KISS: 'keep insulin safe and simple'

Part 3: troubleshooting insulin problems in type 2 diabetes

The variable blood glucose levels that may occur in patients who have type 2 diabetes and are taking insulin can have several causes, including injection and blood glucose monitoring techniques, physical activity and eating schedules, concurrent illness and insulin type and dosages.

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The number of adult Australians with type 2 diabetes has doubled in the last 20 years. Almost all these patients are managed by general practitioners, and many of them will require insulin treatment. The reasons for general practitioners to start insulin sooner rather than later are quite clear:

- the Diabetes Control and Complications Trial (DCCT; in type 1 diabetes) and the United Kingdom Prospective Diabetes Study (UKPDS; in type 2 diabetes) established A_{1c} as the 'gold standard' index of glycaemic control with a clear relation to long term

IN SUMMARY

- **Using the correct injection technique minimises variation in insulin absorption. Injection site problems include fat hypertrophy, bruising, pain, occasionally allergy and rarely fat atrophy.**
- **On sick days (everyday illness or infections), patients should continue with insulin and hypoglycaemic medication, with the possible exception of metformin. Blood glucose should be monitored more frequently than usual, hydration maintained and supplemental insulin or medication considered. Hospital admission may be necessary.**
- **Blood glucose swings can be caused by variability in physical activity, food (glycaemic load) and hypoglycaemic medication and/or by concurrent illness, or related to injection and blood glucose monitoring techniques. Swings can usually be smoothed out by education of patients in these areas.**
- **The three classic patterns of morning hyperglycaemia are 'insulin run out', 'the bounce' and 'poor control'.**
- **There is a risk of severe hypoglycaemia in patients with type 2 diabetes, particularly in those with low A_{1c} values or who are older and/or have had diabetes for many years.**
- **Regularly review hypoglycaemic and other medication, self-management techniques (lifestyle, medication and monitoring) and action plans for sick days, hypoglycaemic episodes and mistakes in medication dosing, particularly in patients in whom problems have occurred. These patients should have 24-hour access to advice.**

Figure 1. A lump caused by repeated insulin injections in the same site.

Figure 2. The preferred site for insulin injections is the abdomen. The site of the subcutaneous injections should be rotated, as shown by the spots.

microvascular diabetic complications[1,2]
- in Australia, national guidelines recommend measurement of A_{1c} in patients with type 2 diabetes at least annually[3]
- in Australia, evidence based recommended targets for A_{1c} are less than 7.0%[3]
- the UKPDS found that 50% of newly diagnosed people with type 2 diabetes required insulin therapy within six years to maintain A_{1c} below 7.0%;[4] this need for insulin occurs as the capacity of the pancreas to secrete insulin decreases
- 40% of Australians with type 2 diabetes have A_{1c} above 7.0%[5]
- the Western Australian Fremantle Diabetes Study showed that A_{1c} values in patients at the transition from using oral hypoglycaemic agents to insulin to control glycaemia were above A_{1c} values at the transition from lifestyle to oral hypoglycaemic agents (9.4 and 7.7%, respectively)[6]
- the evidence based recommended starting schedule for insulin in patients with type 2 diabetes is bedtime intermediate acting isophane insulin with continuation of oral hypoglycaemic agents[7]
- there are consensus recommendations for titrating insulin therapy for type 2 diabetes.[8]

Other articles in this series on insulin therapy using the KISS approach ('Keep Insulin Safe and Simple') give some guidelines to starting and living with insulin for patients with type 2 diabetes – see the March and April issues of *Medicine Today*.[9,10] This article reviews some problems that may occur with ongoing use of insulin and suggests ways to anticipate and avoid them, and to identify and manage them should they occur. The final article in the series, due to be published in the June 2007 issue, uses a case study to illustrate the progression of insulin therapy and the titration of insulin in a patient with type 2 diabetes.

Problems with the injection site

'The insulin is working OK but I'm getting these lumps where I inject. They are not uncomfortable but my wife is worried something might be wrong and when I wear my swimmers they look very obvious.'

John is 62 years old and has had type 2 diabetes for eight years. He started taking insulin eight months ago. His medications include intermediate acting isophane insulin (Humulin NPH, Protaphane) 36 units at bedtime, metformin 1 g twice daily and the sulfonylurea glimepiride (Amaryl, Dimirel) 4 mg/day.
- What are the lumps (see Figure 1)?
- What should John do about them?

