Diabetes and dementia

Erratic behaviour, confusion, incontinence, chronic ulceration and polypharmacy are all common problems in people with both diabetes and dementia. Targets for glycaemic control may have to be amended in these people to reduce the risks of hypoglycaemia in some cases and glycosuria in others.

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Diabetes and dementia are both common in older people. The two conditions often interact, each making the management of the other more difficult. The following scenarios illustrate some of the common problems that can arise and suggest some potential solutions.

What are the facts?

Anna, aged 68 years, is concerned about her memory loss and worries that she may be becoming demented. Her son told her that dementia is more common in people with diabetes.

How should you advise Anna?

Anna's son is correct, dementia and Alzheimer's disease are more common in individuals with diabetes. The risk of dementia is roughly doubled in patients with diabetes over the age of 90 years.[1] Moreover, dementia makes diabetes management more difficult, and vice versa.

It is unclear how type 2 diabetes causes dementia but there are several possibilities (Figure 1). Hyperglycaemia may result in extra glucose being attached to proteins (glycation) and these modified proteins then undergo further changes resulting in advanced glycation end products. In Alzheimer's disease (with or without diabetes), advanced glycation end products are found in the plaques and tangles associated with this condition and may lead to cellular damage.

Alternatively, recurrent hypoglycaemia may cause subclinical but permanent neuronal destruction, gradually leading to clinically significant multifocal brain damage. Certainly dementia is more common among those treated with insulin who are, as a result of their insulin treatment, more prone to hypoglycaemia.

Apart from the damage mediated by hypoglycaemia or hyperglycaemia, type 2 diabetes is also associated with cardiovascular disease. Recurrent strokes, clinical, subclinical or both, can also result in multifocal damage.

Most people find they forget things as they get older. This 'benign forgetfulness' is cognitive

IN SUMMARY

- **Concern about memory loss does not always point to a diagnosis of dementia.**
- **Hypoglycaemia in the elderly may present with subtle changes and may be missed.**
- **Nonmixed insulins are preferable to premixed insulins in most elderly people with diabetes.**
- **Postprandial hyperglycaemia may be improved by using a very short acting aspart insulin or lispro insulin or a short acting insulin secretagogue such as repaglinide.**
- **Metformin should be used cautiously in the elderly because of decreased renal function and therefore increased risk of lactic acidosis. The glitazones may be the drugs of choice in elderly people with diabetes because of low risk of hypoglycaemia.**
- **The risk of an adverse drug reaction increases linearly with increasing numbers of medications. Medications that can be given once daily are preferable to those that need to be given thrice daily. NSAIDs and diabetes do not mix.**

