

Diabetes:

Part 2. Management of diabetes including hypoglycaemia and complications

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Introduction

Previously¹ we have discussed the diagnosis, classification and prevention of diabetes mellitus. In this article we provide an overview of management of glycaemic control in diabetes mellitus as well as managing hypoglycaemia. We also look at the management of diabetic complications and provide a basis by which to run a diabetes clinic.

Glycaemic control

Control of glycaemia leads to a reduction in both macrovascular and microvascular complications. There are several methods by which this can be done.

General measures

All patients with diabetes are treated with dietary modification. There is nothing special about a 'diabetic diet' and patients with diabetes should be advised to eat the same healthy diet as promoted to the non-diabetic population. Likewise, patients with diabetes should be encouraged to participate in regular exercise of the kind that would benefit the rest of the population. Most patients with new onset type 2 diabetes should initially be managed with dietary modification (and exercise) alone although there is now a trend towards early use of metformin (see below).

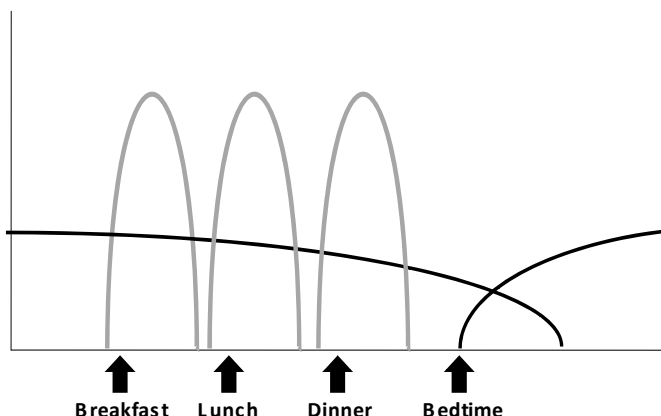
Type 1 diabetes

All patients with type 1 diabetes are treated with exogenous insulin and there are many different types of insulins available, all of which have different profiles. Two main insulin regimens are commonly used.

- A twice daily administration of pre-mixed insulin which contains a mixture of short acting and longer acting insulins in a ratio between 30:70 to 50:50.
- A "basal-bolus" regimen in which the patient takes the longer acting (basal) insulin at night and the shorter acting (bolus) insulin with each meal.

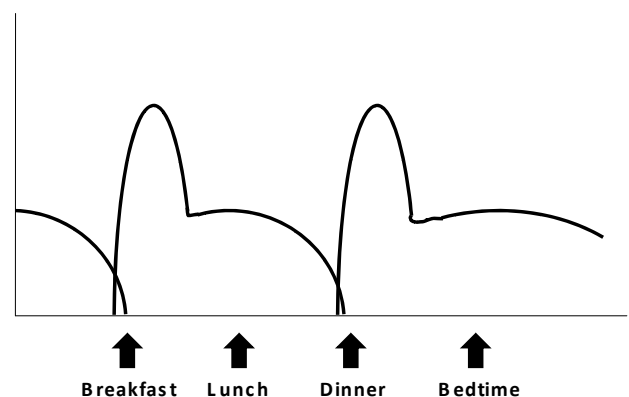
There is no one correct regimen and choice depends on patient preference, education and available support as well as availability of treatment options. In all situations patient education is vital as they are responsible for their own individual day-to-day management. Advice for storing and using insulin are included in the appendix and the plasma insulin levels achieved with basal-bolus and twice daily insulin mixes are illustrated in figures 1 & 2.

