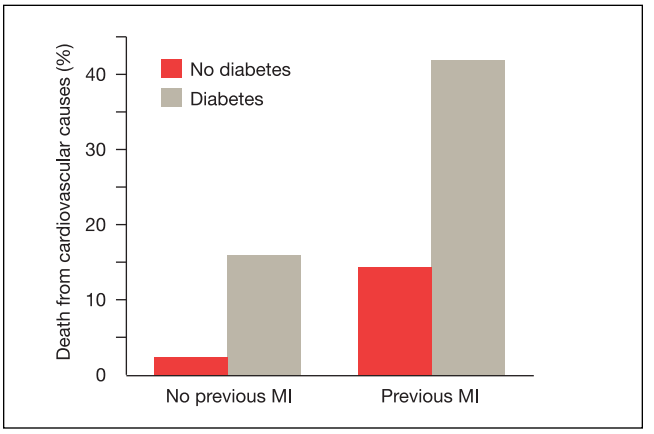


Figure 1 (above). Diabetes and coronary risk: incidence of death from cardiovascular causes during a seven-year follow up of study populations.[1]

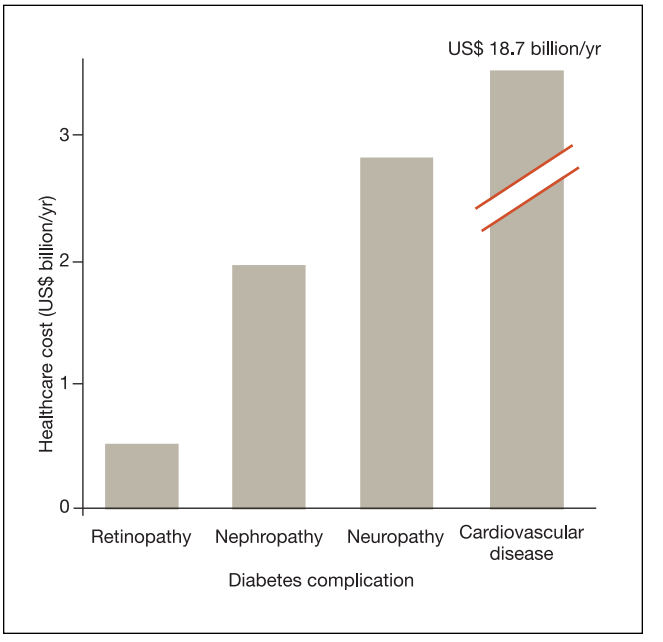


Figure 2 (right). The cost of cardiovascular disease in diabetes outweighs that of any other complications.[2]

The major messages are that preventing cardiovascular events is the first priority in diabetes care, and that controlling blood pressure and reducing cholesterol are the first and second priorities, respectively, in this prevention. We must not forget, however, the other ABCss of diabetes care.

Blood pressure – lower is better

Evidence of the benefits of blood pressure control was available in the 1980s. Since then the target population in whom blood pressure should be reduced has increased and the target blood pressure has decreased.

Table 1. The ABCss of diabetes care

Factor	Target
HbA_{1c}	<7%
Blood pressure	<130/80 mmHg (<125/75 mmHg if proteinuria exists)
Total cholesterol	<4 mmol/L (corresponding to LDL-cholesterol <2.5 mmol/L)
Smoking	Cessation
Salicylates	Aspirin 75 to 150 mg per day

Several trials have shown that blood pressure control in older populations is well tolerated and improves outcomes. Other trials (the Hypertension Optimal Treatment [HOT] study, for example) have shown that lower blood pressure is associated with better outcomes, and the United Kingdom Prospective Diabetes Study (UKPDS) has shown that the benefits associated with lower