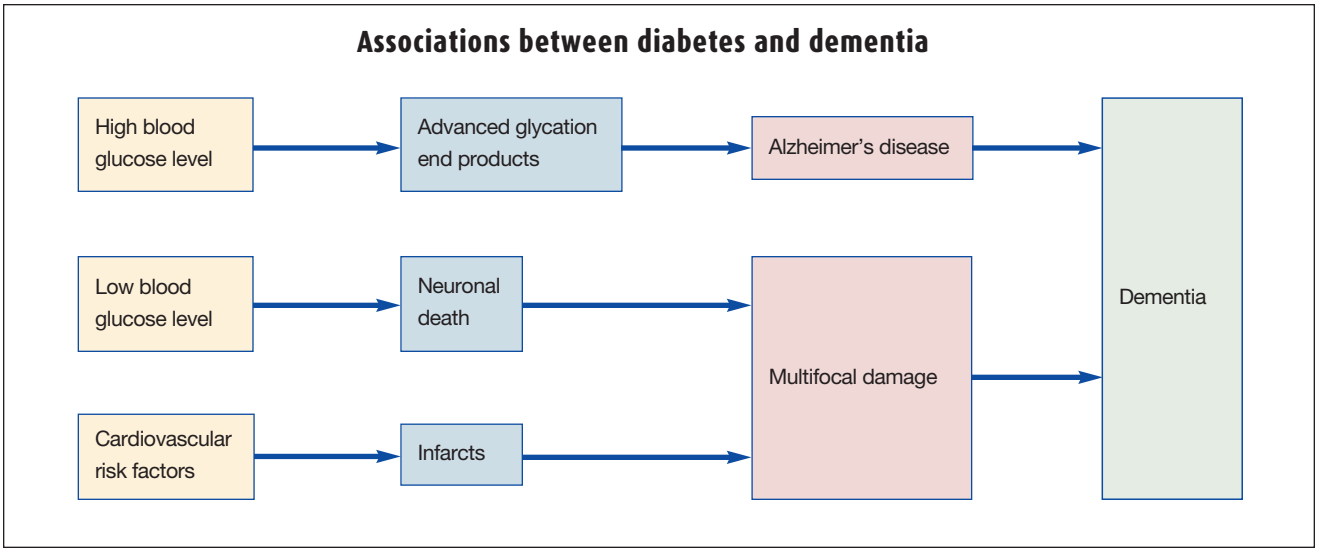

Figure 1. Associations between diabetes and dementia.

impairment associated with normal ageing compared with Alzheimer's disease which is a progressive pathological condition.[2] Fortunately it is possible to assess objectively whether Anna has a normal or pathological cause for her forgetfulness by using the Mini Mental State Examination (MMSE; see the box on page 32).[3]

MMSE scores need to be interpreted in the light of baseline function (a rocket scientist and a school dropout may have similar pathology with very different scores), but generally scores below 13 suggest cognitive impairment and should trigger further assessment and intervention.

Anna's score was, in fact, 26. This reassured her, her family and you that she was not 'losing her marbles'.

Hypoglycaemia as a cause of erratic behaviour

Sarah is 75 years old and was found wandering along an isolated road several kilometres from her home. She has been acting strangely intermittently for some months but seems perfectly all right between episodes. Her diabetes is well controlled (HbA_{1c} 6.5%) on glibenclamide 10 mg twice daily.

How should you assess and manage Sarah?

Hypoglycaemia can cause a range of unusual syndromes in older people in whom neuronal function may be affected by other medical conditions and medications. The classic stages of hypoglycaemia include sympathetic activation, cognitive impairment, loss of consciousness and, if prolonged, death. In older people, hypoglycaemia may also cause confusion (as in Sarah's case) or a focal neurological deficit mimicking a stroke.

Sarah's diabetes is too well controlled. Her blood glucose values before meals range between 3 and 6 mmol/L (fitting with her HbA_{1c} of 6.5%, which is close to the nondiabetic range of <6%). Her oral hypoglycaemic agent, glibenclamide, has active metabolites that are excreted renally and often have a longer half-life in older people in whom renal impairment is common. For this reason, long acting sulfonylureas like glibenclamide (Daonil, Glimel) are not recommended for older people. Glimepiride (Amaryl) is another sulfonylurea that has similar potential problems in the elderly.

Switching to a different hypoglycaemic agent (such as gliclazide [Diamicron, GenRx Gliclazide, Glyade, Nidem] or glipizide [Melizide, Minidiab], which are safer in patients with renal impairment) and loosening glycaemic targets (aiming for blood glucose values before meals of 6 to 8 rather than 3 to 6 mmol/L) would be appropriate.

Sarah has had diabetes for 20 years, with minimal microvascular complications (stable background diabetic retinopathy and no microalbuminuria or neuropathy). She has much more to lose, therefore, from an increased risk of hypoglycaemia than the reduction in risk of microvascular complications that she gains from

The Mini Mental State Examination[3]

The Mini Mental State Examination is commonly used to assess the severity of cognitive impairment in patients with Alzheimer's disease.

Instructions

Before you begin, get the patient's permission to ask some questions. This will help to avoid catastrophic reactions. Provide any hearing or visual aids that the patient needs. You will also need a watch, pencil and some paper.

Do not engage in conversation, give hints or physical clues (such as head shaking). If a question is answered incorrectly, accept the patient's answer and do not ask the question again. The test takes approximately 10 minutes to complete.

Scoring

The test is scored out of 30. A score of 18 to 26 suggests mild dementia; a score of 10 to 17 suggests moderate dementia; and a score of less than 10 suggests severe dementia. However, the score is a guide only, and requires clinical judgement. Scores are influenced by factors such as language, culture, educational background, and visual or hearing impairment.