The lumps

The formation of lumps is a common problem associated with repeated injections in the same site. The damage of repeated injections causes scarring, and the insulin, which is anabolic, causes fat hypertrophy.

Patients may find these lumps unsightly but they also find them convenient to inject into and, because of nerve damage in the area, the injections may cause less discomfort. However, injecting into these lumps may be associated with variability of insulin absorption. One day, the injection may be into a scarred area, and the insulin may be slowly absorbed; another day, it may be into an unscarred area and absorbed normally.

John's response

John should ensure he is using the correct technique when he injects his insulin. Insulin should be given:
- subcutaneously, not intradermally or intramuscularly
- consistently in a given anatomical area, not in the abdomen one day and in the thigh the next (absorption is different in different anatomical areas)
- in sites that are rotated within the same anatomical area, so that local problems do not occur (Figure 2)
- without causing bruising, because this will affect absorption.

Checking injection technique and sites of injection is part of the annual review recommended by the RACGP for patients using insulin.[3] The abdomen is the preferred site for insulin injections. As well as insulin being less well absorbed when injected into other anatomical areas, it is difficult to use the correct technique when injecting into the arm and many people do not have sufficient subcutaneous fat on their thighs.

Injection site problems other than

lumps include:
- bruising
- pain
- allergy (occasionally)
- fat atrophy (rarely).

Sick day management

Helen, John's wife, is seeking your advice over the phone.

'John is sick with vomiting and diarrhoea. What shall I do about his insulin? He's nauseous and not eating but his blood glucose is 17.6.'

- What should Helen do about John's insulin?
- What are the signals that things are getting out of control?

Continue insulin

Everyday illness or infections will usually cause a rise in the blood glucose level (BGL) to outside the normal range in patients with diabetes. The key points in managing such patients are to:[11]

- ensure they continue taking their insulin and hypoglycaemic medication, with the possible exception of metformin (metformin may need to be stopped because it can worsen gastrointestinal problems or cause lactic acidosis if there is significant impairment of cardiovascular, renal or liver function)
- monitor BGLs more frequently than usual
- ensure adequate support for patients and their carers
- ensure the patients maintain hydration (and carbohydrate intake unless BGL exceeds 15 mmol/L)
- consider giving patients supplemental insulin or medication
- avoid hypoglycaemia in those with gastrointestinal disorders associated with nausea and vomiting
- consider hospital admission if their medical or metabolic condition worsens and/or they or their carers cannot cope.

Your advice to Helen about John's medication would be to continue his isophane insulin but to stop the metformin. As his BGL is high, he should take 4 units of quick acting insulin (10% of his total daily intermediate insulin dose) if he has access to it, and review his blood glucose in two hours. Either quick acting neutral insulin (Actrapid, Humulin R) or very quick acting analogue insulin (insulin aspart [NovoRapid], insulin lispro [Humalog]) may be used. If John's BGL is still high, he should repeat the short acting insulin supplement and, if the level continues to exceed 15 mmol/L, he should consider transfer to hospital. (The advice if the BGL exceeds 22 mmol/L is to take a dose of quick acting insulin equal to 20% of the total daily intermediate insulin dose, and follow the same procedure.)

It is important that Helen understands when John should be transferred to hospital. Apart from continuing hyperglycaemia, John is at risk of dehydration because of his vomiting and diarrhoea. If the vomiting prevented any fluid intake for more than four hours and/or there was continuing profuse diarrhoea, intravenous fluid and electrolyte therapy would be required. Helen should be encouraged to take John to hospital (or call an ambulance) sooner rather than later, and not feel obliged to cope on her own.

Fortunately, all went well – Helen coped and John recovered.

BGL variability

Six weeks later John reports another blood glucose problem.

'Up and down like a yoyo. Yesterday before lunch 5.6, beautiful. Today, sky high, 12 before lunch and "HI" after. I just can't get it right.'

- What might be causing the blood glucose variability?
- Should John change his insulin dose or type?

Sources of blood glucose variability

Blood glucose swings are usually caused by variabilities in physical activity, food (glycaemic load) and hypoglycaemic medication and/or by concurrent illness. These variabilities may be intended or unintended. John and Helen may not understand the effect of lifestyle change (activity and glycaemic load) on blood glucose, and John might make mistakes in his doses of insulin or tablets. A diabetes management update may be due. Occasionally the problem lies with the insulin itself. Out of date insulin or insulin that has been stored incorrectly (allowed to become too hot or too cold) may not retain its effectiveness.