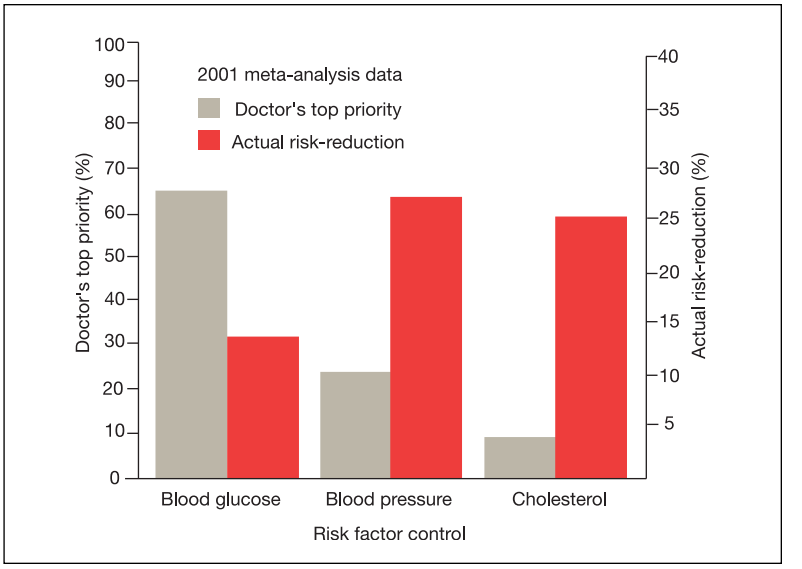


Figure 3. Controlling blood pressure and cholesterol gives greater reduction in risk for cardiovascular disease than controlling glycaemia (2001 meta-analysis data).[4]

continued

Table 2. Steps in reaching target blood pressure[5]

Step 1: Lifestyle modification – healthy eating, physical activity, weight control

Step 2: Add an ACE inhibitor

Step 3: Add a diuretic

Step 4: Add a beta blocker

blood pressure continue to a systolic of 120 mmHg.

The current blood pressure target for diabetic patients is below 130 mmHg systolic and 80 mmHg diastolic, but this may change as more evidence becomes available (Table 1).

Reducing blood pressure

The Royal Australian College of General Practitioners recommends a step approach to reaching target blood pressure in people with diabetes (Table 2).[5] The Heart Outcomes Prevention Evaluation (HOPE) and European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) studies showed that ACE inhibitors provided cardiovascular benefits over and above those associated with lower blood pressure (ramipril [Ramace, Tritace] and perindopril [Coversyl] were used in these studies). The Prospective Study of Myocardial Infarction (PRIME) studies showed that angiotensin receptor antagonists (ARAs) provided cardiovascular and renal benefits in patients with type 2 diabetes and albuminuria over and above that associated with lower blood pressure (irbesartan [Avapro, Karvea] and losartan [Cozaar] were used in these studies).

Thiazide diuretics (chlorthalidone [Hygroton], hydrochlorothiazide [Dithiazide], indapamide) complement ACE inhibitor or ARA therapy, and the low doses usually used (equivalent to hydrochlorothiazide 8 or 12.5 mg/day) are not associated with the problems of the previously used higher doses. Combined once daily preparations avoid increased number and/or cost of medications for the patient. The mechanism of action of the various types of antihypertensive agents is summarised in Table 3.

Before the UKPDS, many people believed that beta blockers were potentially dangerous in those with diabetes, one of their side effects then being thought to be increased hypoglycaemic risk. However, in the UKPDS the beta blocker atenolol gave equivalent benefits to the ACE inhibitor captopril, apart from being associated with extra weight gain (1.8 kg over 10 years). A recent meta-analysis suggested that beta blockers were not associated with increased risk of hypoglycaemia (and, interestingly, suggested that there was such an association with the ACE inhibitor enalapril).[6] Given the high risk of coronary events in patients with diabetes, beta blockers may add antiarrhythmic protection for those having such events. There are, however, no prospective trials to confirm this.

Calcium channel blockers (CCBs) are popular antihypertensive agents but in recent years have become less favoured for patients with diabetes. In part, this is because of the perceived extra benefits associated with the other classes of medications, and in part because side effects from CCBs may be more common in those with diabetes. (Centrally acting CCBs, such as verapamil and diltiazem, have the side effects of gastro-oesophageal reflux and constipation, and peripherally acting CCBs, such as the dihydropyridines, the side effect peripheral oedema.) Nonetheless, the CCBs are effective hypotensive agents, particularly in combination with the above agents.

The management of hypertension is not really a question of which antihypertensive agent is best, as most patients will require multiple agents in the long term. In the UKPDS, for example, an average of 4.5 different antihypertensive medications were required to achieve and maintain the blood pressure of 144/82 mmHg in the intensive treated group.