Questions	Score
Orientation	
1. Ask the following questions about time. Score 1 point for each correct response.	
a. What year is this?	/1
b. What season is this?	/1
c. What is today's date?	/1
d. What day of the week is it?	/1
e. What month is it?	/1
2. Ask the following questions about location. Score 1 point for each correct response.	
a. What State/Territory are we in?	/1
b. What country are we in?	/1
c. What town or city are we in?	/1
d. In clinic: What is the name of this hospital (or building)? At home: What is the street address of this house?	/1
e. In clinic: What floor of the building are we on? At home: What room are we in?	/1
Registration	
3. Tell the patient that you are going to name three objects, and that you will then ask him or her to name them. The objects can be an apple, table and penny. Score 1 point for each correct reply on the first attempt only.	/3
Explain that you want the patient to remember the three objects because you are going to ask him or her to repeat them again in a few minutes. If the patient does not repeat all three objects, repeat up to six times until they are learned (for the recall test in Question 5).	
Attention	
4. Ask the patient to subtract 7 from 100, then subtract 7 from the result, and so on, for 5 subtractions. Score 1 point for each correct answer.	
Alternatively, ask the patient to spell the word 'world' backwards. Score 1 point for each correct letter.	/5

Recall	Score
5. Ask the patient to name the three objects that you asked him or her to remember earlier (in Question 3). Score 1 point for each correct response, regardless of order, on the first attempt only.	/3
Language	
6. Show the patient a pencil and a watch. Ask the patient to name the two objects. Score 1 point for each correct name.	/2
7. Ask the patient to repeat the following sentence after you: 'No ifs, ands or buts'. Score 1 point for a completely correct repetition.	/1
8. Ask if the patient is left- or right-handed. Then ask him or her to follow a three-stage command, including the other hand in the instruction. For a right-handed patient, say 'Take a paper in your left hand, fold it in half and put it on the floor'. Score 1 point for each part correctly executed on the first attempt only.	/3
9. Hand the patient a sheet of paper with 'close your eyes' written on it. Tell the patient to read the message and then follow the instruction. Score 1 point if the patient closes the eyes.	/1
10. Hand the patient a pencil and paper and ask him or her to write any sentence on the paper. Score 1 point for a sentence that makes sense, ignoring spelling errors.	/1
11. Give the patient a paper, pencil and eraser. Show the patient a design of two intersecting pentagons, and ask the patient to copy it. Score 1 point for a correctly copied design (i.e. a four-sided figure between two five-sided figures). 	/1
TOTAL SCORE	/30

tight glycaemic control. The Diabetes Complications Control Trial (DCCT) for type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS) for type 2 diabetes show that the risk of hypoglycaemia increases considerably at low HbA_{1c} values while there is a reduced absolute risk of microvascular complications at these low levels.[4,5] Setting a target for glycaemic control is, therefore, a trade off between the risk for hypoglycaemia and the risk for microvascular complications. These studies also show that the higher the HbA_{1c}, the greater the benefits and the smaller the costs of improving glycaemic control.

Disadvantages of premixed insulins

Matthew is aged 70 years and is in the early stage of dementia (MMSE score 22) but is managing at home with his wife, Tessa. He recently started using premixed insulin twice daily. Tessa is distraught because yesterday he became abusive, violent and refused any help. The ambulance paramedics had to overcome him by force and take him to hospital.

How can you help prevent Matthew's hypoglycaemic episodes?

Premixed insulins – mixtures of intermediate plus short or very short acting insulin (Humalog Mix25, Humulin, Mixtard, NovoMix 30) – offer great advantages to patients (draw or dial up and shoot) and their doctors (one size fits all). However, they also have significant potential disadvantages and may compromise the important KISS (keep it safe and simple) principle in managing people with dementia.

One disadvantage is their inflexibility – changing the dose changes both the long and short acting components at the same time. Another disadvantage is that they increase the risk of hypoglycaemia and weight gain. People with type 2 diabetes starting insulin often do not need short acting insulin but can be well controlled on intermediate insulin alone. The premix puts them at risk of hypoglycaemia when the short acting insulin peaks (mid-morning and evening for a twice-daily schedule); they may need to take extra carbohydrate at these times, thus increasing weight gain.

