Module 6  
Drug Treatment for Hyperglycaemia

General principles (Figures 1 and 2)

- **HbA1c**<7.5%: Start metformin (now first line blood glucose lowering drug unless contraindicated) in addition to lifestyle modification and self-management.
- **HbA1c** >7.5-9%: consider early oral combination therapy (predominantly metformin-based) to attain and maintain target HbA1c (generally <7%).
- **HbA1c** >9%: consider basal insulin or addition of insulin to oral blood glucose lowering agents if HbA1c fails to improve within 3-6 months of optimised drug treatment, to reduce acute glucotoxicity, followed by fine tuning of treatment regimen.
- In obese patients, avoid drugs which may cause excessive weight gain, e.g. high dose sulphonylurea, insulin or glitazone.
- Early intensive glycaemic control is critical and reduces macrovascular as well as microvascular complications in the long term.
- Treatment individualised over time to maintain an optimal balance between the benefits and risks of an intensive glucose control strategy.

Blood glucose lowering drugs can be broadly divided into:

- Insulin sensitisers, e.g. metformin, thiazolidinediones
- Insulin secretagogues, e.g. sulphonylureas, glinides, incretin mimetics and enhancers (glucose-dependent insulin secretagogues)
- Exogenous insulin
- Drugs that modulate food absorption, e.g. α-glucosidase inhibitors
- Drugs that lower glucose reabsorption by the kidneys, e.g. sodium-glucose cotransporter 2 inhibitors

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*Haemoglobin A1c (HbA1c) is a minor component of haemoglobin to which glucose is bound. HbA1c is also referred to as glycated haemoglobin. HbA1c levels depend on the blood glucose concentration. That is, the higher the blood glucose concentration, the higher the level of HbA1c. Levels of HbA1c are not influenced by daily fluctuations in blood glucose concentration but reflect the average glucose levels in the past 8 to 12 weeks. HbA1c is a useful indicator of glycaemic control and reflects the summation of fasting and post-prandial blood glucose. It is a gold standard used to monitor the effects of diet, exercise, and drug therapy in diabetic patients. In the absence of confounding factors (e.g. anaemia and haemoglobinopathy), 6% of HbA1c correlates to mean plasma glucose of 7 mmol/L while 12% of HbA1c correlates to mean plasma glucose of 16.5 mmol/L.*
Choice of blood glucose lowering drugs should be based on

- Knowledge of the underlying pathophysiology
- Degree of hyperglycaemia: metformin and sulphonylureas are more effective in lowering blood glucose in general
- Risk of hypoglycaemia: high dose sulphonylureas should be avoided in patients at risk of hypoglycaemia, e.g. elderly, alcoholics, patients with renal or liver disease
- Side effect profile: e.g. metformin is contraindicated in patients at risk of lactic acidosis due to reduced clearance (e.g. moderate renal impairment with eGFR <40 ml/min/1.73m² or liver failure) or increased production of lactic acid due to hypoxia (e.g. severe heart failure or lung disease)
- Most of these drug classes have similar efficacy with greater reduction in patients with high HbA1c. In general, combination drug therapy within the same drug class is not preferred.

Dosage, efficacy and side effects of commonly used oral blood glucose lowering drugs¹ (Table 1)

**Metformin**
Metformin reduces blood glucose mainly by reducing hepatic glucose production and promoting peripheral glucose uptake. Available formulations include 500mg, 850mg, and 1000mg tablets; 500mg, 750mg and 1000mg (extended release form) and 500mg per 5ml (liquid form). The recommended starting dose is 500mg (250mg twice daily) or 850mg once daily on a full stomach, to reduce gastrointestinal side effects². The dose should be increased gradually to the full maximum effective dose of 1500-2000mg per day (in 2 to 3 divided doses)³.
Efficacy: unless contraindicated, metformin is now considered the first line therapy along with dietary and exercise therapy. It reduces HbA1c by 1-2%. In the United Kingdom Prospective Diabetes Study (UKPDS), metformin and sulphonylurea therapy were the drugs used in the intensive treatment arm and confirmed to reduce all diabetes-related endpoint (nonfatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous haemorrhage, retinopathy, blindness, or cataract) by 21%. In obese subjects, metformin-based monotherapy reduced cardiovascular events compared to patients treated with lifestyle modification alone. Metformin therapy is associated with some weight loss or no weight gain which may confer additional benefits in overweight/obese subjects.