Remember the rule of halves

The rule of halves reminds us that priorities, guidelines and targets are all very well, but in the real world half of all patients with a risk factor are undiagnosed, half of those diagnosed are not treated, and only half of those treated are achieving targets (that is, 12.5% of the total number of patients with the risk factor).

Diabetes and its risk factor blood pressure are no exception to this general rule, with a recent study showing that only 45% of patients with diabetes were achieving the target blood pressure of below 130/80 mmHg.

Cholesterol – again, lower is better

High total cholesterol and diabetes both increase cardiovascular risk, and the

Table 3. Antihypertensive agents: actions

Drug type	Action		
	Diuretic	Dilator	Cardiac
Thiazides	✓	✖	✖
ACE inhibitors and ARAs*	✓	✓	✖
Calcium channel blockers	✖	✓	✓
Beta blockers	✖	✖	✓

*ARAs = angiotensin II receptor antagonists.

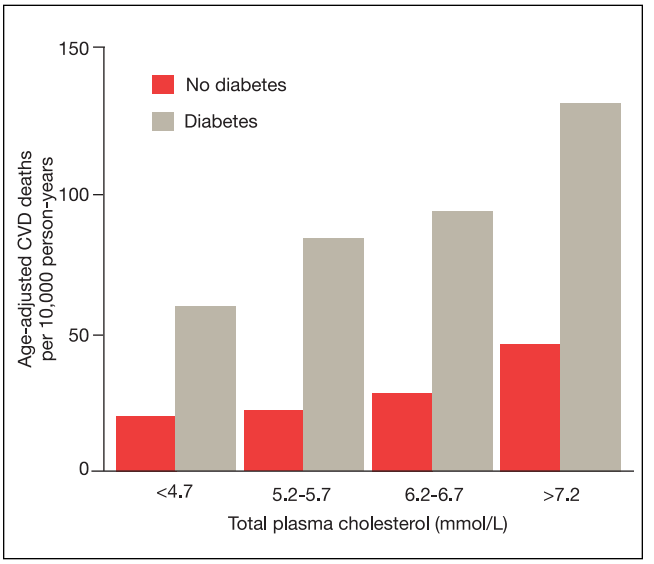


Figure 4. Having both high total cholesterol and diabetes more than doubles a patient's cardiovascular risk.[7]

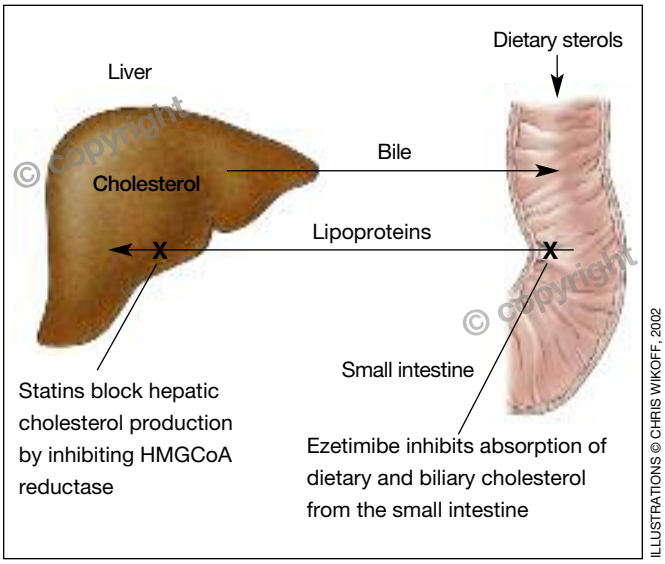


Figure 5. Sites of action of statins and ezetimibe on cholesterol metabolism.

combination more than doubles this risk (Figure 4).[7] A series of trials in the 1980s showed cardiovascular benefits for secondary prevention in patients with cardiovascular disease.

Just as blood pressure got its evidence for primary cardiovascular protection in the 1980s, so did cholesterol in the 1990s. The Heart Protection Study (HPS) and, more recently, the Cardiovascular Atorvastatin Reduction Diabetes Study (CARDS) showed a 25% risk-reduction in cardiovascular events with an absolute risk-reduction of 4.2 and 3.2% over 4.8 and 3.9 years, respectively. In both studies the relation between cardiovascular risk and cholesterol reduction was linear, suggesting, as for blood pressure, that lower is better.