Sometimes the cause of variable BGLs is less easily identified, and related to techniques used in giving injections and testing blood glucose.

Injecting insulin

As mentioned earlier, the technique used when injecting insulin can affect the absorption of the insulin. Alternatively, John may not be completely mixing the cloudy isophane insulin. Incomplete mixing of the protamine zinc insulin suspension (the 'cloud') means that variable amounts of insulin are given. Many patients do not realise the importance of thorough mixing in three dimensions and they just dial or draw up and shoot. Some mistakes can be picked up by watching the injection process from start to finish.

It should not be assumed that because a person has had diabetes for many years that his or her diabetes techniques are correct. Some people make the same mistakes over and over again. Patients may find helpful the handout entitled 'How to inject insulin' in the March 2007 issue of *Medicine Today* (pages 35 and 36).

Blood glucose monitoring

The BGL results you are seeing may not be complete or correct. The current measuring systems are much simpler to use and give more accurate and reliable results than the older systems but blood glucose tests can still be done incorrectly (Table 1).[12] A quality control check and, as for

Table 1. Blood glucose monitoring: misleading information

Sources of misleading information include:

- Test results – dirty meter, expired or incorrect strips, incorrect calibration or codes, suboptimal patient technique
- Timing – lowest preprandial or highest postprandial BGL tested
- Recording – high or low values omitted, 'good' results made up

injection, watching the process of testing from start to finish can identify problems.

The fasting (pre-breakfast) BGL is the most convenient for patients to check and often is the only one they do. Fasting values may give 'good' results as blood glucose often rises progressively through the day in patients with diabetes. The selective testing and reporting of fasting values may explain why the A_{1c} might predict a higher blood glucose than that reported. (Average BGL in mmol/L = $2A_{1c} - 6$. At an A_{1c} of 6%, the average BGL is 6 mmol/L; above this value, for each 1% A_{1c} increase, average BGL increases by 2 mmol/L). Patients should be asked to perform blood glucose tests before lunch and the evening meal as well.

In patients who have been told to check their BGL two hours after the evening meal (this is often the highest value for the day), the A_{1c} will predict a lower BGL than reported. Checking that the pre - prandial BGL and A_{1c} are both on target usually gives a reasonable picture of daily and long term glycaemia. If A_{1c} prediction and reported BGLs differ significantly then look for 'hidden' hyperglycaemic or hypoglycaemic episodes. Hypers 'hide' postprandially or during the night, and hypos 'hide' preprandially or during the night.

Doctors like to see and patients like to report 'good' results. Patients may omit high values because they think they are not representative or 'forget' to record them because they want 'good' numbers. Some patients have even been known to make up a week's results before the consultation. Checking the memory of the blood glucose meter may give you insight into the completeness and accuracy of a patient's records.

Patients who are reluctant to change their erratic physical activity or eating schedules, their misuse of alcohol or their nonadherence to medication do not often volunteer the cause of variable BGLs. Others may not remember events clearly enough to recognise something associated with higher or lower BGLs. If any of these factors are possible, a third party, like Helen, may be able to help.

Changing insulin

Usually blood glucose swings can be smoothed out by education in lifestyle, medication and diabetes techniques. If the person cannot reliably manage self-care routines and techniques because of incapacity or forgetfulness then a third party may need to take control of part of the diabetes management.

Changing the insulin dose or type may be necessary in some patients, for example:

- if the person cannot reliably mix the insulin, a clear long acting insulin analogue (detemir [Levemir]or glargine [Lantus]) would help solve the problem because it does not need mixing. At the time of writing, glargine is subsidised by the PBS for all forms of insulin therapy in type 2 diabetes but detemir is approved only for use in basal–bolus schedules in type 2 diabetes
- if the person has difficulty with the process of drawing or dialling up the insulin, or with the injection, the larger isophane insulin injecting device, InnoLet, might help. People with limited vision or manual dexterity find that the large clock face dial and the size of the device make it easier to see, dial up and inject.

John has had diabetes for eight years and may have nerve damage affecting the autonomic nervous system, which controls gastric emptying. Variable food delivery to the small intestine can cause unpredictable glucose swings. Usually there would be other signs of somatic or autonomic neuropathy, such as painful or painless peripheries and postural hypotension.

