Evidence Summary

Medication

Diabetes Service, Country Health SA

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Medication

Therapeutic approaches vary for all types of diabetes. In this section we will outline the oral medications, injectables and insulin therapy available for use in the management of diabetes in Australia for type 1, type 2 diabetes and gestational diabetes mellitus.

It is important to point out that whilst treating hyperglycaemia is extremely important in managing diabetes, other metabolic abnormalities such as dyslipidaemia, hypertension, hypercoagulability and smoking cessation are also extremely important in reducing microvascular and macrovascular complications.

In addition, the target glucose levels may vary depending on type of diabetes, duration of diabetes, presence or absence of other co-morbidities, the frequency of hypoglycaemia and quality of life.

The aim of this evidence summary is to provide basic information about each of the diabetes medications. We recommend you refer to the current Australian Medicines Handbook[1], National Prescribing Service (NPS)[2] or Therapeutic Guidelines[3] for specific details including interactions between various medications.

Contents

National Safety and Quality Health Service

The Australian Commission on Safety and Quality in Health Care was initially established in 2006 by the Australian, state and territory governments to lead and coordinate national improvements in safety and quality in health care.

In 2017, the second edition of the National Safety and Quality Health Service (NSQHS) Standards was released and encompass:


Clinical Governance


Partnering with Consumers


Preventing and Controlling Healthcare-Associated Infection


Medication Safety


Comprehensive Care


Communicating for Safety


Blood Management


Recognising and Responding to Acute Deterioration

NSQHS Standard 4: Medication Safety

The Medication Safety Standard aims to ensure clinicians are competent to safely prescribe, dispense and administer appropriate medicines and to monitor medicine use. To ensure consumers are informed about medicines and understand their individual medicine needs and risks. This standard highlights the following criteria for improving medication safety by preventing medication incidents:

- Clinical governance and quality improvement to support medication management using organisation-wide systems are used to support and promote safety for procuring, supplying, storing, compounding, manufacturing, prescribing, dispensing, administering and monitoring the effects of medicines.
- Documentation of patient information when commencing an episode of care which includes medication history, and information relating to medicine allergies and adverse drug reactions.
- Continuity of medication management in that the patient's medicines are reviewed, and information is provided to them about their medicine needs and risks. A medicines list is provided to the patient and the receiving clinician when handing over care.
- Medication management processes in which health service organisations procure medicines for safety. Clinicians are supported to supply, store, compound, manufacture, prescribe, dispense, administer, monitor and safely dispose of medicines.

Quality use of medicines

Australia's National Strategy for Quality Use of Medicines (QUM)[4] recognises that whilst many people with diabetes maintain their health without using medicines, most people with diabetes require medications to maintain health, prevent illness and improve health outcomes.

The Australian Pharmaceutical Advisory Council (APAC)[5, 6] guiding principles to achieve continuity in medication management aim to improve medication management as individuals move through the health care system and offer the following key points:

- Information resources

The NPS provides accurate, unbiased, evidence-based information and services to health professionals and the community on QUM. Health professionals can access evidence-based information from the NPS website.

- Self-administration

People should be encouraged to maintain their independence for as long as possible in a safe and effective way. The NPS has an online search facility where Consumer Medicines Information (CMI) product sheets can be downloaded at NPS - Medicine Finder.

- Medication review

People at high risk of medication misadventure may benefit from information about how they can access a Home Medicines Review (HMR). A HMR involves pharmacist visiting the person at home, reviewing their medication regimen and providing the general practitioner with a report which is then used to develop a medication management plan.

- Medication lists

People should be supported in maintaining a current list of all their medications. NPS - Keeping a medicines list is an excellent resource to keep all the information about your medications together.

> Medication action plans

Medication action plans should be developed with the person and relevant health care professionals and provide information about the plan eg affordability, treatment goals, any changes to medication management and the overall care plan. Training and support materials are available on the Australian Commission on Safety and Quality in Health Care website.

Other issues to consider

Although medications for diabetes are highly effective and can improve blood glucose, and reduce the complications of diabetes, many people do not take the medications as prescribed thus substantially reducing their effectiveness. It is important that the person understands that they cannot stop their medications just because they are feeling okay.

Common factors leading to difficulties include:

> fears (of the disease worsening, hypoglycaemia, weight gain)

> knowledge and skill

> self efficacy

> health beliefs

> depression

> lack of confidence in the immediate or future benefit of taking the medication

> remembering doses and refills

> complexity of the regimen (more than one medication, splitting tablets)

> frequency of dosing (2 or more times per day results in poorer adherence)

> cost

> adverse effects.[7]

Possible strategies for addressing barriers to adherence include:

> use of standard questionnaires to explore the persons beliefs

> mailed medication reminder 10 days before refill date

> assistive technology devices eg TabTimers, automated pill dispensers, medical watches, vibrating watches & clocks, talking watches & clocks

> unit dose packaging (blister packs) - eg webster packs

> cue-dose training (linking medication with daily activities)

> use of fixed dose fixed dose combination medications- these products may improve adherence by simplifying the treatment regimen but they are not suitable for all patients because of limited combination and dosing options

> mobile and web apps with advanced software platform that supports and empower people with diabetes and their families/carers to manage - eg MedAdvisor. For more information, visit the MedAdvisor website.

Medication management in type 2 diabetes

Type 2 diabetes is a progressive condition that is characterised by insulin resistance and insulin deficiency.

Ideal management involves:

- active involvement of the person with diabetes and their family members/carers
- appropriate treatment plan and associated self-management action plans
- appropriate nutrition and weight control
- appropriate physical activity
- advice for maintaining a healthy lifestyle eg stress management, reduce or quit smoking.[8]

Medications are required over time to meet glycaemic goals. The landmark UKPDS demonstrated that 50% of people with type 2 diabetes will require insulin therapy within 6 years.[9] Lifestyle factors should be reinforced at each step at which titration of medication is considered. Weight loss in the overweight or obese, and prevention of weight gain are important.

There are various treatment algorithms that have been designed to navigate choice that are being used nationally and internationally.