Reducing cholesterol

The statins, which reduce hepatic cholesterol production by inhibiting the key synthetic enzyme hydroxymethylglutaryl co-enzyme A (HMGCoA) reductase, are a major advance in cardiovascular protection, but their use has the following limitations:

- the rule of 6s – doubling the dose of a statin only reduces total cholesterol by a further 6%[8]
- statin escape – in the long term statins lower cholesterol less (even in trials where adherence is less of an issue than in the real world)[9]
- toxicity – although doubling the dose does not double the therapeutic effects, it more than doubles toxicity in terms of potential liver and muscle damage.[10]

Medications used to potentiate the effect of statins themselves have serious limits:

- bile acid binding resins decrease cholesterol but are unpalatable to take
- nicotinic acid has significant side effects, including hyperglycaemia
- fibrates, such as gemfibrozil, may potentiate statin side effects
- fish oils (omega-3 fatty acids) do not meet pharmaceutical quality standards, provide extra calories and may impart a fishy odour to the patient.

Ezetimibe (Ezetrol), the first of a new class of drugs, has the same effect as a bile acid sequestrant but better tolerability and can be administered once daily. It is systemically absorbed, being taken up by the gastrointestinal mucosa, and inhibits cholesterol absorption. Cholesterol levels are lowered by about 20% by ezetimibe either as monotherapy (when a statin is not tolerated) or in combination with a statin.[11] Figure 5 shows the sites of action of statins and ezetimibe on cholesterol metabolism.

Both statins and ezetimibe are subsidised by the PBS to eligible patients (see the flowchart on page 64). Although many people with diabetes will not meet the usual criteria, they may still qualify if their total cholesterol exceeds 4 mmol/L and they have evidence of coronary heart disease (either by history or ECG).

It is likely that combination preparations of statin and ezetimibe will become available in Australia.