Side effects: The most common side effect is gastrointestinal disturbances ranging from 5% to 20%, including nausea, abdominal discomfort and diarrhoea. Metallic taste and decreased vitamin B12 absorption have also been reported. The possibility of vitamin B12 deficiency should be borne in mind for patients receiving high dose metformin therapy (e.g. >1.5 gram daily) on a prolonged period. Lactic acidosis is very rare (0.4 cases /10,000 treatment years) in the absence of risk factors or contraindications.

Contraindications: renal insufficiency (e.g. stop when eGFR <30 ml/min/1.73m² or serum creatinine >150 micromol/L, and prescribed with caution or at reduced dose when eGFR <45 ml/min/1.73 m² or serum creatinine >130 micromol/L), congestive heart failure, previous history of lactic acidosis or metabolic acidosis, impaired hepatic function, alcoholism, states with reduced peripheral circulation (e.g. dehydration) or severe infections. It should be used with care in the elderly who often have reduced organ function. Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore for patients with normal renal function, metformin should be discontinued at the time of the investigation and withheld for the subsequent 48 hours. For those with abnormal renal function, metformin should be discontinued 48 hours prior to and withheld for 48 hours subsequent to the investigation. Re-start metformin only after renal function has been re-evaluated and found to be unchanged.
**Sulphonylureas**

These drugs block potassium channels in the beta cells and enhance insulin secretion. It can be used in either monotherapy or combination therapy with other oral drugs. Once daily dosage is appropriate for most formulations whilst glibenclamide and glipizide can be given twice daily if needed. They are effective within 24 hours of initiation and reach a steady state after 1-2 weeks of therapy\(^1\). Due to the long duration of action of its metabolite, high dose glibenclamide should be avoided.

**Efficacy:** A decrease of 2% in HbA1c is expected\(^{17,18}\). Failure of monotherapy with sulphonylurea occurs at a rate of 5-7% annually. After 10 years of treatment, most patients require additional treatment to achieve glycaemic control\(^{19}\). All agents in this class have similar efficacy at equivalent doses\(^{20}\).

**Side effects:** Hypoglycaemia is the most common side effect. There is no evidence that this class of drugs worsens cardiac ischemia. Sulphonylurea and metformin were the two oral blood glucose lowering drugs used in the intensive treatment arm of the UKPDS. After seven years of treatment, there was 0.9% difference in HbA1c between the intensive (7%) and conventional treatment group (8%). While intensive treatment was associated with 25% reduction in microvascular complications (p = 0.001), the 16% risk reduction for cardiovascular events fell short of significance (p = 0.052). However, 10 years after completion of the UKPDS, the benefits of attaining glycaemic control became evident for cardiovascular diseases with a relative risk reduction of 15% (p = 0.014)\(^{21}\). Mild weight gain is also commonly observed.

**Contraindications:** The drug should be used with caution in elderly patients (>80 years) and patients with liver or renal insufficiency.
**Thiazolidinediones**

This class of drug promotes differentiation of preadipocytes to adipocytes, reduces circulating fatty acids, shifts ectopic fat to subcutaneous fat, enhances peripheral glucose uptake and reduces insulin resistance. Pioglitazone is available in 15mg, 30mg and 45mg tablets. It could be used as monotherapy or in combination with other blood glucose lowering drugs. Rosiglitazone, with dosage forms of 2mg, 4mg and 8mg, has had marketing authorisations suspended by the European Medicines Agency (EMA)\(^\text{22}\) and further restriction of use by the Food and Drug Administration (FDA)\(^\text{23}\) in late September 2010, in view of its increased risk of cardiovascular events.

**Efficacy:** Pioglitazone 30mg-45mg daily reduces HbA1c by 1-1.5% after 6 months of treatment\(^\text{24,25}\) with maximum effects occurring 3-4 months after treatment initiation\(^\text{26}\). It has better durability of glycaemic control\(^\text{27}\) but lower efficacy in reducing blood glucose compared with sulphonylureas or metformin.