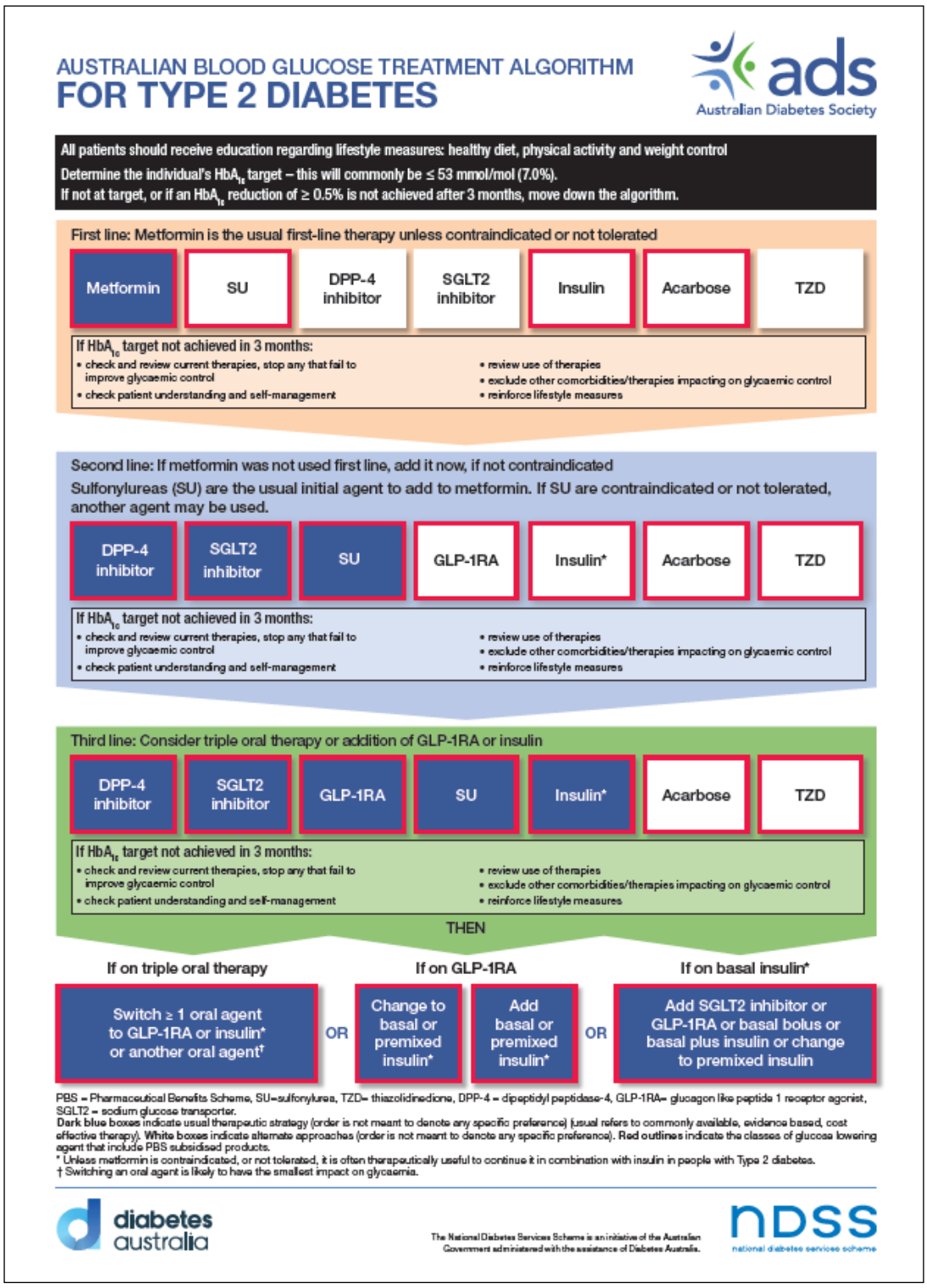
In 2016, the Australian Diabetes Society (ADS) revised its position statement for the Blood Glucose Management Algorithm for Type 2 Diabetes. The ADS Position Statement identifies that:

- Lowering blood glucose levels in people with type 2 diabetes has clear benefits for preventing microvascular complications and potential benefits for reducing macrovascular complications and death.
- Treatment needs to be individualised for each person with diabetes. This should start with selecting appropriate glucose and glycated haemoglobin targets, taking into account life expectancy and the patient's wishes. For most people, early use of glucose-lowering therapies is warranted.
- A range of recently available therapies has added to the options for lowering glucose levels, but this has made the clinical pathway for treating diabetes more complicated.[10]

The revised ADS statement incorporates new random control trial evidence and outlines the risks, benefits and costs of the available therapies. A treatment algorithm shown in Figure 1 incorporates both the older and newer agents and includes the following list of abbreviations:

- SU = Sulfonylureas
- DPP-4 = Dipeptidyl peptidase inhibitor
- SGLT2 = Sodium glucose co-transporter 2 inhibitor
- GLP1RA = GLP-1 receptor agonist
- TZD = Thiazolidinedione.

Figure 1: Australian Diabetes Society Blood Glucose Management Algorithm for Type 2 Diabetes



First Line Treatment

The ADS Position Statement identifies that if blood glucose levels are very high, or remain high overnight, insulin should be considered early.

When diet and exercise no longer achieve the individualised treatment target, the first treatment step for people in whom there is no contraindication should be metformin. If metformin is not tolerated or is contraindicated, a sulfonylurea may be introduced.

Other medications are also available but (apart from acarbose and insulin) are not currently subsidised for use as initial monotherapy of the Pharmaceutical Benefits Scheme (PBS).[10]

Second Line Treatment

The ADS Position Statement identifies that if glycaemic control is not achieved with a single agent, there are many second-line treatment options (Figure 1).

Sulfonylureas are good second-line agents, achieving similar decreases in HbA1c levels as other second-line oral agents for approximately 25% of the daily cost. For patients who experience problematic hypoglycaemia, weight gain, other side effects, or in whom it is considered that the potential for hypoglycaemia should be minimised, an alternate agent may be considered (Figure 1).

DPP-4 inhibitors are the most commonly used alternative second-line agent. These are now all available in combination tablets with metformin, which may improve patient compliance.

SGLT2 inhibitors are another option and are also PBS subsidised for use with either metformin, sulfonylurea or insulin therapy. SGLT2 may also contribute to mild weight loss. They can also be tried if glycaemic control is not achieved with a DPP-4 Inhibitor.

GLP-1RA reduces HbA1c levels with the added benefit of facilitating weight and blood pressure reduction (however heart rate may increase). As second line therapy, GLP-1RA can be used in combination with metformin or a sulfonylurea. Currently there are no data examining the efficacy of GLP-1RA in combination with a DPP-4 inhibitor or SGLT2 inhibitor.

Acarbose, in some people, may be a useful agent, particularly where post-prandial hyperglycaemia and/or obesity are issues. Where the patient remains keen to avoid injectable therapy, this can be trialled.

In carefully selected insulin-resistant individuals, a TZD may be used, preferably in combination with metformin.

As always, insulin is an option and should be considered, especially in patients in whom HbA1c is above 75 mmol/mol (9.0%) on oral therapy.

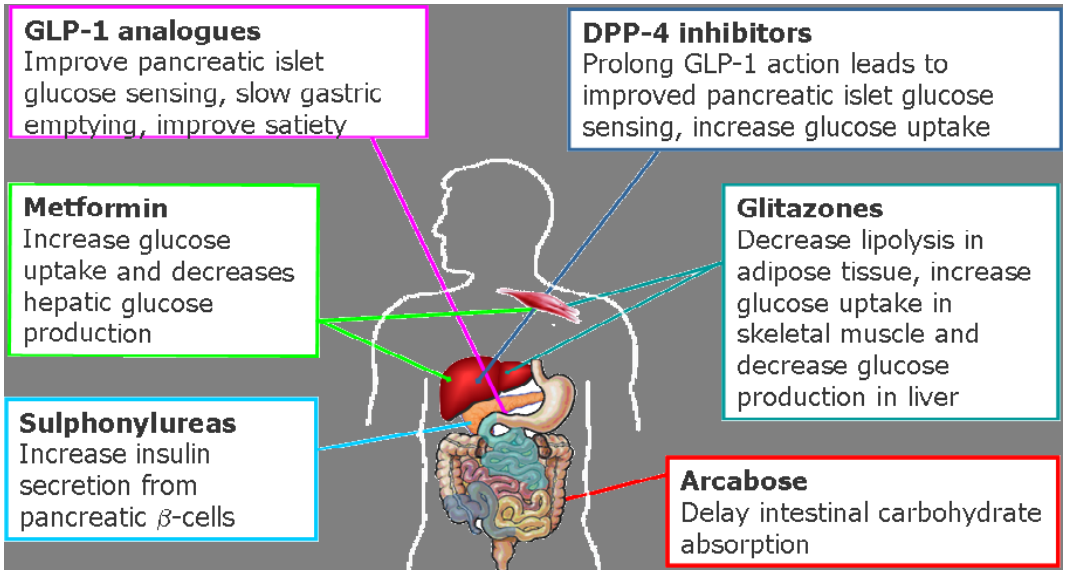
When a decision has been made that a second agent is needed, the choice of second-line agent should be individualised, based on issues such as potency, body weight, risk of hypoglycaemia, comorbidities, patient acceptance of injection therapy, PBS subsidy and cost.[10]