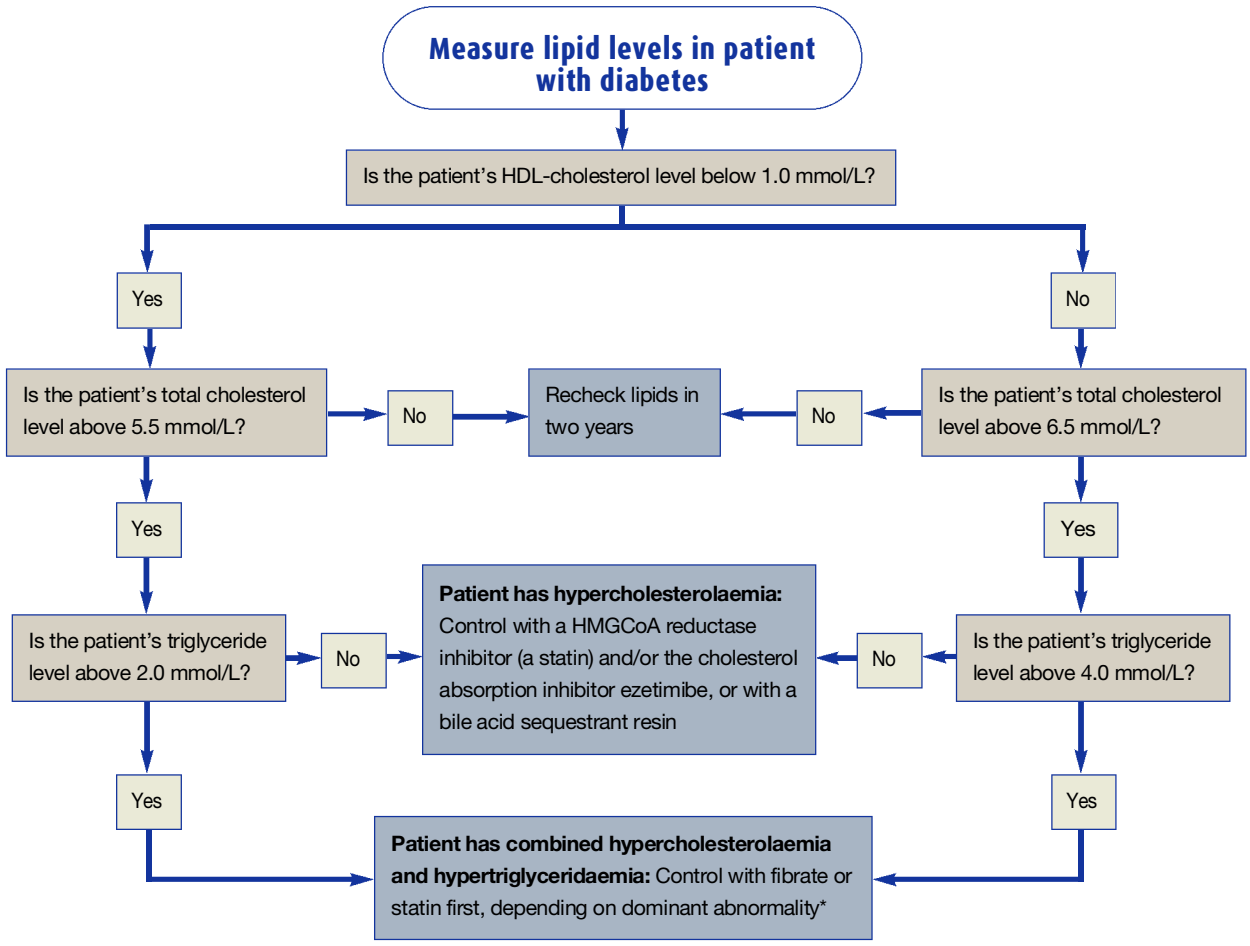
Meeting targets, or not

Even in clinical trials where investigators are monitoring participants closely and adherence is required to exceed 80%, targets are not met.

In the recently published Steno-2 Study, for example, despite the best efforts of investigators, only 18% and 21% of patients achieved systolic blood pressure and total cholesterol targets, respectively.

continued

Dyslipidaemia in patients with diabetes: PBS guidelines[10]



* Combining a fibrate and a statin should be considered only after specialist consultation; combining a fibrate and a resin is an alternative.

However, cardiovascular events were halved in this study, even though targets were not met in most patients. These trials show us that we mustn't expect too much from our patients or ourselves.

In patients in whom blood pressure or total cholesterol remains well above target and does not respond to therapy, two questions may help to identify correctable problems in therapy:

- Is the patient taking the medication? After all, the pills won't work unless they are taken. You may notice that medication prescriptions are not required as often as you expected. You may ask a pharmacist to visit the patient for a home medications review – the pharmacist may identify a drug interaction, or that scripts are not being filled or medication is being stockpiled rather than taken.
- Is there a secondary condition affecting blood pressure or cholesterol? Blood pressure may be affected by two disorders, each of two organs: arterial (coarctation of the aorta or renal artery stenosis) and adrenal (hyperaldosteronism or phaeochromocytoma). Cholesterol may be affected by two common disorders: hypothyroidism and renal dysfunction (albuminuria and/or decreased glomerular filtration rate).

If no progress is made, consider referring the patient to a specialist with an interest in cardiovascular protection (an endocrinologist or a cardiologist).

Remember your ABCss

Once you and the patient have done as much as you can, or are prepared to do, to control blood pressure and reduce total cholesterol, check the other ABCss – that is glycaemic control, smoking cessation and salicylate taking (Table 1).

Although blood glucose is not one of the priority cardiovascular risk factors, the UKPDS and other studies suggest that lowering glycaemia reduces cardiovascular risk. Certainly glycaemic control reduces the development and progression of microalbuminuria, and thus will reduce the associated cardiovascular risk.

Some 20% of patients with type 2 diabetes continue to smoke, and you won't know if the patient is prepared to consider quitting unless you ask.[12]

Salicylate (aspirin) is recommended for people with type 2 diabetes at risk of cardiovascular disease (that is, for virtually all of them), yet only a minority take it.[13] Patients may accept aspirin when they might have reservations about prescription medication: aspirin does not require a doctor's visit for a script, is cheap and is a common and familiar treatment. Tell the patient that 'An aspirin a day keeps heart attacks and strokes away.'