The recommended schedule for starting insulin in type 2 diabetes is a night-time dose of intermediate or long acting insulin and daytime metformin where tolerated.[6]

You could change Matthew to this schedule if glycaemic control is inadequate and also suggest that his blood glucose level is tested when values are likely to be low (before meals and during or after exercise). Tessa may also be able to predict when Matthew will increase

Table 1. Insulin preparations for use with pen injectors – pros and cons in dementia*

Insulin type	Pros	Cons
Premixed Isophane plus neutral – Humulin preparations, Mixtard preparations Lispro mixture – Humalog Mix25 Aspart mixture – NovoMix 30	'One size fits all'	Fixed insulin combination Short acting insulin may cause hypoglycaemia and weight gain
Intermediate Isophane (human) – Humulin NPH, Protaphane	Once daily dose plus oral hypoglycaemic agent is the best starting schedule Twice daily schedule covers daytime and night-time glycaemia	Postprandial hyperglycaemia may be a problem
Short acting Neutral (human) – Actrapid, Humulin R	Reduces postprandial hyperglycaemia	May cause hypoglycaemia between meals and weight gain
Very short acting Lispro (synthetic) – Humalog Aspart (synthetic) – NovoRapid	Reduces postprandial hyperglycaemia	Abrupt onset may cause hypoglycaemia if carbohydrate is not eaten immediately

* All these preparations can be used with pen injectors and other devices that simplify dosage and administration. Insulin zinc suspensions (ultralente and lente types) are not listed since a syringe must be used and this is usually more difficult for the patient or carer. However, ultralente preparations may be useful where a flatter baseline insulin profile is desirable (e.g. when night-time hypoglycaemia is a problem).

continued

his activity and encourage him to eat beforehand.

As in Sarah's case, higher targets for glycaemic control might be appropriate.

The pros and cons of the various insulin preparations are summarised in Table 1.

Causes of confusion

Liza is 76 years old and is severely but cheerfully demented (MMSE score 13). The nursing staff are concerned because she consistently becomes very confused and drowsy in the early evening. Blood glucose results have been 'reasonable' (fasting 8 to 12 mmol/L) on twice-daily intermediate insulin (isophane).

How might you manage Liza's confusion?

If Liza's blood glucose values before meals are 8 to 12 mmol/L, they are likely

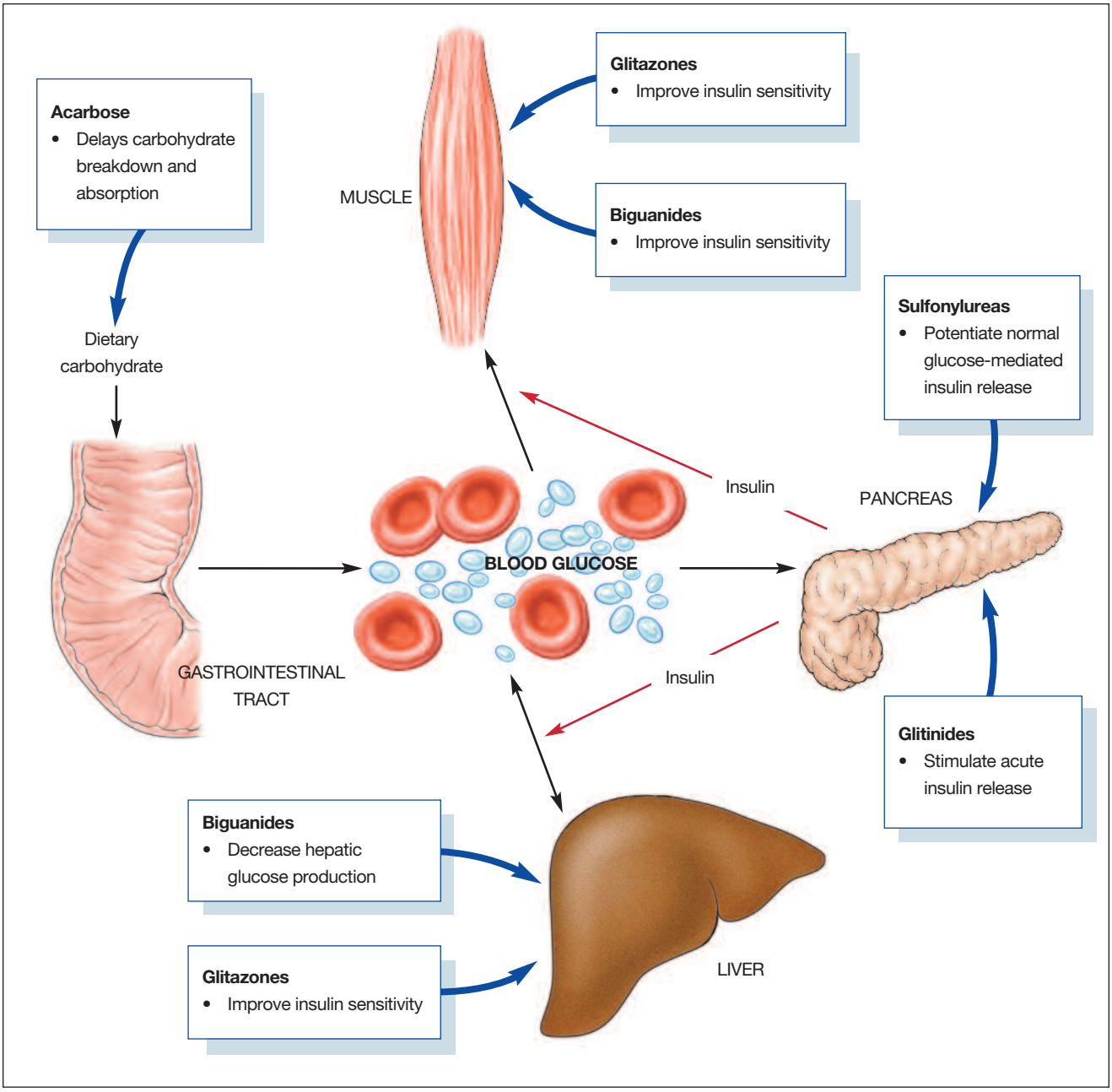

Figure 2. Mechanism of action of oral hypoglycaemic agents.

to be high after meals, especially after larger meals like dinner. Checking the blood glucose about two hours after beginning to eat dinner showed that Liza's blood glucose values in the evening were, in fact, consistently high, and were probably the cause of her regular confusion. Two potential approaches are to:

- decrease blood glucose values before meals (remembering the risk of hypoglycaemia) by increasing the intermediate insulin dose
- increase insulin activity after meals by adding a short acting insulin (a very short acting aspart insulin [NovoRapid] or lispro insulin [Humalog] or the short acting neutral [human] insulin [Actrapid, Humulin R]) or a short acting insulin secretagogue (such as the glitinide repaglinide [NovoNorm]).

Decreasing blood glucose values before meals will reduce the values after meals. Therefore, aiming for blood glucose values before meals at the lower end of the range 8 to 12 mmol/L may avoid hyperglycaemia after meals.

One of the factors causing hyperglycaemia in patients with type 2 diabetes is the combination of the progressive failure of insulin secretion and the increase in insulin resistance with age. This leads to a progressively reducing capacity to respond to blood glucose increases after meals. Adding a short acting insulin (e.g. about half of the intermediate insulin dose) may be needed. There may be a convenient insulin premix that will not complicate Liza's management by adding another injection – remembering the potential problems of premixed preparations.

Alternatively, Liza might have enough pancreatic function left to respond to a short acting insulin secretagogue like repaglinide. This drug acts quickly to increase residual pancreatic insulin secretion, thus controlling the blood glucose rise after meals. Its action also stops quickly, reducing the risk of hypoglycaemia between meals. A suitable starting dose of repaglinide for Liza would be 0.5 mg before her main meals.

Theoretically, acarbose (Glucobay) could also be useful since it inhibits the enzymes breaking down carbohydrate and the subsequent slowing of carbohydrate digestion gives more time for glucose disposal after the meal. However, the commonly associated gastrointestinal side effects (particularly flatulence and diarrhoea) of this drug make it a less practical option.

Coping with incontinence

Albert, 85 years old, is mildly demented but is coping at home with the care of his wife, Beverly. He has recently become incontinent of urine by day and night. Beverly complains that she spends all day cleaning up after him, saying that 'The house smells like a urinal'. His medication includes gliclazide 160 mg twice daily.

How can you help prevent Albert's hyperglycaemia?

Hyperglycaemia can cause or worsen incontinence in several ways:

- increased renal excretion of glucose increases the solute load and causes an osmotic diuresis – Albert may then experience the urge to void at times when he is not prepared or able to void in a toilet or urinal
- high blood glucose levels can cause confusion and thus make it less likely that Albert will void appropriately
- glycosuria predisposes to genital thrush, urethral irritation and urge incontinence where the person cannot control the urge to void.

Albert is already mildly demented and any one of the above factors might tip the balance to incontinence. He is also likely to have other problems contributing to the tendency to incontinence, such as autonomic neuropathy associated with his diabetes and benign prostatic hypertrophy, both of which predispose to overflow incontinence.