Morning hyperglycaemia

'My evening blood glucose was always high so I switched the insulin injection to the morning. Now my morning glucose is always high. Helen has cut back my eating starchy vegetables, bread and sweets at tea and I've even started walking before bedtime, but my blood glucose is still high. Should I cut out more carbohydrate or increase my insulin?'

John's fasting BGL of 7 to 10 mmol/L is high but the other values – lunch and tea, both 4 to 7 mmol/L, and bedtime 7 to 10 mmol/L – seem to be on target. He is now on 45 units of intermediate insulin in the morning.

- Should John eat less carbohydrate?
- Should he increase his insulin?

Carbohydrate cuts

John does not need to cut out more carbohydrate from his diet. People often believe that the food they eat in the evening affects the BGL the next day, such as 'the chocolate biscuit I ate at bedtime' being the reason for their high fasting glucose. However, this is not so, unless they eat a very large amount of carbohydrate late in the evening.

During the night, the glucose from the evening food is cleared from the circulation and the liver supplies glucose to the blood. The morning blood glucose reflects hepatic gluconeogenesis, not the effect of the previous evening meal or snack. Further carbohydrate cuts will not solve John's morning hyperglycaemia

Three classic patterns of morning hyperglycaemia

A: 'Insulin run out'

In 'insulin run out', the patient's blood glucose rises steadily through the night. This is a particular problem in people on single morning dose insulin schedules using human intermediate insulins as increasing the morning dose might cause hypoglycaemia through the day. An evening injection might be necessary.

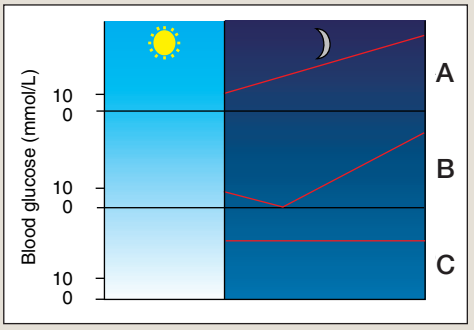

Figure. Morning hyperglycaemia: three patterns.

B: 'The bounce'

In 'the bounce', the patient's blood glucose falls to hypoglycaemic levels and then increases. This is the classic 'Somogyi effect' in which hypoglycaemia during the night causes physiological responses that lead to morning hyperglycaemia. Checking the 2 a.m. BGL will identify 'the bounce'. Although this pattern is uncommon, when it does occur less insulin is required.

C: 'Poor control'

In this situation, the patient's blood glucose is high before bedtime and high through the night. The morning hyperglycaemia reflects general hyperglycaemia. The insulin dose will need to be adjusted to achieve better control in the evening as well as through the night.

but might make him hypoglycaemic when he goes for his walk before bedtime.

Insulin increase

John does not need to increase his morning insulin. In both people without and those with diabetes, blood glucose falls during the night and then increases in the early hours of the morning. The morning hyperglycaemia of this 'dawn phenomenon' can be a problem in people with diabetes. To sort out which of the three classic patterns of morning hyperglycaemia is occurring in John's case, ask him to check his BGL before bed, at 2 a.m. and upon waking in the morning. The three patterns – 'insulin run out', 'the bounce' and 'poor control' – are described in the box about morning hyperglycaemia on this page.

It is most likely that John's daily dose of basal insulin given in the morning is 'running out' by the next morning. Remember that as type 2 diabetes progresses, insulin secretion progressively decreases (and insulin resistance progressively increases). John's pancreas may have produced enough insulin to control night-time glycaemia a few years ago but may no longer have that capacity. A bedtime dose of basal insulin will control night-time glycaemia and can be titrated to keep fasting BGL on target. The morning dose will continue to control basal daytime glycaemia.

It should be noted that a similar situation can occur with a single basal bedtime insulin dose. The fasting glucose may be well controlled but the blood glucose rises before lunch and/or the evening meal. This is what happened to John before and prompted him to change his insulin schedule. Increasing the bedtime dose will cause night-time or morning hypoglycaemia but blood glucose through the day will remain high. In this case, a morning dose should be added to control daytime glycaemia and the bedtime dose continued to control night-time and fasting blood glucose.

Risk of severe hypoglycaemia

John doesn't like the idea of taking insulin at bedtime.

'I could have a bad hypo. If I'm asleep, I won't know if my blood glucose is going low.'