**Adverse effects:** Fluid retention causing peripheral oedema, congestive heart failure and weight gain are common adverse effects of thiazolidinediones. Small increase risk of distal long bone fracture particularly in women is documented. Long term studies have confirmed the increased risk of heart failure, and in the case of rosiglitazone, increased cardiovascular risk of myocardial infarction and stroke\(^\text{28,29}\).

**Contraindications:** History of congestive heart failure, history of bladder cancer or in patients with uninvestigated visible blood in the urine\(^\text{30,31}\), established or high risk of osteoporosis, and caution to be exercised if used together with insulin.
Dipeptidyl peptidase 4 – inhibitors (DPP4-I)
This class of drugs inhibits the breakdown of glucagon-like peptide 1 (GLP-1) which is an incretin hormone produced by the L cells of the distal small intestine after food intake and gastric inhibitory polypeptide (GIP), produced by the K cells at the proximal small intestine. These gut hormones potentiate glucose-stimulated insulin secretion during meal time and also inhibit glucagon secretion, retard gastric emptying, and reduce appetite. By inhibiting the degradation of incretins, DPP4-I have weight neutral effect and low risk of hypoglycaemia. Examples of currently available DPP4-I in Hong Kong include sitagliptin, vildagliptin, and saxagliptin.

Efficacy: This class of oral medications lowers HbA1c by 0.7-1.4%, depending on the baseline DM control. The drugs can be used as monotherapy or in combination with other oral blood glucose lowering drugs 32,33.

Adverse effects: Side-effects appear minor, though clinical experience is limited with this new class of medications. The risk of hypoglycaemia is low as the drug effect is mediated through glucose-dependent insulin secretion. Headache and nasopharyngitis occur in 1-2% patients.

Incretin mimetics (GLP-1 analogues / agonist)
These long acting GLP-1 analogues bind to the human GLP-1 receptors and result in glucose-dependent stimulation of insulin secretion and glucose-dependent suppression of glucagon secretion. Used alone or in combination with 1 or 2 blood glucose lowering drugs lead to substantial improvement of glycaemic control in certain individuals without significant increase in risk of hypoglycaemia. GLP-1 analogues also have central nervous system effects to reduce appetite and increase the sense of satiety resulting in decreased food intake and weight loss. The major side effects are gastrointestinal, with nausea and vomiting which resolve or improve with time in most patients.
**Insulin**
Insulin therapy should be added if glycaemic target is not attained with combination of oral blood glucose lowering drugs. When once daily supplementary insulin is added, metformin can be continued with reduction in sulphonylurea dosage. Alternatively, if basal insulin or twice daily insulin regimen is initiated because of significant symptoms upon diagnosis, or unsatisfactory control despite optimised oral combination therapy, discontinuation of sulphonylurea is preferred while metformin is often continued for its complementary action in reducing insulin resistance\(^{34,35}\).
(Refer to appendix of this Module for supplementary information on the use of insulin)

**Alpha-glucosidase inhibitors**
This class of drugs inhibits the enzyme, α-glucosidase, located at the intestinal brush border and thus slows the rate of intestinal glucose absorption with reduced excursion of post-prandial blood glucose level. They, however, have only modest effect on lowering fasting glucose. The most common side effects are gastrointestinal e.g. flatulence, soft stools, diarrhoea, abdominal distension and pain, and they are not to be used in patients with cirrhosis, severe renal insufficiency, history of malabsorption, inflammatory bowel disease or intestinal obstruction.

**Sodium-glucose cotransporter 2 inhibitors (SGLT2-I)**
This class of drugs inhibit sodium glucose cotransporter 2 (SGLT2) in the proximal renal tubules, thus lower glucose reabsorption by the kidneys and increase glucosuria. These drugs reduce hyperglycaemia without inducing hypoglycaemia, promote weight loss (due to caloric loss) and exert a modest diuretic effect with blood pressure reduction\(^{36}\). Examples of currently available SGLT2-I in Hong Kong include dapagliflozin, canagliflozin, and empagliflozin.