Figure 1: Basal-Bolus Regime



Plasma insulin concentrations over time with a basal bolus insulin regime

Figure 2: Premixed twice daily regime



Plasma insulin concentrations over time with a twice daily insulin mix regime

Special considerations in type 1 diabetes - sick day rules:

- When ill, blood glucose levels may rise above normal even if patients are not able to eat normal meals or drink anything, so NEVER STOP INSULIN.
- Test blood glucose levels approximately every 4 hours and adjust dose of insulin. Hypoglycaemia is common in malarial illnesses both because of the disease and also potentially as a result of drugs used in its treatment (e.g. quinine or mefloquine) so very frequent monitoring is advised and insulin dose reductions may be necessary.
- To prevent dehydration encourage the patient to drink 2-3 litres of sugar free liquids per day. This is approximately one glass every hour.
- If the patient is vomiting or unable to eat solid carbohydrate foods replace this with liquid carbohydrates such as fruit juice, sugary drinks.

Type 2 Diabetes

Oral hypoglycaemic agents

- Metformin reduces blood glucose levels by decreasing hepatic glucose output and increasing peripheral glucose uptake and utilisation in insulin sensitive tissues. It is the mainstay of treatment in obese individuals with type 2 diabetes and can be used alone or in combination with other medications including sulphonylureas and insulin. Approximately one-third of patients on metformin will have transient nausea, anorexia or diarrhoea, abdominal discomfort, and metallic taste. These side effects can be minimised by starting with a low dose (e.g. 500 mg daily with the main meal) gradually increasing the dose up to a maximum of 2 g per day in divided doses. The main limitation to metformin use is the risk of developing the potentially fatal complication of lactic acidosis. This is higher in individuals with either renal (creatinine >130-150 micromol/l), cardiac or hepatic failure where either the metabolism of metformin is impaired or lactate production is increased. Metformin must be used with caution or stopped in these individuals. Also be aware that chronic metformin use can lead to Vitamin B12 deficiency.
- Sulphonylureas (Gliclazide, Glibenclamide, Glipizide, Tolbutamide) increase the pancreatic release of insulin and are used to treat patients with type 2 diabetes who have adequate insulin

Hypoglycaemia

Hypoglycaemia is the commonest complication of type 1 diabetes and is frequent in type 2 diabetes with insulin or sulphonylureas. Always try to find out

reserve. Because of their tendency to promote weight gain, they are best used as first line agents in non-obese patients but may be added to metformin in obese patients with inadequate control. The main side-effect associated with this class of medication is hypoglycaemia and all patients need to be warned of this possibility.

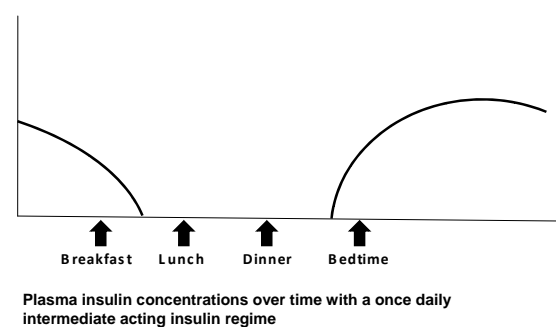
- Thiazolidinediones are also insulin sensitizing agents. They are second-line agents that can be used in combination with metformin and sulphonylureas but are contraindicated in individuals with ischaemic heart disease, cardiac failure, severe renal insufficiency, pregnancy, breastfeeding and hepatic dysfunction. The most significant side effect is weight gain mainly due to fluid retention.

Insulin in type 2 diabetes

Patients with type 2 diabetes require treatment with insulin on average 7 years after diagnosis. Insulin treatment of patients who are already overweight or obese carries the risk of inducing further weight gain. Unfortunately this can lead to further increases in insulin requirements and more weight gain. However, as these patients do not usually require exogenous insulin action throughout the 24 hour period other regimes may be considered, particularly addition of once-daily longer acting insulin (e.g. NPH insulin, insulin glargine or insulin detemir) in combination with oral hypoglycaemic agents. Plasma insulin concentrations achieved with once daily intermediate acting insulin is illustrated in figure 3. The main limitation to insulin use is hypoglycaemia.

Most patients with type 2 diabetes, especially those who are overweight, should remain on metformin when insulin is instituted/started in whatever form unless there are contraindications to its use.