- How likely is severe hypoglycaemia?
- What factors make severe hypoglycaemia more likely?

Likelihood of severe hypoglycaemia

Patients with severe hypoglycaemia need help from another person to prevent or treat loss of consciousness.

Many people think all those using insulin are in the same category. When a person with 'non-insulin dependent' (type 2) diabetes needs insulin, they think the diabetes has become 'insulin dependent' and that the person is then prone to the wide glycaemic swings and hypoglycaemic risk associated with type 1 diabetes. However, the pathophysiology of the two types is very different, as is the likelihood of glycaemic swings.

In patients with type 1 diabetes, practically no endogenous insulin is produced. If the insulin dose is exactly right, blood glucose is on target. More insulin requires the body to 'counter-regulate'. The sympathetic nervous system and hypothalamic pituitary adrenal axis are activated and glucagon is secreted, as long as these responses have not been affected by autonomic neuropathy (sympathetic nervous system) or by abnormal alpha cell regulation (glucagon), both of which can occur in those with type 1 diabetes. This overall response is associated with symptoms. If the insulin excess is considerable, counter-regulation may be overcome, blood glucose progressively falls and the person loses consciousness.

In patients with type 2 diabetes, endogenous secretion continues and endogenous insulin levels may be even higher

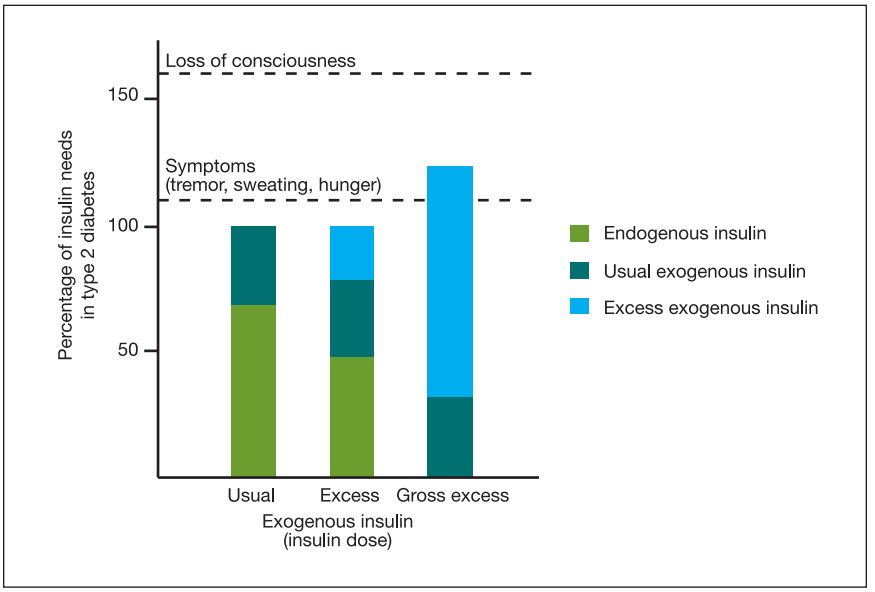

Figure 3. Insulin dose and hypoglycaemia. In patients with type 2 diabetes, endogenous insulin secretion decreases if excess exogenous insulin is taken (centre bar), reducing the risk of severe hypoglycaemia. Endogenous insulin can be totally supressed if a gross excess of exogenous insulin is taken (bar on right). (Derived from data in references 1 and 2.)

than in people without diabetes because high insulin levels are required to overcome insulin resistance. Exogenous insulin supplements the endogenous insulin but is only part of the total circulating insulin (Figure 3). If excess insulin is taken, blood glucose falls a little, endogenous insulin secretion decreases and the balance between insulin and glycaemia is restored. Even if a large excess is taken, the potential for suppression of endogenous insulin secretion reduces the risk of severe hypoglycaemia (Figure 3).

This expected lower rate of hypoglycaemia in patients with type 2 compared with type 1 diabetes was shown in the two trials assessing the relation between glycaemia and complications, DDCT and UKPDS.[1,2] At the same level of glycaemia (A_{1c}), the risk of severe hypoglycaemia in patients with type 1 diabetes was very much higher than in those with type 2 diabetes.

There is, however, still a risk of severe hypoglycaemia in patients with type 2 diabetes, particularly in those who have low A_{1c} values or who are older, have autonomic neuropathy or have had diabetes for many years (in whom endogenous insulin secretion is low and whose diabetes resembles type 1).