It is also true that there may be benefits in targeting abnormalities in HDL-cholesterol and triglyceride levels (which are the common causes of dyslipidaemia in type 2 diabetes). Certainly lifestyle changes such as decreasing adiposity, quitting smoking and increasing activity are recommended for many reasons apart from increasing HDL-cholesterol and decreasing triglyceride levels. There is post hoc evidence from the Veterans Affairs HDL Intervention Trial (VA-HIT) that fibrates (gemfibrozil) may improve cardiovascular outcomes. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study is a current prospective randomised controlled trial with cardiovascular outcome as a primary end point and findings will be presented towards the end of 2005.

There is evidence that the benefits of multiple interventions are additive: a little bit of this, a little bit of that, and that… may add up to a large total effect. In the Steno-2 study, trying harder in five patients for eight years prevented one cardiovascular event.

Conclusion

In a general practice of 1000 patients, 40 or so will have known diabetes and most could benefit from more active management of cardiovascular risk. Making a review of ABCss part of your annual diabetes check and trying a bit harder to hit those targets will help prevent cardiovascular events. MT

A list of references is available on request to the editorial office.

DECLARATION OF INTEREST. Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a number of pharmaceutical companies. He does not think that these associations have influenced the content of this article.

The ulcer that wouldn't go away

PAT J. PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHlthEcon(UNE)

What should you do when a patient with diabetes says about her foot ulcer, 'It just won't heal'?

Case history

Ruth is 68 years old and has a 3 cm wide, shallow ulcer on the ball of her left foot, which also is misshapen by a bunion (Figure). She says that she first became aware of the ulcer about three weeks ago when her foot stuck to her shoe; on looking, she had found a large sore on the sole of her foot. Within a week, the sore had enlarged. Since then, it had not worsened, but also it had not improved. There was no pain and Ruth was not too worried about it. However, when her daughter found out she insisted that Ruth come and see you.

Ruth has had moderately controlled type 2 diabetes for 11 years (HbA_{1c}, 7 to 9% [normal range, 4 to 6%]).

What should you consider?

Given that the ulcer is not improving and Ruth is not showing much concern, consider the following:

- What are the likely major contributors to Ruth's foot ulcer?
- With appropriate care, is her ulcer likely to heal or will surgical intervention be required?
- How likely is she to develop another ulcer?
- How might you reduce her risk of future ulcers?

Risk factors for foot ulcers

Ruth has decreased sensation on her feet and a misshapen foot and is pretty casual about her foot care. However, on the upside, on examination her feet are warm and well perfused.

Neuropathy, deformity, poor foot care and vascular disease are four of the major risk factors for foot ulcers.[1] Ruth has three of these. Her misshapen foot means that pressure is loaded unevenly on her foot, making it more likely that footwear and weight bearing will cause excess skin pressure followed by compensatory skin thickening (callus or corn). The thickened skin aggravates the problem by increasing disruptive forces in the subdermal tissues. Damage, haemorrhage, skin breakdown, a sore and finally an ulcer follow.[2]

Ruth's neuropathy means that her feet are vulnerable to painless injury – otherwise the callus and ulcer would hurt and would have caused her to seek help much earlier. She was able to continue walking on the initial callus and the continued pressure caused further thickening of the callus, tissue breakdown and, consequently, the ulcer. People with diabetes often find it difficult to accept that neuropathy destroys the early warning system of pain in situations that might damage a foot, thereby making damage more likely.

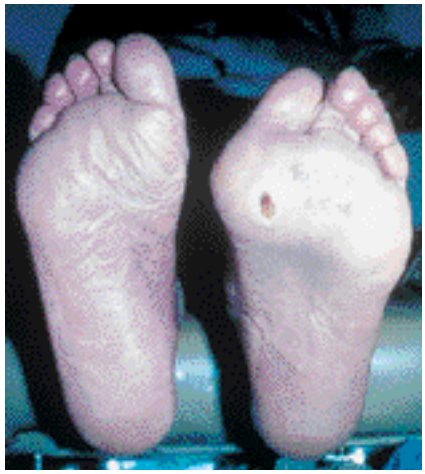


Figure. The ulcer on Ruth's left foot.