Figure 3: Once daily regime



the cause of any hypoglycaemia as it will determine future management. Common causes include:

- Malaria
- Dietary – missing or delaying a meal
- Too much insulin: inadvertent administration
- Unaccustomed exercise
- Alcohol/recreational drugs
- Over dosage of sulphonylureas.

Symptoms can be classified as:

- early autonomic symptoms: sweating, shaking, palpitations, hunger, nausea
- later neuroglycopenic symptoms: confusion, poor concentration, and co-ordination

Occasionally seizures or localising signs such as hemiparesis occur.

The risk of hypoglycaemia provides the main limitation to the achievement of good glycaemic control in diabetes. Effects may be devastating, permanent and may occur over minutes or hours. Some 2-4% of deaths in type 1 diabetes are thought to be due to hypoglycaemia.

Patient education and recognition of hypoglycaemia with appropriate management is an important aspect of diabetes management. In the event of symptomatic hypoglycaemia or a blood glucose 72g/dl (<4mmol/l) treat with 20g of fast acting oral carbohydrate (3-4 cubes sugar/glucose tablets) followed up with a longer acting carbohydrate (bread, biscuits). In the event of severe hypoglycaemia the patient may be unable to help themselves and management includes intravenous glucose (20-30ml of 50% dextrose) repeated as necessary or glucagon (1mg im, iv or sc). Both of these treatments need following up with further oral or iv carbohydrate depending on response with ongoing capillary glucose monitoring until stable.

Complications

The many complications related to diabetes mellitus can be divided into:

- macrovascular – stroke, MI, peripheral vascular disease
- microvascular – nephropathy, retinopathy, neuropathy.

To achieve good glycaemic control aim for blood glucose values to be:

- 70-125 g/dl (4-7mmol/l) fasting,
- <140g/dl (7.8mmol/l) post prandial,
- <35g/dl (2 mmol/l) with prandial excursions;

or ideally an HbA1c of 6.5-7.5% (48-59mmol/mol). Ideally blood pressure should be < 140/80 mmHg but patients with nephropathy may benefit from even tighter control e.g. 130/70 mmHg.

Lipid control in type 2 diabetes usually requires an HMG CoA Reductase Inhibitor e.g. simvastatin 40 mg od to achieve target LDL levels of below 2-3 mmol/l. Some advocate the addition of a fibrate

such as fenofibrate if triglyceride remains elevated (e.g. above 2.3-2.8 mmol/l).

Nephropathy

Prolonged hyperglycaemia leads to glomerular hyperfiltration which eventually can lead to proteinuria. A stage of microalbuminuria is detectable by laboratory analysis of urine before a urine dipstick becomes positive for proteinuria (which almost always precedes a fall in renal function). Good glycaemic control with aggressive blood pressure control (<130/80) and use of ACE-Inhibitors or Angiotensin II receptor blockers can delay the progression of microalbuminuria to proteinuria. Other causes of renal failure (e.g. stones, infections, renovascular disease) should be considered if there is no evidence of proteinuria or retinopathy: diabetic nephropathy without retinopathy is almost unheard of.

Eye disease (retinopathy)

This is a common cause of blindness worldwide and after 15 years of diabetes about 2% of people are blind with 10% having severe visual impairment. In addition, cataracts and glaucoma are more common in people with diabetes. There are 2 main stages of diabetic retinopathy:

- pre-proliferative (almost always asymptomatic)
- microaneurysms and small haemorrhages visible on retina
- proliferative (usually asymptomatic but can cause blurring or reduced vision and dark spots)
- new vessel formation on retina and optic disc with risk of retinal detachment.

Maculopathy is another significant complication caused by reduced blood supply to the macula which in turn leads to macular oedema and blindness. There is no treatment for the early stages of diabetic retinopathy and prevention is achieved by good glycaemic and blood pressure control. Later stages of retinopathy can be treated with laser therapy by experienced specialists. Ideally all diabetic patients should have annual retinal examinations.