Factors increasing hypoglycaemic risk

Personal, medical, medication related and diabetes management factors increase the risk of hypoglycaemia (Table 2). These factors increase the hypoglycaemic effect of insulin, reduce the effectiveness of counter-regulation or delay recognition of hypoglycaemia.

Type 2 diabetes is much more common in older people and, because of their age, these people are more likely to have social and medical problems and to be taking potentially dangerous medications. As people with diabetes age they develop all these problems as well as microvascular complications (loss of vision, renal impairment and somatic and autonomic nerve damage). Moreover, as noted above, the risk of severe hypoglycaemia increases as diabetes progresses.

Table 2. Type 2 diabetes: hypoglycaemic risk factors

Personal
- Erratic lifestyle
- Lives/sleeps alone
- Older age
- Longer diabetes duration

Medical
- Liver and/or renal dysfunction
- Hypothyroidism and/or adrenalism
- Autonomic neuropathy

Medication
- Affecting sulfonylurea pharmacokinetics:
  - sulfonamides
  - cimetidine
  - azole antifungal agents
  - NSAIDs
  - fluoxetine
  - fluvoxamine
- Causing hypoglycaemia or reducing response:
  - alcohol
  - beta blockers
  - ACE inhibitors
  - high dose salicylates
  - perhexiline

Management
- Lifestyle
- Medication adherence
- Diabetes techniques (injection, monitoring)

This increased risk of severe hypoglycaemia with age may also be associated with an increased likelihood of permanent neurological damage if hypoglycaemia occurs. A 'watershed' area in the brain, with marginal blood and oxygen supply, is susceptible to hypoxic damage associated with decreased blood supply (e.g. as with hypotension). The marginal circulation also delivers a marginal glucose supply, and decreases in blood glucose can cause the same permanent

Table 3. Type 2 diabetes and insulin therapy: getting and keeping blood glucose on target

- Check the blood glucose level (BGL) readings are accurate
- Check the patient's adherence to lifestyle recommendations and medications
- Check the injection technique and expiry date and storage of the insulin
- Regularly review the insulin type and schedule
- Remember the potential overnight variability of BGL and assess the patient's overall diabetes management if fasting BGL is not controlled
- Prevent hypoglycaemia
- Provide action plans for sick days, low BGLs and mistakes in medication dosing

damage as hypoxia.

Hypoglycaemia is more likely in older people because they are more likely to have hypoglycaemic risk factors. Hypoglycaemia in these patients is more likely to have catastrophic effects, including myocardial infarct, stroke, seizure or trauma caused by falling.

An often underestimated risk for hypoglycaemia is living or sleeping alone. John has Helen to notice disturbed sleep, night-time sweating or morning unconsciousness. She can also help with recovery or can phone an ambulance.

In patients with a history of severe hypoglycaemia and in those with hypoglycaemic risk factors, the following should be reviewed:

- hypoglycaemic and other medication (e.g. by a Home Medicines Review)
- self-management techniques (lifestyle, medication and monitoring)
- action plans for sick days, hypoglycaemic episodes and mistakes in medication dosing, and 24-hour access to advice.

Conclusion

Keeping insulin safe and simple (the KISS approach) in patients who have type 2 diabetes and are taking insulin requires anticipation and avoidance of problems, and management of them if they occur (Table 3).

Blood glucose swings can be caused by variability in physical activity, food and hypoglycaemic medication and/or by concurrent illness. However, it may be that the blood glucose results being reported by patients are not complete or correct because of inaccurate monitoring technique or selective testing and reporting. The patient's injection technique, including site of injection and mixing of cloudy insulin, should also be checked to ensure that day-to-day insulin absorption rates are relatively constant. Blood glucose swings can usually be smoothed out by education in lifestyle, medication and diabetes techniques. Changing the insulin type is not usually necessary.

When a person cannot reliably manage self-care routines and techniques because of incapacity or forgetfulness then it may be necessary to simplify the insulin schedule and/or for a third party to take control of part of the diabetes management.

A second dose of basal insulin (intermediate or long acting) may be required when the BGL is consistently above target 24 hours after a single daily basal insulin dose.

Action plans for sick days, hypoglycaemic episodes and mistakes in medication dosing should be in place, particularly for patients with a history of these problems. MT

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

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