Ruth's response to her injury indicates poor foot care or poor knowledge of the need for such care. Fortunately she has a supportive family.

Ulcer resolution

Ruth has reasonable tissue perfusion and the foot ulcer should heal without the need for surgical intervention if the excess pressure is deflected from the wound. Ruth and her family need specific and relevant education regarding her neuropathy and the need for better foot care and awareness. (See 'Reducing the risk of future ulcers' below).

The key to ulcer healing is ensuring good blood flow (which Ruth has), keeping the healing surface moist and clean, and removing any pressure that might damage the healing surface. A podiatrist can remove any thickened skin that might cause pressure, and can modify or design footwear and padded orthotics that will transfer pressure from the overloaded ulcer area and distribute this more evenly across other areas of the foot. Ruth's wound care should involve keeping the ulcer area clean without damaging the healing surface. Bulky dressings increase pressure on the ulcer, and many of the traditional full strength antiseptic solutions and ointments may be toxic to healthy tissue as

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well as to bacteria. Ruth's ulcer is not infected and, therefore, does not require antiseptics.

Likelihood of another ulcer

A major indicator of ulcer risk is a history of a previous ulcer. The risk factors that cause the first ulcer are often not addressed, leaving the foot susceptible to future damage.

Ruth's left foot is misshapen by her bunion but foot structure may also be changed by the effects of motor neuropathy and the loss of intrinsic muscle function, leading to problems in weight bearing. The forces under the feet can also be affected by footwear; for example, high heeled shoes would increase Ruth's forefoot loads and should, therefore, be avoided. Ruth's neuropathy may not trouble her but, as mentioned earlier, does mean that her feet are vulnerable to mechanical, thermal or chemical damage that could be avoided if she had the warning signs of pain.

In the future, Ruth may develop significant peripheral vascular disease associated with her diabetes, and her ulcers may then be larger, less likely to heal and more likely to become infected. Circulation that may be good enough to maintain intact skin may not be sufficient to repair tissue damage or resist infection. If circulation is poor, vascular surgery may be required to improve arterial flow and subsequent tissue perfusion and ulcer healing.

Often it is the combination of the two most potent foot risk factors, neuropathy and peripheral vascular disease, that puts diabetic feet at extreme risk and leads to loss of limbs. The mechanical loads on misshapen feet and poor foot care are often the inciting triggers.

If the wound was infected, regular dressings would remove debris and pus. If cellulitis were present, antibiotics would be necessary. Rarely are antiseptics needed: if they are, simple ones are all that are required, such as povidone–iodine.

Table. Warning signs of increased risk of foot ulcers

Signs	Comments
Vascular disease • Reduced healing • Reduced capillary refill time	• Beware of increased risk of infection
Sensory neuropathy • Decreased pain sensation on testing • Dry skin cracks	• Patient or carer needs to inspect feet daily • Prevent progression of dry skin cracks to ulceration
Mechanical dysfunction • High pressure areas	• Special footwear required
Self-hygiene • Poor skin and nail care • Unable to see, reach or feel feet • Lack of monitoring schedule, action plan or access to health professionals	• Focus on patient and/or carer education

Reducing the risk of future ulcers

Appropriate footwear, foot care and foot health monitoring with clear action plans will identify early problems and allow intervention before major problems occur. For example, detection of skin callus before it becomes a major breakdown can lead to prevention of progression by removal of the pressure that causes damage. Warning signs of increased risk of ulcers are listed in the Table.

Ruth needs to understand her risk of undetected and painless injury. She should be visually checking her feet on a daily basis to detect any trouble spots. If her eyesight deteriorates, someone else will need to inspect them for her, and if she becomes unable to reach or care for her feet herself, someone else will need to do this for her. The education needs to be specific, individualised and reinforced, and it is important to involve family or other carers wherever possible.

The GP or podiatrist can show Ruth how to care for her skin and nails, advise her on appropriate footwear, teach her the signs of potential problems and establish action plans to address the problems.