**Efficacy:** The efficacy is dependent on renal function. This class of oral medications has been reported to lower HbA1c by 0.7-1.0%\(^{37}\). Findings for empagliflozin suggest that SGLT2 inhibitors may protect against cardiovascular outcomes and death, and thus may provide benefit in patients with type 2 diabetes at high risk of cardiovascular events\(^{38}\).

**Adverse effects:** The risk of hypoglycaemia is low. Genitourinary infections, polyuria and volume depletion, increased LDL-C level may occur. Cases of diabetic ketoacidosis (may occur with no hyperglycaemia) and acute kidney injury have been reported\(^{39-41}\).
Figure 1. Treatment options for type 2 diabetes

Remarks:
- Lifestyle modification should be included in all stages of treatment
- Oral Combination = metformin + one or more of sulphonylurea, DPP4 inhibitor, thiazolidinedione, α-glucosidase inhibitor, SGLT2 inhibitor

(modified from IDF-WPR guideline 2005, ADA/EASD 2012, AACE2009)
Figure 2. Algorithms of drug treatment for control of hyperglycaemia

HbA1c ≥ 7% after lifestyle modification

Step 1: monotherapy

Use Metformin as monotherapy

Consider sulphonylurea if:
- Metformin not tolerated or contraindicated
- Rapid response desired for hyperglycaemic symptoms

HbA1c ≥ 7%

Consider alternatives instead of adding sulphonylurea if:
- significant risk of hypoglycaemia
- intolerant of or contraindicated to sulphonylurea

Step 2: dual therapy

Sulphonylurea
Where blood glucose control remains inadequate on metformin

TZD (pioglitazone)
may be preferable if:
- patient has marked insulin insensitivity, or
- poor response, or intolerant to other alternatives, or
- other alternatives are contraindicated

DPP4 inhibitor
may be preferable if:
- further weight gain would cause or exacerbate significant problems, or
- poor response, or intolerance to other alternatives, or
- other alternatives are contraindicated

SGLT2 inhibitor
may be preferable if:
- weight loss and blood pressure lowering effects are desirable, or
- poor response, or intolerance to other alternatives, or
- other alternatives are contraindicated

HbA1c ≥ 7.5% despite adjustment / addition of blood glucose lowering drugs

Step 3: triple therapy or insulin-based treatment

Consider to use insulin
Monitor use and response and adjust dose if necessary

Add TZD (pioglitazone), DPP4 inhibitor or SGLT2 inhibitor
when insulin is unacceptable or inappropriate

Add GLP-1 agonist
if BMI ≥ 35kg/m² and weight loss would be benefit co-morbidities

(Modified from UK NICE 2015 42)
Table 1. Mode of actions, benefits and side effects of blood glucose lowering drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Reduction in glycate...</th>
<th>Main Mode of action</th>
<th>Benefits</th>
<th>Side effects and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.5</td>
<td>Lower production of hepatic glucose</td>
<td>No weight gain; cheap</td>
<td>Gastrointestinal complaints; lactic acidosis (very rare)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.5</td>
<td>Stimulate insulin secretion</td>
<td>Cheap</td>
<td>Hypoglycaemia, sometimes severe and of long duration; weight gain</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.5-1.5</td>
<td>Improve insulin sensitivity</td>
<td>Improve lipid profile and may reduce risk of cardiovascular disease</td>
<td>Fluid retention, which can cause heart failure (rare), weight gain, bone fracture, expensive</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>0.5-0.8</td>
<td>Retard intestinal absorption of glucose</td>
<td>No weight gain Low risk of hypoglycaemia</td>
<td>Gastrointestinal side effects; multiple daily dosing required; expensive</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>1-1.5</td>
<td>Stimulate insulin secretion</td>
<td>Short acting, less risk of hypoglycaemia</td>
<td>Need to be taken at meal time; expensive</td>
</tr>
<tr>
<td>Dipeptidyl peptidase 4 inhibitors</td>
<td>0.5-1.0</td>
<td>Stimulate insulin secretion Suppress glucagon production</td>
<td>Low risk of hypoglycaemia No weight gain</td>
<td>Experience limited; expensive</td>
</tr>
<tr>
<td>GLP-1 analogues</td>
<td>0.5-1.0</td>
<td>Stimulate insulin secretion Suppress glucagon production</td>
<td>Low risk of hypoglycaemia Promote weight loss</td>
<td>Experience limited; needs to be injected</td>
</tr>
<tr>
<td>Sodium-glucose cotransporter 2 inhibitors</td>
<td>0.7-1.0</td>
<td>Lower glucose reabsorption by the kidneys</td>
<td>Low risk of hypoglycaemia Promote weight loss Lower blood pressure</td>
<td>Genitourinary infections; diabetic ketoacidosis (rare) Experience limited; expensive</td>
</tr>
<tr>
<td>Subcutaneous insulin</td>
<td>&gt;2</td>
<td>Stimulate peripheral glucose uptake and inhibits hepatic glucose output</td>
<td>Reduces severe hyperglycaemia; cheap; much experience</td>
<td>Weight gain; hypoglycaemia; needs to be injected; blood glucose must be monitored</td>
</tr>
</tbody>
</table>
Reference:


Appendix of Module 6 - Supplementary information on the use of insulin

When do patients with type 2 diabetes become candidates for insulin therapy?
The most recent position statement from the American and the European Association for the Study of Diabetes recognises that insulin is the most effective diabetes medication for lowering hyperglycaemia 1,2.

Insulin therapy should be considered if a patient presents with significant symptoms and/or markedly raised blood glucose levels, especially in the presence of catabolic features, at the beginning or during the course of treatment. Insulin may also be added when a combination of oral agents (e.g. metformin and sulphonylurea) fails to achieve the HbA1c target range appropriate for the patient (e.g. HbA1c <7% in general, but control at 7-8 % for the elderly especially those with established complications and history of severe hypoglycaemia).

Other indications for insulin therapy in patients with type 2 diabetes include pregnancy, acute illness necessitating surgery, and admission to an intensive unit. Insulin is, however, not a substitute for healthy eating activity and weight control in type 2 diabetes. Inappropriate use of insulin produces weight gain and continuing poor control5.

Recent landmark clinical trials and current guidelines2-6 suggest that the target range (HbA1c) for glycaemic control and the decision to initiate insulin should be individualised with due considerations of the risk and benefits of insulin therapy. Important factors for consideration include clinical characteristics of the patient (notably degree of hyperglycaemia, age, life expectancy, presence of macrovascular complications and comorbidities, and risk of hypoglycaemia), as well as economic and psychosocial circumstances (e.g. self-care ability, family and social support, and patient’s needs and belief). Comprehensive education and patient / family’s understanding regarding glucose monitoring, insulin injection technique, insulin storage, recognition / treatment of hypoglycaemia, and “sick day” rules are also imperative before commencing insulin.

Most patients are reluctant to start insulin injection, but if considering the most appropriate treatment modality, the reticence can usually be overcome with detailed discussion, encouragement and patient empowerment.
Initiation options depend on the pattern of the patient’s blood glucose levels\textsuperscript{2,8}:

**High fasting glucose**

**Basal Insulin (usually administered at bedtime)**
1) Intermediate-acting NPH insulin OR
2) Long-acting insulin analogue (with less risk of hypoglycaemia)

Basal insulin added to metformin, and also sulphonylurea if previously used in oral combination

Initial dose usually 10 units per day (0.1-0.2 units/kg per day) and titrated the dose around every 1-2 weeks\textsuperscript{9}

Consider long-acting insulin analogue if
- Recurrent hypoglycaemia with NPH insulin especially in those with established cardiorenal complications, OR
- Patients would otherwise need twice daily NPH insulin injection and metformin, OR
- Patients cannot use the device to inject NPH insulin

- HbA1c above treatment target (e.g. >8%) and significant postprandial excursion (e.g. >10 mmol/L)
- Need to consider adding pre-meal short-acting regular human insulin or rapid-acting insulin analogue (basal bolus regimen) – refer to specialist
- Stop sulphonylurea upon introduction of basal bolus insulin regimen

**Predominantly high daytime or postprandial blood glucose**

**Intermediate-acting insulin** (usually given before breakfast)

NPH insulin added to metformin, and also sulphonylurea if previously used in oral combination