Third Line Treatment

The ADS Position Statement identifies that after failure of dual oral therapy treatment of type 2 diabetes becomes more complex. Metformin should be continued for its insulin-sensitising effects unless contraindications develop. Ineffective therapies should be ceased and substituted with a different medication.

Comparative evidence from random control trials to inform prescribing is relatively scarce.[10]

Figure 2: Mode of action



Oral medications

Metformin

Metformin reduces hepatic glucose output and insulin resistance. It is the only medication in the biguanide class.

Typically metformin used on its own will lower HbA1c by up to 2% (22 mmol/mol). However, the actual reduction will depend on the starting HbA1c. Metformin on its own does not cause hypoglycaemia.[8] Metformin therapy is usually weight neutral and can assist with weight loss.

Gastrointestinal side effects are common and it is recommended that doses are started low and titrated up. Metformin taken with or after food may minimise adverse effects. Metformin should be used with caution in people with renal impairment and is contraindicated when the glomerular filtration rate is less than 30 mls/min.

For information about side effects, dosage and administration, visit the Australian Medicines Handbook - Metformin.

Sulfonylureas

Sulfonylurea (SU) agents reduce glycaemia by enhancing insulin secretion. There are a number of different medications available in this class. Sulfonylureas have favourable long-term safety and outcome data.

When combined with metformin, SU agents will lower HbA1c level by up to 0.6-1.5% (7-16 mmol/mol).[10] Glibenclamide and gliclazide have been shown to significantly reduce the incidence of diabetes-related microvascular complications; equivalent long-term efficacy data are not available for other sulfonylureas.[10]

The major side effects are hypoglycaemia and weight gain.[5] The risk of hypoglycaemia is highest with sulfonylureas with long half-lives and renally-excreted active metabolites such as glibenclamide.

Sulfonylurea dosage reduction may be required in severe renal impairment and use should be avoided in severe hepatic impairment.

For information about side effects, dosage and administration, visit Australian Medicines Handbook - Sulfonylureas.

Dipeptidyl peptidase 4 inhibitors (DPP-4)

Dipeptidyl peptidase-4 inhibitors are agents which increase incretin levels (GLP-1 and GIP) which inhibit glucagon release, which in turn increases insulin secretion, slows gastric emptying, and decreases blood glucose levels. There are a number of different medications available in this group of medications that are called the 'gliptins'.

This inhibition of DPP-4 increases and prolongs the action of the endogenous GLP-1 resulting in a prolonged effect in stimulating insulin release and decreasing glucagon secretion. DPP-4 improve post-prandial BGLs, are weight neutral and do not cause hypoglycaemia unless used with sulphonyureas.

At maximal doses, the average reduction in HbA1c is up to 0.6-0.7% (7-8 mmol/mol) except for vildigliptin (3.2% or 11 mol/mol). This DPP-4 agent reduction will depend on the actual starting HbA1c level, however, is generally inferior to the reduction offered by other oral hypoglycaemic agents.

Common side effects are mild gastrointestinal disturbances and nasopharyngitis which often subside during the first 10-14 days. Rash is rare but potentially a serious side effect. To date, long term random controlled trial and efficacy data is limited to 3 years.[10]

DPP-4 inhibitors are not PBS subsidised for use as monotherapy.

DPP-4 inhibitors dosage reduction may be required in renal impairment. Limited data suggests that hepatic impairment does not affect vildagliptin's pharmacokinetics, however, the manufacturer does not recommend use in hepatic impairment.

For information about side effects, dosage and administration, visit Australian Medicines Handbook - DPP-4.

Sodium glucose co-transporter inhibitors (SGLT2)

SGLT2 inhibit a renal sodium-glucose cotransporter, which exchanges sodium and glucose in the kidney. The kidneys normally filter approximately 180g of glucose per day, and the SGLT2 allow renal loss of glucose, thereby decreasing blood glucose level.

SGLT2 has an average reduction in HbA1c of 0.5-0.8% (6-9 mmol/mol) in comparison to placebo.

The SGLT2 class is associated with weight loss due to caloric loss via the urine and decreased blood pressure due to tubuloglomerular feedback. They cause approximately 10% decrease in serum urate and lower systolic blood pressure by 3-6 mmHg. They have diminished or no efficacy with increasing renal impairment. Because of their diuretic effect, their use with loop diuretics should be avoided.

Due to the mechanism of action, the most common side effects are dehydration, dizziness, and increased risk of genito-urinary infections.[10]

For information about side effects, dosage and administration, visit Australian Medicines Handbook - SGLT2.

Glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RA)

There are two agents that are currently available in Australia and both are analogues of human GLP-1 which are administered by subcutaneous injection.

Both agents stimulate beta-cell insulin release and slow gastric emptying, the shorter acting GLP-1RA acts primarily to reduce post-prandial blood glucose levels while the longer acting analogue have greater effect on basal glycaemia.

Because pharmacological rather than physiological GLP-1 activity is achieved with recommended doses, there is an effect on gastric emptying that is not observed with DPP-4 inhibitors. The above and the central nervous system effects contribute to weight loss, but also to nausea and vomiting.

The GLP-1RA has a beneficial effect on blood pressure but is also associated with a mild increase in resting heart rate. An increased risk of pancreatitis and tumours of the thyroid has been reported.[10]

For information about side effects, dosage and administration, visit Australian Medicines Handbook - GLP-1.

Acarbose

Acarbose is an alpha-glucosidase inhibitor. It is the only agent available in this class. It can be useful when blood glucose remains high after a meal as it inhibits the digestion of carbohydrate thus slowing down the rate of glucose delivery into the blood stream.

The common side effect of increased flatulence has led to discontinuation of use. If tolerated, it can be effective, particularly when combined with metformin. Acarbose is weight neutral.[10] In the event of hypoglycaemia, glucose; must be given (not sucrose) as sucrose absorption will be delayed.

For information about side effects, dosage and administration, visit Australian Medicines Handbook - Acarbose.

Thiazolidinediones (TZDs)

TZDs are transcription factor peroxisome proliferator-activated receptor PPAR-gamma antagonists, which lower blood glucose levels through insulin sensitising action. TZDs enhance insulin sensitivity at muscle, liver and fat tissues and decrease hepatic glucose output.

Side effects include weight gain, fluid retention and heart failure, and an increased risk of non-axial fractures in women.

Rosiglitazone was reportedly associated with an increased risk of cardiovascular events however, in 2013, the Australian Therapeutic Goods Administration concluded that the cumulative evidence did not support this premise and removed the prescribing and dispensing restrictions. Pioglitazone is also associated with an increased risk of bladder cancer.