Summary

A callus on the weight bearing surface of the foot may appear innocuous but, given the possible complications that can arise with diabetic neuropathy, must be seen as a potential risk factor and eradicated effectively well before an ulcer occurs. Patients with diabetes should understand the significance of the risk of undetected and painless injury and be taught how to care for their feet on a daily basis. MT

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Visible manifestations of diabetic retinopathy

PAT J. PHILLIPS MB BS, MA(Oxon), FRACP, MRACMA, GradDipHlthEcon(UNE)

Are you sure of the significance of the various retinal lesions of diabetes?

Much of the blindness associated with diabetes can be prevented if retinopathy is detected and treated early enough – that is, before the patient experiences visual symptoms. Changes that might be seen when examining the fundus of a patient with diabetes who is not yet experiencing any loss of vision include red dots, red blots, hard exudates and cotton wool spots (Figure). These are indicators of the progression of diabetic retinopathy.

Red dots

Red dots are microaneurysms of the retinal arterioles. They are an early indicator of diabetic retinopathy and become more common with increasing diabetes duration. In the 1980s it was thought that virtually everyone with diabetes would develop microaneurysms and other signs of diabetic retinopathy. More recently, it has been suggested that diabetic retinopathy is not inevitable and it appears that more people with diabetes are remaining free of eye disease, presumably because of improved glycaemic control. Red dots are clearly defined because they are contained within the vessel wall.

Red blots

Red blots are small haemorrhages from retinal arterioles and indicate more serious microvascular disease than red dots. Blots are blood in the retinal layers and are therefore not clearly defined.

Red blots may also occur in hypertensive eye disease but then there is usually more extensive haemorrhage that spreads into the nerve layers. This causes more 'flame' haemorrhages radiating from the leaking vessel rather than the more confined blot haemorrhages of diabetic retinopathy.

Hard exudates

If the retinal vessels leak because of diabetes related damage, lipids and other serum components can accumulate in retinal layers and show as yellow to white hard exudates. They generally have a fairly clearly defined edge and tend to occur in the central areas around the macula and optic disc.

The exudates may track down nerve layers radiating around the macula, causing a spectacular macular star. The star is an ominous sign because the exudates may damage the macula and thus affect the central vision mediated by the cones concentrated there. In the same way, a central hard exudate is much more significant than a more peripheral exudate. Early detection of central exudates is important because early local laser therapy can prevent exudate extension and associated visual loss.

Cotton wool spots

Retinal tissue will die if retinal vessels are blocked. This is associated with local oedema, as in the brain and other organs when they become ischaemic. In the retina, the excess extravascular fluid radiates into the neural layers, causing an ill defined white cotton wool-like opacity that resolves with time.

Like the blots of retinal haemorrhage, cotton wool spots are not diagnostic of diabetic retinopathy and can occur with hypertensive eye disease (where they reflect the same pathophysiology). In diabetic retinopathy, they indicate a more serious stage than haemorrhages because the ischaemia that causes local retinal tissue to die also triggers new vessel growth in an attempt to counteract the ischaemia.

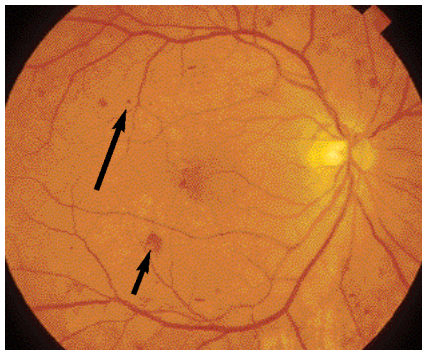

Figure. Red dots (long arrow) and blots (short arrow) in early diabetic retinopathy.

Symptomatic retinopathy

With time, delicate new retinal vessels may grow into the vitreous where they are not supported by surrounding tissues and are prone to bleeding. This so-called 'proliferative' retinopathy is associated with vitreous haemorrhage, scarring, retinal retraction and loss of vision.

A note on treatment options

Early detection of the pre-proliferative stage associated with the cotton wool spots of ischaemia (this stage is also called advanced nonproliferative retinopathy) allows the opportunity for prophylactic pan retinal laser photocoagulation. This therapy destroys ischaemic retinal tissue, thereby stopping the new vessel growth and reducing the risk of vitreous haemorrhage, scarring and visual loss.

Another possible approach is the use of antagonists to the substances triggering new vessel growth. Antagonists to vascular endothelial growth factor have proved promising in early trials. MT

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