Neuropathy

Almost any neuropathy can be caused by diabetes and may be focal (e.g. cranial and peripheral mononeuropathies), diffuse (e.g. painful sensory neuropathy) or autonomic. Alternative diagnoses must always be considered as patients are at risk of neuropathies of other cause (e.g. thyroid dysfunction, B12 deficiency, vasculitis, malignancy, drugs, alcohol, infection). There are no specific treatments for diabetic neuropathies but most will respond to improved glycaemic control, sometimes with insulin. Pain can be treated with simple analgesics initially although they are not always successful and medications such as amitriptyline (e.g. 10mg od) or gabapentin can be tried.

Mononeuropathies will usually resolve spontaneously over 6-24 months.

Diabetic foot disease

This is a complex pathological process in which the culmination of vasculopathies and neuropathies associated with the poor wound healing of diabetes can lead to foot ulceration, infection and ultimately amputation. Routine foot examination is an important part of preventing this potentially fatal complication and should be performed regularly by all patients. The presence of callus often implies abnormal loading and high risk for ulceration. Simple advice includes:

1. Look carefully at the feet each day including in between the toes for signs of infection or deformity. If the patient is unable to do this then someone should do it for them.
2. Cut nails following the curvature of the toe.
3. Wash feet regularly and dry carefully.
4. Try to avoid walking barefoot.
5. Wear well-fitting footwear.

Running a diabetes service

When setting up a diabetes clinic ideally all people with diabetes have an annual review with interim visits guided by the availability of access, presence/absence of complications, glycaemic control and patient choice.

In Table 1 we provide a checklist for covering what should be addressed at each annual review. Specifics need to be targeted to each individual as appropriate.

Table 1. What to do at a patient's annual review

HISTORY	
General medical and non medical events	
Specific problems	
Problems with diabetes treatment	e.g. assessment of adherence, side effects, interactions etc.
Problems with other treatment	e.g. assessment of adherence, side effects, interactions etc.
Glycaemic control	Barriers to, treatment for, understanding of, goal setting for, fasting, postprandial, other
Hypoglycaemia	Frequency, severity, awareness, precipitants, driving, acceptability, avoidance etc
Education	Sick day rules, hypoglycaemia, good control, foot care, specific issues, glycaemic control etc
Lifestyle factors	Diet, exercise, smoking, weight, other drugs, other factors
Contraception/Conception	Higher dose folic acid (5 mg) pre-conception. Close antenatal care with tight glycaemic control to reduce risk of foetal anomalies, macrosomia etc
Vascular risk assessment and treatment (e.g. ?aspirin, ACE etc)	Glycaemic control, microalbuminuria, smoking, BP, lipids, FH, duration of diabetes, FH of microvascular complications etc.
Diabetes prevention	Post GDM, family members, IGT etc.
EXAMINATION	
Microvascular Complications	Neuropathy (autonomic or peripheral), nephropathy, retinopathy, foot examination
Macrovascular Complications	Claudication, Stroke, amaurosis fugax, MI, angina
Other complications	Infections, bladder, bowel, muscle, cognitive etc.
Erectile Dysfunction	Detection, ask, differential diagnosis, testosterone, prolactin, treatments for etc
Injection sites	Inspect for lipoatrophy or hypertrophy
BLOOD AND OTHER TESTS	

Use this checklist when assessing the foot:

1. Inspection – colour, shape, hard skin, cracked skin, ulcers, hair distribution
2. Palpation – pulses (dorsalis pedis and posterior tibial), warmth, capillary refill time
3. Assessment of protective sensation (10g monofilament, vibration sense, light touch perception).

Treatment measures include appropriate treatment of infections with anti-microbial therapy (e.g. flucloxacillin as 1st line therapy but directed as appropriate to suspected or cultured organism) and the ulcer base should be debrided of any non-viable tissue as appropriate. Equally important is appropriate footwear with offloading any pressure on the affected area and appropriate dressings in order to prevent further infection/ulceration. Hyperglycaemia over around 200g/dl (11.1 mmol/l) is associated with marked reduction in immune function and tissue repair and should be tackled where possible.

BP	Postural hypotension, pulse (autonomic neuropathy)
Urine dipstick	Proteinuria, haematuria, glycosuria, infection
Blood tests	Creatinine, HbA1c, Lipids, LFTs, TFTs, Autoantibodies etc
AGREED MANAGEMENT PLAN	Specific targets and management plan for factors identified

Appendix: Advice for insulin usage

1. Storage - keep unopened vials/cartridges of insulin in the fridge until needed. Once open each vial/cartridge can be safely stored at room temperature for 1 month. Insulin should not be exposed to extremes of temperature (very hot or very cold) as this will affect its action.
2. Mixing – pre-mixed insulins need to be rocked/rolled approximately 20 times until the mixture is uniformly cloudy before use to ensure the ratio administered is correct.
3. Expiry – all insulin has an expiry date, do not use after this date as the action of the insulin cannot be guaranteed
4. Changing needles – needles are designed for single use only and repeated use of needles reduces the accuracy of insulin administration.
5. Needle disposal – all needles should be disposed of safely into a sharps bin. If a sharps bin is not available a thick plastic bottle with a child-proof lid (e.g. empty bleach bottle) is a good substitute.

Reference and further reading

1. Lawrence V. 2009 Diabetes. Part 1. Definition, Diagnosis and Prevention *Southern Sudan Medical Bulletin* 2:2 p7
The following on-line resources provide further information and links to other relevant sites:

- American Diabetes Association (ADA) *Clinical Practice Guidelines* <http://www.diabetes.org/for-health-professionals-and-scientists/cpr.jsp>
- ADA *Guidelines on Diabetic Emergencies* http://care.diabetesjournals.org/cgi/content/full/27/suppl_1/s94
- National Diabetes Information Clearing House <http://diabetes.niddk.nih.gov/>

See also:

Lancet special issue on diabetes 23 May 2009 Volume 373 Number 9677

<http://www.thelancet.com/journals/lancet/issue/current>

The editorial states, "..... Four-fifths of all patients with diabetes live in developing countries. Across Africa, the Middle East, and South and Central America, the prevalence of diabetes is estimated to rise by about 80% over the next 15 years." It points out that research efforts in developed countries have produced effective screening and prevention programmes and drug treatments for the management of diabetes, but that "...little of this expertise is available in developing countries that are only now beginning to recognise the burden of chronic non-communicable diseases. Few diabetes drugs feature on essential drugs lists, and those countries that have access to insulin often store it at a central location, beyond the reach of the majority."

Articles in this issue include:

- A comprehensive meta-analysis showing that women with gestational diabetes have a seven-fold increased risk of subsequently developing type 2 diabetes compared with women with a normoglycaemic pregnancy (and an accompanying Seminar on gestational diabetes).
- A meta-analysis suggesting that intensive glucose control can significantly reduce rates of adverse coronary events, without increasing the risk of death.

HIV infection and diabetes A recent study shows that HIV infection itself does not increase the risk of diabetes. The results showed that at the start of the study, people with HIV had a lower risk of diabetes than HIV-negative individuals. However, this was because of the low body mass index (BMI) of untreated HIV-positive individuals; an improving immune status, treatment with antiretroviral drugs, and hepatitis C virus were all shown to increase diabetes risk in people with HIV. There is general agreement that traditional risk factors for diabetes, such as increasing age, obesity, and race, are responsible for most cases of the condition diagnosed in people with HIV. What is less clear is the role of risk factors such as the use of antiretroviral drugs and co-infection with hepatitis C virus. *Butt AA. HIV infection and the risk of diabetes mellitus. AIDS 23: 1227-34, 2009.*

The Diabetes Foundation report on implementing national diabetes programmes in sub-Saharan Africa
http://www.access2insulin.org/Diabetes_Foundation_report_on_implementing_national_diabetes_programmes_in_sub-Saharan_Africa_full_report.pdf