Treatment with either pioglitazone or rosiglitazone equally can result in pulmonary oedema and/or heart failure and its use is contraindicated in people with heart failure and/or other underlying cardiac disease.

TZDs combine well with metformin and sulfonylureas and pioglitazone may be suitable for use with insulin.[10]

For information about side effects, dosage and administration, visit Australian Medicines Handbook - Thiazolidinediones.

For further information, refer to the CHSA factsheets - *'Medication for type 2 diabetes' and 'SGLT2 Inhibitors - Medication for type 2 diabetes'.*

Insulin

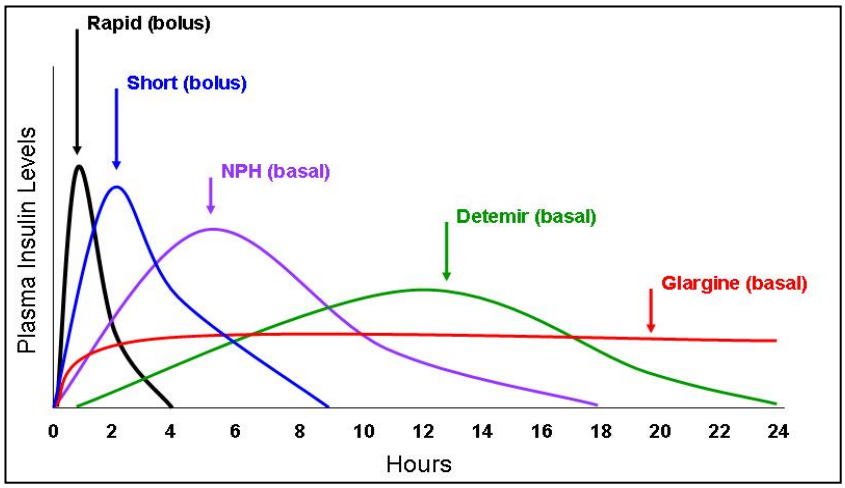
Insulin is a hormone which is secreted by the pancreatic beta cells in response to elevated blood glucose levels, and acts to limit the production of glucose from the liver and to stimulate glucose uptake by other tissues.

Insulin can be used at any stage in the treatment cascade but is often reserved for when other therapies fail to achieve glycaemic targets. Insulin is administered subcutaneously via injection and is commonly initiated as once daily basal insulin added to oral agents, particularly metformin (Figure 1).

Rare adverse events associated with the use of insulin have been reported in observational studies. Such events include congestive heart failure, oedema, lipodystrophy, allergic reactions, reversible transaminitis, reversible nephrotic syndrome and ß-cell destruction. Common side effects include hypoglycaemia and weight gain.

Insulin therapy can be intensified by increasing the frequency of insulin injections, combining long-acting insulin with one or more injections of short-acting insulin, or by continuous subcutaneous insulin infusion (this latter strategy is not very commonly used in type 2 diabetes) (Figure 3).

Figure 3: Insulin Action Profiles



It is important that people with type 2 diabetes are not made to feel as though they have failed if insulin therapy is prescribed. Referral to a credentialled diabetes educator is recommended so that the person can discuss any concerns and receive appropriate education regarding safe insulin self administration and prevention and treatment of hypoglycaemia.[10]

For information about side effects, dosage and administration, visit Australian Medicines Handbook - Other drugs for diabetes.

For further information, refer to the CHSA factsheets - *'Medication for type 2 diabetes' and 'Starting insulin in type 2 diabetes'*.

Insulin titration and intensification

People with type 2 diabetes can often be managed using a single daily dose of intermediate or long acting insulin added to their existing oral hypoglycaemic agents. This basal therapy provides background insulin and prandial (bolus) doses can be added if needed. However, prandial doses should only be added once basal dose has been optimised.[10]

The Royal Australian College of General Practitioners (RACGP) suggest a starting dose of 10 units of basal insulin (glargine or isophane) at bedtime or breakfast (Figure 4).[11] Glargine may cause less hypoglycaemia than isophane due to its flatter profile.

If glycaemic targets are not achieved using basal insulin alone then prandial insulin (bolus) will be required (Figure 5). The RACGP guidelines suggest;

Basal plus – where additional pre-prandial injection of short-acting insulin is added to basal insulin.

Basal bolus – where short-acting insulin injections are used before each meal in addition to basal insulin.

Premixed – where additional injections of premixed are added to meals - either two or three times a day, or alternatively basal insulin is switched to premixed insulins.

The RACGP also provides a guideline for starting and adjusting pre mixed insulin (Figure 6) which recognises the different ways in which insulin can be commenced in type 2 diabetes eg basal or premix.

Note: The target glucose levels will depend on the persons individual risk factors. For further information, refer to the Evidence Summary - *'Monitoring glycaemia'*, CHSA factsheets - *'Medication for type 2 diabetes' and 'Starting insulin in type 2 diabetes'*.

Figure 4: RACGP Guide to starting and adjusting basal insulin[11]

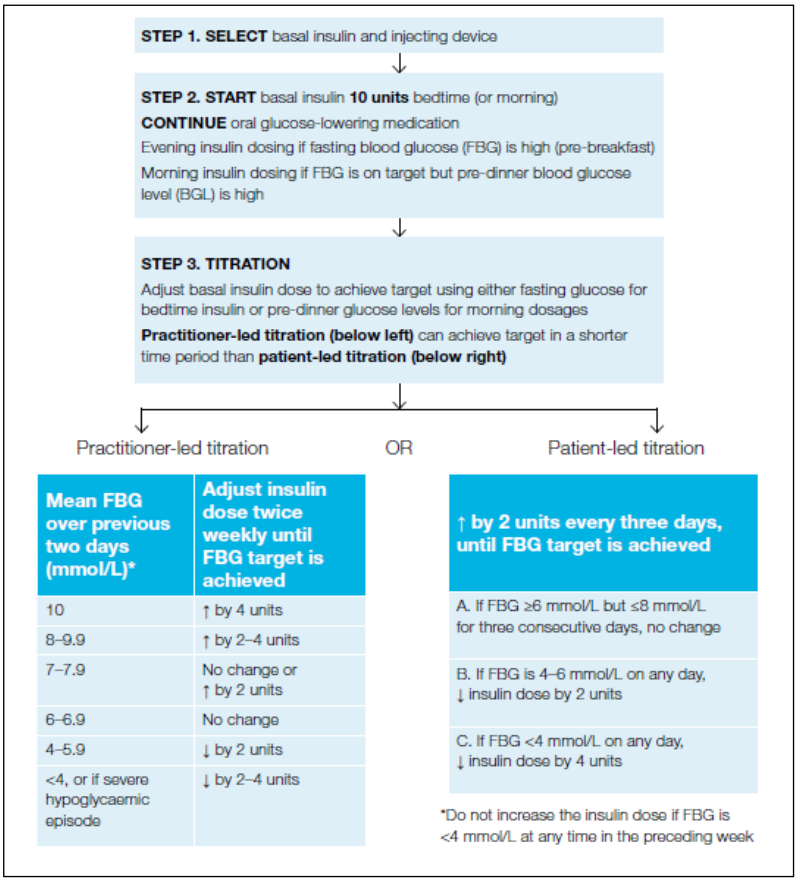
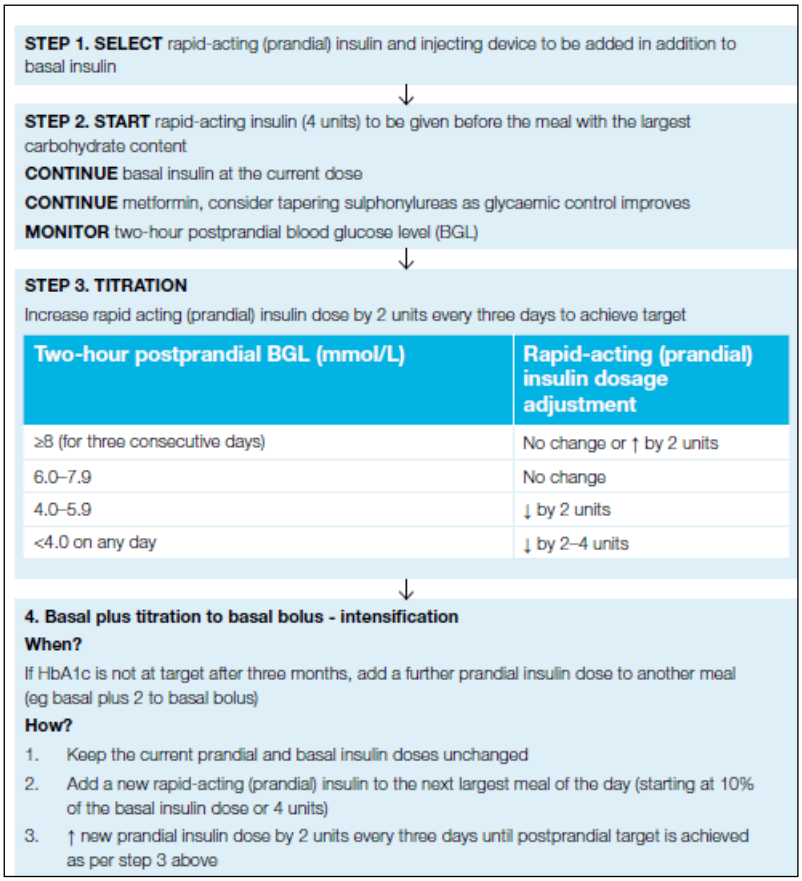


Figure 5: RACGP Algorithm for insulin intensification[11]



STEP 1. SELECT rapid-acting (prandial) insulin and injecting device to be added in addition to basal insulin

↓

STEP 2. START rapid-acting insulin (4 units) to be given before the meal with the largest carbohydrate content

CONTINUE basal insulin at the current dose

CONTINUE metformin, consider tapering sulphonylureas as glycaemic control improves

MONITOR two-hour postprandial blood glucose level (BGL)

↓

STEP 3. TITRATION

Increase rapid acting (prandial) insulin dose by 2 units every three days to achieve target

Two-hour postprandial BGL (mmol/L)	Rapid-acting (prandial) insulin dosage adjustment
≥8 (for three consecutive days)	No change or ↑ by 2 units
6.0–7.9	No change
4.0–5.9	↓ by 2 units
<4.0 on any day	↓ by 2–4 units

↓

4. Basal plus titration to basal bolus - intensification

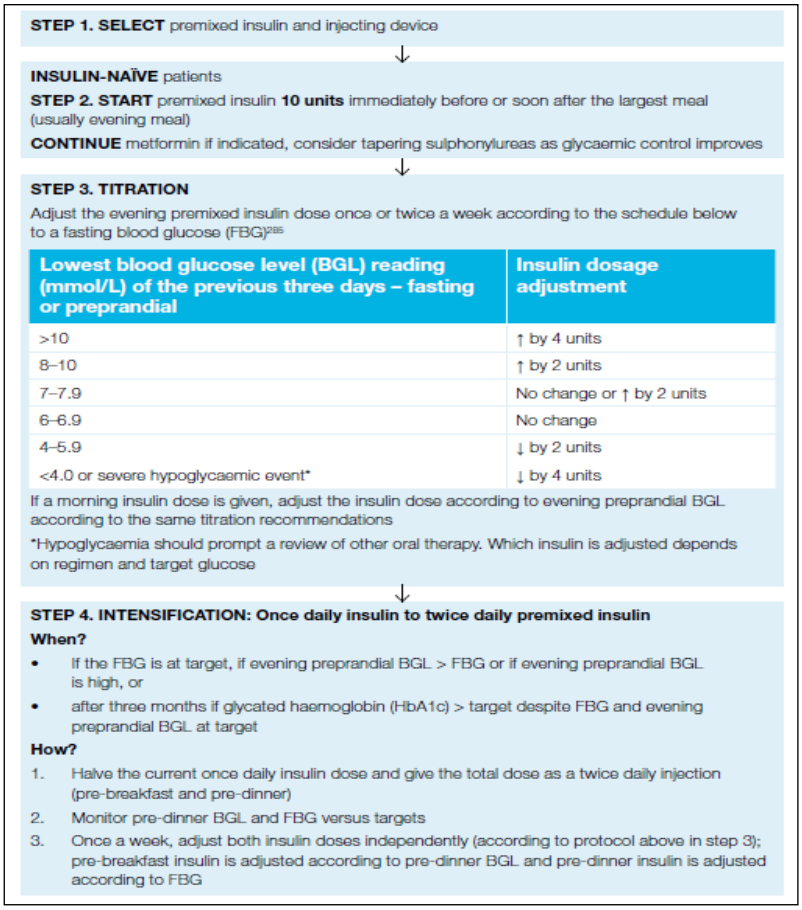
When?

If HbA1c is not at target after three months, add a further prandial insulin dose to another meal (eg basal plus 2 to basal bolus)

How?

1. Keep the current prandial and basal insulin doses unchanged
2. Add a new rapid-acting (prandial) insulin to the next largest meal of the day (starting at 10% of the basal insulin dose or 4 units)
3. ↑ new prandial insulin dose by 2 units every three days until postprandial target is achieved as per step 3 above

Figure 6: RACGP Guide to starting and adjusting pre mixed insulin[11]



STEP 1. SELECT premixed insulin and injecting device

↓

INSULIN-NAÏVE patients

STEP 2. START premixed insulin **10 units** immediately before or soon after the largest meal (usually evening meal)

CONTINUE metformin if indicated, consider tapering sulphonylureas as glycaemic control improves

↓

STEP 3. TITRATION

Adjust the evening premixed insulin dose once or twice a week according to the schedule below to a fasting blood glucose (FBG)[285]

Lowest blood glucose level (BGL) reading (mmol/L) of the previous three days – fasting or preprandial	Insulin dosage adjustment
>10	↑ by 4 units
8–10	↑ by 2 units
7–7.9	No change or ↑ by 2 units
6–6.9	No change
4–5.9	↓ by 2 units
<4.0 or severe hypoglycaemic event*	↓ by 4 units

If a morning insulin dose is given, adjust the insulin dose according to evening preprandial BGL according to the same titration recommendations

*Hypoglycaemia should prompt a review of other oral therapy. Which insulin is adjusted depends on regimen and target glucose

↓

STEP 4. INTENSIFICATION: Once daily insulin to twice daily premixed insulin

When?

- If the FBG is at target, if evening preprandial BGL > FBG or if evening preprandial BGL is high, or
- after three months if glycated haemoglobin (HbA1c) > target despite FBG and evening preprandial BGL at target

How?

1. Halve the current once daily insulin dose and give the total dose as a twice daily injection (pre-breakfast and pre-dinner)
2. Monitor pre-dinner BGL and FBG versus targets
3. Once a week, adjust both insulin doses independently (according to protocol above in step 3); pre-breakfast insulin is adjusted according to pre-dinner BGL and pre-dinner insulin is adjusted according to FBG

Medication management in type 1 diabetes

Insulin therapy in type 1 diabetes is essential for survival. The insulin regimen needs to:

- Provide appropriate basal insulin requirements to cover the metabolic needs across 24 hours.
- Provide sufficient insulin levels when needed to cover food (eg carbohydrate) intake.
- Have adequate provision for adjustment and correction when needed.
- Minimise blood glucose fluctuation and risk of hypoglycaemia and hyperglycaemia.
- Achieve short-term and long-term metabolic targets.

Intensive diabetes management can be delivered either by multiple daily injections (MDI) as part of a basal bolus approach or rapid-acting insulin therapy via continuous subcutaneous insulin infusion (CSII) or insulin pump.[12]

Insulin requirement is based upon the body weight, age, and in children, their pubertal developmental stage.

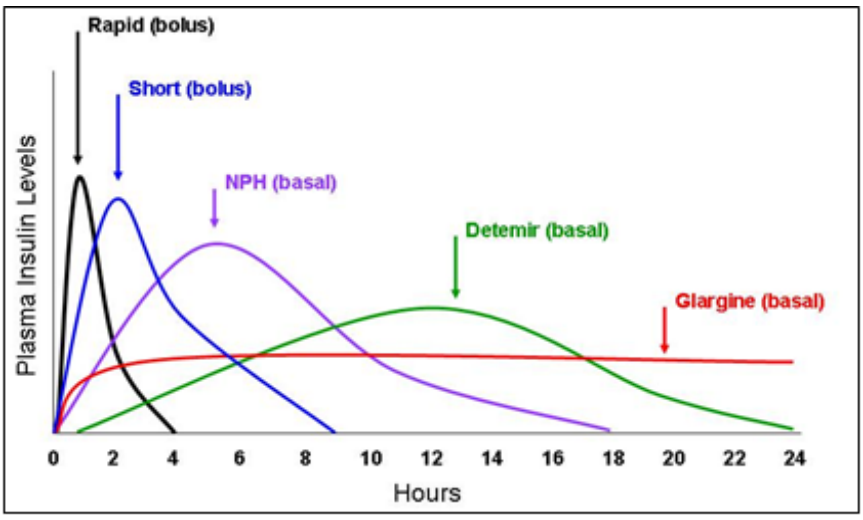
In general, the newly diagnosed child requires an initial total daily insulin dose of 0.5 to 1.0 units/kg. Prepubertal children usually require lower doses, and the dose requirement may be as low as 0.25 units/kg for a variable period following diagnosis. The newly diagnosed adult requires an initial total daily dose of 0.2 to 0.4 units of insulin per kg. Higher insulin doses are needed in patients in ketoacidosis, or in patients receiving glucocorticoid therapy and infection.[13]

The choice of insulin types (Figure 7) and regimen has to be guided by a variety of factors, including;[13]

- Age of the person.
- Lifestyle factors.
- The person and family preferences and management skills.
- Metabolic targets.
- Duration of diabetes.
- Experience of the health care team.
- Affordability and sustainability.
- Associated complications, including hypoglycaemia (awareness).

Children and adolescents have special needs and requirements in relation to insulin. Please consult a paediatric endocrinologist or staff in a paediatric diabetes education service for advice if required.

Figure 7: Insulin Action Profiles



Multiple dose insulin injection therapy

MDI therapy involves injecting long acting insulin once or twice daily as a background (basal) dose and having further injections of rapid acting insulin at each meal time. MDI therapy will usually involve at least four injections a day but allows the patient with diabetes to be more actively involved in the adjustment of their insulin basal and bolus doses.

When commencing MDI, the person requires education and support from a multi-disciplinary team including an endocrinologist, credentialled diabetes educator and dietitian to calculate insulin doses to carbohydrate intake, physical activity and blood glucose levels.

This team will need to provide ongoing education and support throughout the person's life. Shared care is an option for those living in rural and remote areas, as distance technologies enable contact with specialist teams based in larger centres or metropolitan health services.

Total Daily Dose (TDD)

The total daily dose is the number of units of insulin prescribed in 24 hours added together. Using this information, multi-disciplinary team can assist the person to estimate:

> The amount of insulin required per grams of Carbohydrate to be consumed. This is known as the Insulin:Carbohydrate (CHO) Ratio.

> The insulin sensitivity factor for correctional insulin (also known as supplementary insulin) doses. The insulin sensitivity factor identifies how much the blood glucose level will lower if an extra 1 unit of rapid acting insulin is given.

Insulin:Carbohydrate (CHO) Ratio

All carbohydrate (CHO) foods are digested into glucose. The amount and type of CHO will affect how high the blood glucose levels will rise after a meal and how quickly. It is important to match the CHO food with the insulin dose correctly to avoid post meal hypoglycaemia or hyperglycaemia.

It is important to note that the Insulin:CHO ratio is based on current insulin doses and may require fine tuning. It should be reviewed if the person's insulin requirements change (eg change in activity, weight, illness, medication, pregnancy).

Correctional Insulin

Out of target blood glucose levels increase the person with diabetes' risk of hypoglycaemia, hyperglycaemia and diabetic ketoacidosis. Correctional doses (also known as supplemental insulin) are commonly used to manage hyperglycaemia and ketosis. Only rapid acting insulin is used due to its quick action time.

Correctional doses are commonly used in addition to bolus insulin at meal times. Correctional insulin doses are given straight away and should not be delayed until the next usual insulin dose is due. To avoid insulin doses 'overlapping' and an increased risk of hypoglycaemia, a correctional dose must not be given within 2 hours of the last dose of rapid acting insulin. Medical assistance should be sought if the blood glucose remains high despite two extra correctional insulin doses.

Correctional doses are guided by the insulin sensitivity factor (ISF) and a percentage of the TDD. It is important to note that these doses should be reviewed if the person's insulin requirements change (eg change in activity, weight, illness, medication, pregnancy).

Whilst people with type 1 diabetes can adjust their insulin doses, they require education and support from a multidisciplinary team including an endocrinologist, credentialled diabetes educator and dietitian to do so safely. This team will need to provide information and training in hypoglycaemia, hyperglycaemia and sick day action plans, adjustments to calculations and support throughout the person's life.

For further information, refer to the CHSA factsheet - *'Insulin in type 1 diabetes – Basal bolus'*.

Insulin pump therapy (Continuous Subcutaneous Insulin Infusion – CSII)

Insulin pump therapy refers to the use of an infusion system for the purpose of delivering a continuous supply of rapid acting insulin. The pump is programmed to deliver basal rates of insulin to match the person's daily needs thus mimicking the normal physiologic response more closely. To cover meals and correct hyperglycaemia, bolus insulin doses are activated by the person. The pump is attached via tubing to a small cannula which is inserted subcutaneously by the person with diabetes and/or their carer. The insertion site used commonly the abdomen but as the site must be changed every 3 days, could also be the leg, buttock or arm.[14]

Insulin pump therapy can be interrupted safely for short periods of time such as showering and physical activity. Usually 60 minutes of interruption can occur in a well person without causing problems. However, it is important to be aware that the person will become relatively insulin deficient within 1 hour and absolutely insulin deficient within 4 hours. Consequently there is a major risk of severe hyperglycaemia and diabetic ketoacidosis occurring within hours following cessation of pump.[15]

When a person is started on an insulin pump, they require intensive education and support by a multidisciplinary team including endocrinologist, credentialled diabetes educator and dietitian. This team has been trained and is experienced at managing insulin pump therapy. If the person lives in a rural or remote area arrangements will need to be made for a shared care arrangement with a CHSA Regional Insulin Pump Diabetes Service.

For further information on insulin pump therapy, refer to the CHSA Factsheet 'Insulin pump therapy in type 1 diabetes' and for information about insulin pump therapy whilst a person is in hospital, refer to CHSA Continuous Subcutaneous Insulin Infusion Clinical Protocol.

For further information, refer to the CHSA factsheet - *'Insulin pump therapy in type 1 diabetes'*.

Metformin

Metformin may be considered in individuals who have a high insulin requirement (eg overweight or obese subjects with total daily insulin dose at or above 2.0 IU/kg body weight), although the evidence demonstrates only a modest overall reduction in insulin requirement.

Metformin is not contra-indicated in type 1 diabetes however, is not recommended in metabolically unstable patients, have high alcohol consumption or who are at high risk of developing diabetic ketoacidosis.

Metformin is not approved by the Therapeutic Goods Administration and is an 'off-label' indication in Australia. Long term use of metformin has been associated with an increased risk of vitamin B-12 deficiency, and this should be monitored.[12]

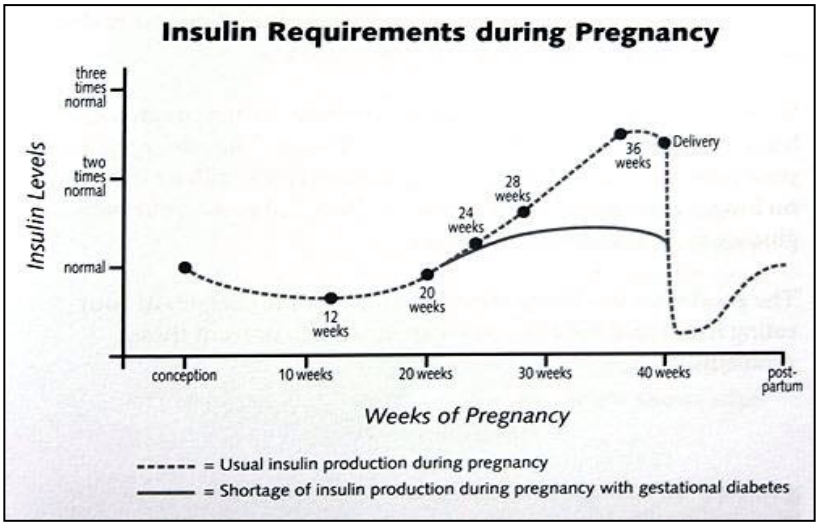
Medication management in gestational diabetes mellitus

If target blood glucose levels cannot be maintained by dietary and physical activity modifications, then diabetes medications and/or insulin therapy should be initiated in women with gestational diabetes mellitus (GDM).

Insulin requirements vary during gestation. Early in the first trimester, there is slight decline in insulin requirements. From the second trimester, insulin requirements increase and continue to do so into the third trimester. Figure 8 identifies the progressive rise in insulin requirements in pregnancy and the shortage of insulin production at approximately 24-28 weeks in woman with gestational diabetes compared to those women without diabetes who have adequate insulin production.

These changes in insulin requirements likely reflect pregnancy-related alterations in glucose homeostasis, decreased caloric intake in women with nausea and vomiting of pregnancy, efforts to improve glycaemic control, increased foetal demand for maternal glucose and increased maternal sensitivity to insulin in the fasting state.[13]

Figure 8: Insulin requirements in pregnancy

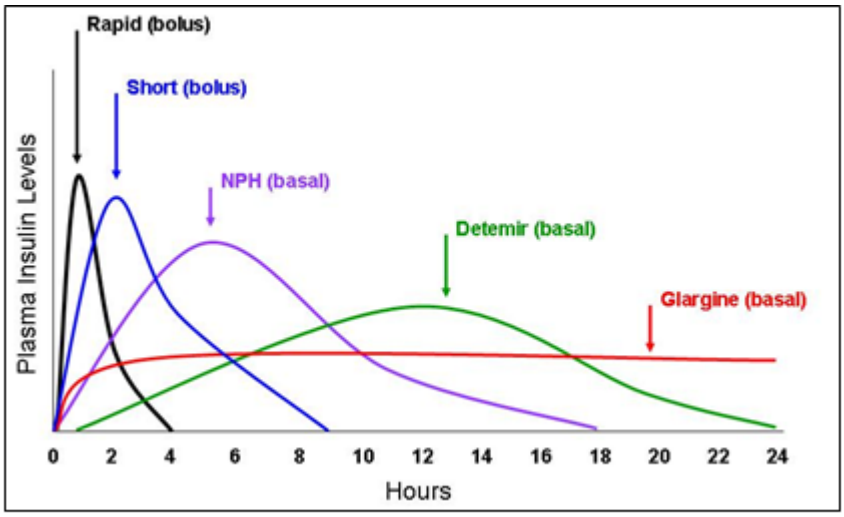


Based on evidence and expert opinion, the recommendations for insulin therapy are as follows:

> Choice of insulin therapy (Figure 9) should be discussed, ideally as part of pre-pregnancy (if there has been a past medical history of GDM) counselling.

- Rapid-acting insulin analogues (lispro (Humalog®) and aspart (NovoRapid®)) are safe to use in pregnancy and may be considered in individual patients where hypoglycaemia is problematic.
- Intermediate acting insulin (NPH (Protaphane®)) should remain the basal insulin of choice in pregnancy unless the clinical benefit of a basal insulin analogue has been demonstrated on an individual basis.
- There is no evidence available to support the use of either of the basal insulin analogues detemir (Levemir®) or glargine (Lantus®) in women who are pregnant or considering pregnancy. However, several case control studies suggest no increase in adverse outcomes with glargine (Lantus®).[13]
- The dose of insulin varies due to body weight, ethnic characteristics, degree of hyperglycaemia, and other demographic criteria. The SA Maternal and Neonatal Clinical Network recommend a starting dose of approximately 0.5 units per kilogram bodyweight per day and titration of insulin dose/s based on blood glucose monitoring results.[16]

Figure 9: Insulin Action Profiles



After delivery of the placenta, the insulin resistant state that characterises pregnancy rapidly dissipates and insulin requirements drop quickly. Whilst women with GDM are encouraged to maintain dietary recommendations and physical activity recommendations (as tolerated), routine blood glucose monitoring and injected insulin can be ceased.

Metformin

The Metformin in Gestation (MiG) trial showed that use of metformin gives comparable outcomes to insulin in the management of women with gestational diabetes mellitus and that their offspring had less severe neonatal hypoglycaemia. Although this follow up is promising, there is no long-term data available at this time.

The use of metformin in pregnancy is therefore not currently endorsed by regulatory authorities or professional bodies, including the Australian Diabetes in Pregnancy Society. However Metformin:

- Is used for the treatment of gestational diabetes in many centres around Australia and New Zealand.
- Could be considered for use in women who have failed non-drug treatments and who either refuse or are unable to take insulin. The mother should be educated about the

potential risks, benefits and areas of uncertainty so that an informed decision can be made.

- Should only be in consultation with a physician / endocrinologist with specialised knowledge of its use in pregnancy.
- Long acting (XR) metformin may be considered, particularly at night for those with fasting hyperglycaemia, and may be better tolerated.
- An initial dose of standard metformin 500 mg 1-3 times a day, depending on the blood glucose level profile.
- Where blood glucose control is not achieved with metformin, insulin therapy is added.[16]

For further information, refer to the CHSA factsheet - *'Starting insulin in gestational diabetes'*.

Principles for subcutaneous injection

People with diabetes may be prescribed insulin therapy or glucagon-like peptide (GLP-1) mimetic both of which must be injected subcutaneously. It is important to understand that inappropriate equipment and incorrect injection technique can affect medication absorption causing poor and varied response to medication.

For correct administration and documentation of subcutaneous insulin for diabetes management, refer to the *CHSA Subcutaneous Insulin Administration in Hospital and Aged Care and Subcutaneous Insulin Administration in the Community Setting* Protocols.

Patient education

All people with diabetes should have access to initial and yearly diabetes education that encompasses;

- Information about the insulin regimen.
- Choice and management of the insulin device used.
- Choice, care and self-examination of injection sites.
- Correct injection technique (including site rotation, injection angle and possible use of a skinfold).
- Injection complications and how to avoid them.
- Optimal needle length.
- Safe disposal of used sharps.[12, 13, 16]

All health professionals but particularly credentialled diabetes educators, Aboriginal health workers, practice nurses and general nursing staff can play an active role in regularly reviewing and documenting peoples injection technique knowledge including observation of technique.

Patient psychological support

Although many individuals have anxiety about injection therapy very few have true needle phobia. To reduce feelings of anxiety and stress for individuals it is recommended that;[17]

- Health professionals can explain the natural and progressive nature of type 2 diabetes, stating that insulin therapy, in time, is likely to be required. Health professionals should make it clear from the outset that insulin treatment is not a sign of failure.

> Health professionals need to avoid using terms that suggest injectable therapy is a sign of failure, a form of punishment or a threat.

Insulin titration – Credentialled Diabetes Educator legislative requirements

The CHSA Insulin Titration Service – Stabilisation of diabetes in the community setting Clinical protocol is supported by the Controlled Substances Act 1984, SA Health Directive: High Risk Medicines Management and SA Health Directive: Patients' own medications.

This protocol outlines responsibilities and actions required by specialist physicians, general practitioners, endocrinologist and credentialled diabetes educators in the management and titration of insulin in adults with type 1 diabetes, type 2 diabetes and in women with gestational diabetes. The management and titration of insulin in children and those patients using continuous subcutaneous insulin infusion (insulin pump) is not addressed.

The protocol includes the following approved documents for use:

> CHSA Authorisation to titrate insulin dose (CHSA Diabetes Service) form

> CHSA Diabetes Service Blood Glucose ad Insulin Titration Record form

> ADEA Checklist for Education of Initiation of Injectable Therapies

Prior to any titration of insulin, appropriate authorisation **MUST BE** completed and signed by the referring specialist physician, general practitioner or endocrinologist. The authorisation is only valid for the period of time indicated on the referral.

References

1. The Royal Australian College of General Practitioners, Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, and Pharmaceutical Society of Australia. 2018, *Australian Medicines Handbook*. Accessed online, Available from: https://amhonline.amh.net.au/.

2. Department of Health. 2018, *National Prescribing Service*. Accessed online, 2018 Available from: https://www.nps.org.au/.

3. Therapeutic Guidelines Limited. 2018, *Therapeutic Guidelines*. Accessed online, Available from: https://www.tg.org.au/.

4. Australian Commission on Safety and Quality in Health Care and NSW Therapeutic Advisory Group Inc, 2014, *National Quality Use of Medicines Indicators for Australian Hospitals*, ACSQHC, Sydney.

5. The Commonwealth of Australia, 2002, *The National Strategy for Quality Use of Medicines*, Canberra.

6. Australian Pharmaceutical Advisory Council, 2005, *Guiding principles to achieve continuity in medication management*, July, Commonwealth of Australia, Canberra.

7. Odegard, P S and Capoccia, K, 2007, Medication taking and diabetes: A systematic review of the literature, *The Diabetes Educator,* 33(6): p. 1014-1029.

8. Nathan, D, Buse, J B, Davidson, M B, Ferrannini, E, Holman, R R, Sherwin, R, and Zinman, B, 2009, Medical management of hyperglycaemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy, *Diabetes Care,* 32(1): p. 193-203.

9. Wright, A, Burden, A, Paisey, R, Cull, C, and Holman, R, 2002, Sulfonylurea inadequacy: Efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UK Prospective Diabetes Study (UKPCS 57), *Diabetes Care,* 25(2): p. 330-336.

10. Gunton, J, NW, C, Davis, T, Zoungas, S, and Colagiuri, S, 2014, A new blood glucose management algorithm for type 2 diabetes; Position statement of the Australian Diabetes Society, *Med J Aust* 201(11): p. 650-653.

11. Royal Australian College of General Practitioners, 2016, *General practice management of type 2 diabetes: 2016–18*, Royal Australian College of General Practitioners and Diabetes Australia,, East Melbourne, VIC.

12. Craig, M, Twigg, S, Donaghue, K, Cheung, N, Cameron, F, Conn, J, Jenkins, A, and Silink, M, 2011, *National evidence-based clinical care guidelines for type 1 diabetes in children, adolescents and adults* Australian Government Department of Health and Ageing, Canberra.

13. McCulloch, D, Nathan, D, and Mulder, J. 2018, *General principles of insulin therapy in diabetes mellitus*. Accessed online, Available from: https://www.uptodate.com/contents/general-principles-of-insulin-therapy-in-diabetes-mellitus.

14. Department of Health and Ageing. 2014, *SA Health Directive: High risk medicines management*. Accessed online, Available from: http://www.sahealth.sa.gov.au/wps/wcm/connect/2993a88045b1165b836bebac725693cd/Directive_High+Risk+Medicines+Management_Oct2014.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-2993a88045b1165b836bebac725693cd-lYyvS96.

15. Steering Committee Statewide Diabetes Council Network, 2010, *In-patient guidelines: Insulin infusion pump management*, July, Clinical Practice Improvement Centre.

16. Department of Health and Ageing. 2015, *Diabetes Mellitus and Gestational Diabetes Clinical Guideline*. Accessed online, Available from: http://www.sahealth.sa.gov.au/wps/wcm/connect/146238004ee2144cb404bdd150ce4f37/Diabetes+Mellitus+and+Gestational+Diabetes_July2015.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-146238004ee2144cb404bdd150ce4f37-lqLPOUO.

17. Australian Diabetes Educators Association, 2011, *ADEA clinical recommendations for subcutaneous injection technique for insulin and glucagon-like peptide 1*, August, Woden, ACT.