Checking Albert's blood glucose values before meals and aiming for a level of about 8 mmol/L will not put him at much risk of hypoglycaemia but will probably reduce his glycosuria. Remember that older people tend to have a higher renal threshold for sugar excretion (usually above 15 mmol/L) than younger people do (they 'spill' sugar at levels below about 10 mmol/L).

The choice of additional oral hypoglycaemic therapy will be guided by the mechanisms of action of the various hypoglycaemic drugs (Figure 2 and Table 2).[7] Albert is already on a high dose of the sulfonylurea gliclazide and

Table 2. Oral hypoglycaemic agents

Sulfonylureas

Glibenclamide (Daonil, Glimel)*
Gliclazide (Diamicron, GenRx Gliclazide, Glyade, Nidem)
Glimepiride (Amaryl)*
Glipizide (Melizide, Minidiab)

Glitinides

Repaglinide (NovoNorm)†

Biguanides

Metformin (Diabex, Diaformin, GenRx Metformin, Glucohexal, Glucomet, Glucophage, Metformin-BC)

Glitazones

Pioglitazone (Avandia)†
Rosiglitazone (Actos)†

Others

Acarbose (Glucobay)

* The sulfonylurease glibeclamide and glimepiride are not recommended in older people because of their extended half-lives in people with renal impairment.
† At the time of writing (September 2002), repaglinide, pioglitazone and rosiglitazone are not subsidised by the PBS and are only available on private prescription.

further increases are unlikely to be effective. The biguanide metformin, which reduces insulin resistance, might be appropriate if his renal function (glomerular filtration rate) is reasonable and he does not develop diarrhoea and add faecal incontinence to Beverly's troubles. Adding an insulin secretagogue (a glitinide) will not help since his pancreas is already being stimulated by the sulfonylurea. One of the glitazones (which improve insulin sensitivity) once a day would probably be the simplest step. Rosiglitazone (Avandia) and pioglitazone (Actos) are the currently available glitazones. However, at the time of writing (September 2002), they and the glitinide repaglinide are not subsidised by the PBS and are only available on private prescription.

Polypharmacy

Jessica is aged 75 years and is still living at home with the help of her partner, John. She is on maximum doses of multiple oral hypoglycaemic agents (a sulfonylurea, metformin, acarbose) but her blood glucose values are consistently above 10 mmol/L and her HbA_{1c} is 12.2%. You are considering adding another medication but John is concerned about the number of pills and the number of medication-taking occasions each day.

How can you reduce Jessica's medications?

Jessica is also taking tablets for cardiac failure (digoxin 125 µg/day, captopril 50 mg twice daily, frusemide 40 mg in the morning), arthritis (naproxen 250 mg twice daily), dyslipidaemia (gemfibrozil 600 mg twice daily), dementia (clonazepam twice daily), depression (amitriptyline 75 mg at night) and low dose aspirin – another 14 tablets in addition to the 12 for her diabetes.

It is time to review her medication schedule, possibly with input from a pharmacist, and see if things could be made simpler and safer.[8] Table 3 lists the risks associated with the use of some drugs in patients with diabetes.

It may also be time to switch Jessica to insulin treatment (see Table 1).[9] One or two injections of intermediate insulin using a pen injector may be much easier for everyone than Jessica having to take many different tablets several times a day.

Considering the oral hypoglycaemic drugs:

- adding a glitinide will not help since Jessica is already taking a sulfonylurea
- given her cardiac failure, metformin is not appropriate because of the risk of lactic acidosis
- although a glitazone might improve her glycaemia, Jessica is still likely to be significantly hyperglycaemic (the usual response to adding an oral hypoglycaemic agent is, on average, a 0.5 to 1.5% decrease in HbA1c; hers is 12.2%)
- a glitazone would also not be appropriate given her cardiac failure.

Jessica's other medications could also be modified, for example by:

- using a once-daily ACE inhibitor
- considering whether her diuretic could be combined with her once-daily ACE inhibitor
- phasing out her tricyclic antidepressant (which has anticholinergic side effects and may be worsening her dementia) and substituting a selective serotonin reuptake inhibitor (SSRI) in the morning
- stopping her NSAID, which could predispose to fluid retention and hyperkalaemia (the latter made more likely by her ACE inhibitor), and using instead physical measures (heat and massage), topical preparations and paracetamol.

If all these changes were made, Jessica would have two injections and nine tablets all taken on two occasions each day (compared with 26 tablets and 10 medication-taking occasions previously). In addition, her medication costs would be significantly reduced.

Chronic ulceration

Sophia is 82 years old, has been a nursing home resident for 14 months and has longstanding type 2 diabetes associated with retinopathy, neuropathy and nephropathy. She has become significantly demented since she came into the nursing home and her current MMSE score is 15. The nursing staff ask you to review her longstanding foot ulcer which has not responded to therapy over the last two months (Figure 3).

How would you treat Sophia's ulcer?

Sophia has one of the classic pressure ulcers found in patients who are unable to move or, as in her case, feel pain. Other factors may predispose to foot ulcers in diabetic patients but do not seem to be contributing in Sophia's case (Table 4).[10] However, if Sophia did have

Table 3. Risks associated with drugs used in diabetes[8]

Hypoglycaemic agents
Hypoglycaemia (insulin and sulfonylureas – especially the long acting agents glibenclamide and glimepiride)
Lactic acidosis (metformin)

Hypotensive agents
Hypotension
Hyperkalaemia (ACE inhibitors and potassium-sparing diuretics)
Renal impairment (ACE inhibitors)

Hypolipidaemic agents
Drug interactions resulting in rhabdomyolysis

Cardiovascular agents, NSAIDs, antidepressants
Hypotension
Nephrotoxicity

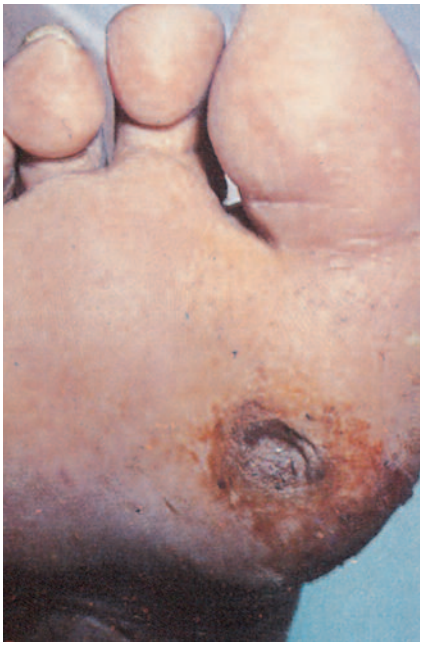

Figure 3. Sophia's foot ulcer should heal with suitable care if her circulation is adequate.

Table 4. Foot ulcers: predisposing factors[9]

Vascular disease	May result in reduced healing and increased risk of infection
Neuropathy	In which damage may become painless and cracks develop in dry skin
Mechanical dysfunction	May result in areas of skin that are subjected to high pressure
Poor self-care	Inadequate skin and nail care may result when patients are unable to see, reach or feel their feet
Poor follow up	Lack of monitoring schedule, action plan or access to health professionals

significant peripheral vascular disease, an infected ulcer would almost certainly cause cellulitis, and urgent action and possibly amputation would be required. Hyperglycaemia can also contribute to nonhealing and to decreased resistance to infection.

The first step would be to assess Sophia's circulation (pulses, capillary return) and sensation. The usual sensory tests may be difficult to interpret, given her dementia, but her withdrawal response to pain would indicate that the messages are reaching the spinal cord at least. If the withdrawal response is negative in the legs, a check on the hands would confirm severe peripheral neuropathy (by the time peripheral neuropathy reaches the knee, the fingers are affected as well – hence the term 'glove and stocking' neuropathy).

Given adequate circulation and suitable care, the ulcer should heal. The key is not what you put on but what you take off: once the ulcer is cleaned of debris and callus, is moist and is not under pressure, it will heal. The best dressings are those that are simple, convenient and do not require frequent changes.

Keeping pressure off ulcers can be difficult, but nursing staff can be quite ingenious in designing ways to support the leg without it resting on the affected parts.

Don't forget to check for other pressure areas as immobility alone can cause ulcers and Sophia's dementia or associated cerebrovascular disease may have limited her capacity to react – and thus the nursing staff's capacity to respond appropriately.

Conclusion

These cases provide a wide range of clinical scenarios relating to dementia and diabetes as two common conditions that coincide. Each condition and treatment of that condition impacts on the management of the other condition. The more severe the cognitive dysfunction, the greater the supervision and care needed in the management of the individual with diabetes. Conversely, it is important that if dementia is present it is not exacerbated by overtreatment of diabetes. Getting the balance right is the key to managing elderly patients with multiple comorbidities. MT

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