Initial dose usually 10 units per day (0.1-0.2 units/kg per day)

- HbA1c above treatment target (e.g. >8%) and fasting glucose remains significantly raised (e.g. > 7 mmol/L)
- Need to consider adding pre-dinner intermediate-acting insulin (twice daily regime) or switch to twice daily pre-mixed short- and intermediate-acting insulin – refer to specialist
- Stop sulphonylurea upon introduction of twice daily insulin regimen
Insulin Titration
- According to latest average of 3 or more haemostix taken at specific times, be careful of hypoglycaemic value
- Titration of insulin with respective haemostix monitoring
- If total daily dose of intermediate-acting insulin exceeds 0.5 unit/kg/day, consider the need to split into twice daily regime or add short- or rapid-acting pre-meal insulin

<table>
<thead>
<tr>
<th>Insulin Regimen</th>
<th>Haemostix monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedtime NPH or long acting</td>
<td>Fasting</td>
</tr>
<tr>
<td>Morning NPH</td>
<td>Post breakfast; pre and post lunch; pre dinner</td>
</tr>
<tr>
<td>Pre dinner NPH</td>
<td>Fasting; post dinner; bedtime</td>
</tr>
<tr>
<td>Pre meal short- or rapid-acting</td>
<td>Post respective meal; pre next meal</td>
</tr>
</tbody>
</table>

**Titration scale**

<table>
<thead>
<tr>
<th>Haemostix (mmol/L)</th>
<th>Insulin dosage (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4.0</td>
<td>+2</td>
</tr>
<tr>
<td>4.0-7.0</td>
<td>+0</td>
</tr>
<tr>
<td>7.1-10.0</td>
<td>+2</td>
</tr>
<tr>
<td>&gt;10.0</td>
<td>+4</td>
</tr>
</tbody>
</table>

Management of oral hypoglycaemic agents upon initiation of insulin

1. Continue with metformin
2. Avoid long acting sulphonylurea (e.g. daonil) and consider changing to a shorter acting sulphonylurea (e.g. gliclazide)
3. Gradually reduce the dose of sulphonylurea especially if high risk of hypoglycaemia
4. Consider stopping sulphonylurea if hypoglycaemia occurs or with introduction of multiple dose insulin regimen

Registered insulin products in Hong Kong can be assessed in Drug Office, Department of Health website:
Self-monitoring of blood glucose (SMBG) serves as an important adjunct to HbA1c because it can identify hypoglycaemia, distinguish between fasting / pre-meal and postprandial hyperglycaemia, and reveal glycaemic excursions. It also helps in adjusting medications (particularly pre-meal insulin doses), diet, and physical activity.

The optimal frequency of SMBG in type 2 DM on insulin is not clearly defined, although it has been shown that insulin-requiring type 2 DM patients who monitor at least once a day have significantly lower HbA1c values than those monitoring less than once a day and each additional monitoring per day is associated with further A1c reduction\(^\text{10}\). It is suggested in Canada that the maximum weekly frequency of SMBG for most adults with insulin-treated type 2 diabetes be up to 14 tests\(^\text{11}\).

For details of SMBG, refer to Module 5 P.2-3.

### Glycaemic targets
- Fasting and pre-meal: 4-7 mmol/L
- Post meal: 5-10 mmol/L
- HbA1c < 7%

### Insulin Delivery \(^\text{12}\)

#### Sites for insulin injections
- Abdominal wall: generally fastest and most uniform rate of absorption
- Legs: slowest absorption (unless exercising), acceptable site
- Arms: not recommended

**Insulin injection devices** for subcutaneous administration include:

1. **Insulin syringe**
   - 100 units, 50 units syringe
   - Standard needle: 8mm, 30 / 31 gauge
   - Short needle: 6mm 31 gauge; 5 mm 31 gauge
   - Insulin syringes are recommended for single use.
2. **Pen devices**
   - Novopen 4 (Novo Nordisk insulins)
   - Humapen (Lilly insulin)
   - Solostar (Sanofi-Aventis long-acting insulin analogue)

3. **Pen needle**
   - 8 or 6 mm, 30 and 31 gauge
   - Short needles: 5 mm 31 gauge, 4 mm 32 gauge (latest available)
   - The short (4 to 5mm) needles reduce pain and anxiety to patients and give the best outcome when injected straight into the skin at 90 degrees, without the need to pinch up skin as in the case of longer needles.

**Advantages of insulin pens:**
1. Easy to handle: large dose dial window and numbers make it easier for those with visual and physical disabilities (e.g. hand tremor)
2. Convenient: pen devices can be carried easily for travel
3. Multiple daily injection schedules become easier and people can be more flexible in their self management.
4. Cost-saving: the price of insulin pen needle is cheaper as compared with conventional insulin syringes

**Disadvantages:**
1. If the patient forgets to remove needles after use, air bubbles may get into the insulin cartridge. This may cause insulin leakage or crystal formation
2. There are more preparatory steps, and therefore the devices may not be suitable for elderly especially for those with cognitive impairment

**Subcutaneous Insulin Injection techniques:**
- Pinch up the skin fold
- Inject slowly into the subcutaneous tissue, maintain “pinch-up” throughout injection
- Inject at 45 degrees for thinner subcutaneous tissue, and 90 degrees for thicker subcutaneous tissue
- (Note: With the short 4 to 5mm needles, there is no need to pinch up skin as in the case for longer needles and injection can be done straight at 90 degrees)
- Advise the patient to press onto the injection site for ~5 seconds and avoid rubbing the injection site after withdrawing the needle

**Sharps Disposal**
Education is needed to teach patients to dispose the sharps in an approved sharps disposal container.
Adverse effects of insulin therapy:

Hypoglycaemia
Insulin can cause symptomatic hypoglycaemia. Patients and their families need to be aware of the risk and be able to manage hypoglycaemia. Hypoglycaemia may arise due to excessive insulin or sulphonylurea, deficient carbohydrate intake or unaccustomed exercise. The cause needs to be identified and the episode dealt with by reinforcing education, counselling the patient and perhaps modifying treatment.

Initial management for hypoglycaemia should be by easily absorbable oral glucose or sucrose if the patient is conscious, generally amounting to 10-15 gram glucose (2-3 sugar cubes, 1/2 box fruit juice or 1/3 can of soft drink), followed by intake of additional carbohydrates (e.g. 2-3 pieces of biscuits, or 1 slice of bread) to prevent recurrence of hypoglycaemia. If the patient is unconscious, emergency call for medical assistance is required. Carers of patients on insulin and health care professionals should be familiar with the identification of hypoglycaemia and its treatment including subcutaneous glucagon administration. Glucagon 1mg should be given subcutaneously or intramuscularly. If glucagon fails to restore consciousness and a doctor is available, intravenous 50% glucose 20-30 ml can be administered. It is important to follow resuscitation with ongoing monitoring and carbohydrate intake.

Weight gain
Weight gain is another common adverse effect of insulin therapy. Improved glycaemic control decreases glycosuria, thereby decreasing the loss of calories through urine, also the direct lipogenic effects on adipose tissue contribute to weight gain, which can lead to increase in insulin resistance and therefore the need to step up insulin dosage.
Lipodystrophy
Repeated injection into the same site can cause pitting or loss of the subcutaneous adipose tissue. This is possibly due to immune complex-mediated inflammatory reaction to insulin or its excipients. Insulin absorption at the sites of lipodystrophy may be erratic and unreliable. It is best prevented by routine rotation of insulin injection sites.

Lipohypertrophy
This is a fatty, tumorous thickening of the subcutaneous tissue at the site of injection occurring because the patient injects into the same site day after day, and is probably a result from the local trophic action of insulin. Again, it can be obviated by regular rotation of insulin injection site, and if developed, usually will disappear over months if injections in the area are avoided.

Endocrinologist Referral
- Patients with contraindication(s) in initiating insulin
- HbA1c not to target but insulin cannot be stepped up due to hypoglycaemia
- Widely fluctuating haemostix pattern/glucose profile likely requiring multiple insulin injections
- Complex insulin regimen not manageable in primary care setting
- Total daily dose of insulin >1 unit/kg (suggestive of significant insulin resistance)
References:


