Diabetes Mellitus – Dr Amanda Lim

How do we diagnose diabetes mellitus? 00:33

- 1 of the following if symptomatic (polyuria, polydipsia), 2 of the following if asymptomatic:
  - Random glucose ≥ 11.1 mmol/L – caution about factors such as sepsis, steroids etc
  - Fasting glucose ≥ 7.0 mmol/L
  - OGTT ≥ 11.1 mmol/L
- Screening with Hba1c in patient with DM risk factors or ≥ 40yo (As per MOH guidelines) https://www.moh.gov.sg/docs/librariesprovider5/licensing-terms-and-conditions/moh-cir-no-08_2019_6mar19_screening.pdf (page 7)
  - 6.0% or below: No further testing
  - 6.1-6.9%: FPG or OGTT
  - 7.0% or above: Diabetes

  Of note ADA uses ≥ 6.5% as diagnostic of DM
- Caveats for Hba1c: Haemoglobinopathies (thalassemia), iron deficiency anemia, blood loss, CKD, chronic liver disease
- Pre-Diabetes
  - Impaired fasting glucose:
    - WHO: 6.1 mmol/L to 6.9 mmol/L
    - ADA: 5.6 mmol/L to 6.9 mmol/L
  - Impaired glucose tolerance: 7.8-11.0 mmol/L
  - Hba1c: 5.7-6.4% (ADA)

Management of Pre-Diabetes? 7:35

- Significance: Increased risk for progression to DM and occurrence of cardiovascular events
- Lifestyle modification: Dietary modification, physical activity
- Consideration of metformin in patients with risk factors – e.g. severely overweight, metabolic syndrome

When do we evaluate for T1 diabetes? 8:44

- T1DM - due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency
- Considerable overlap between T1 and T2 DM in terms of clinical presentation: E.g. younger patients with T2DM, T2DM presenting with DKA, T1DM being more overweight
- Sometimes, only time will clearly reveal whether a patient is T1 or T2
- When to suspect T1DM
  - Evidence of autoimmunity – Vitiligo, thyroid autoimmune disease
  - Recurrent DKAs
- Tests for T1DM:
  - Antibodies: Anti GAD, Anti-islet cells; lower antibody prevalence in local population compared to western population (hence ab negativity does not exclude T1DM)
  - C-Peptide: Ideally sent off in a 'well state'; glucotoxicity can affect C peptide levels

Special Subtypes of DM? 12:25

- Endocrine referral should be considered when there are atypical features of diabetes: E.g. young age, recurrent DKA, difficult to control DM
- Maturity Onset Diabetes of the Young (MODY)
  - Onset of hyperglycemia at an early age
  - Impaired insulin secretion with minimal or no defects in insulin action
  - Pattern of inheritance: Autosomal dominant
  - Suspect if:
    - Diabetes without typical features of type 1 or type 2 diabetes
    - Negative diabetes-associated autoantibodies
    - Non-obese
    - Lacking other metabolic features
    - Strong family history of diabetes (AD pattern, young onset)
- Latent Autoimmune Diabetes in Adults (LADA)
  - A subset of T1DM
  - Autoimmune of beta cell function is gradual, hence often diagnosed with T2DM at first – gradually become progressively independent of DM
  - Clinical clues – Seemingly T2DMs presenting with DKA, progressively becoming insulin requiring, strong autoimmune features
- Mitochondrial diabetes
  - Maternal inheritance
  - Suspect if abnormal neurological features, lactic acidosis (avoid metformin)
  - MELAS, MIDD

Treatment initiation of T2DM? 20:33

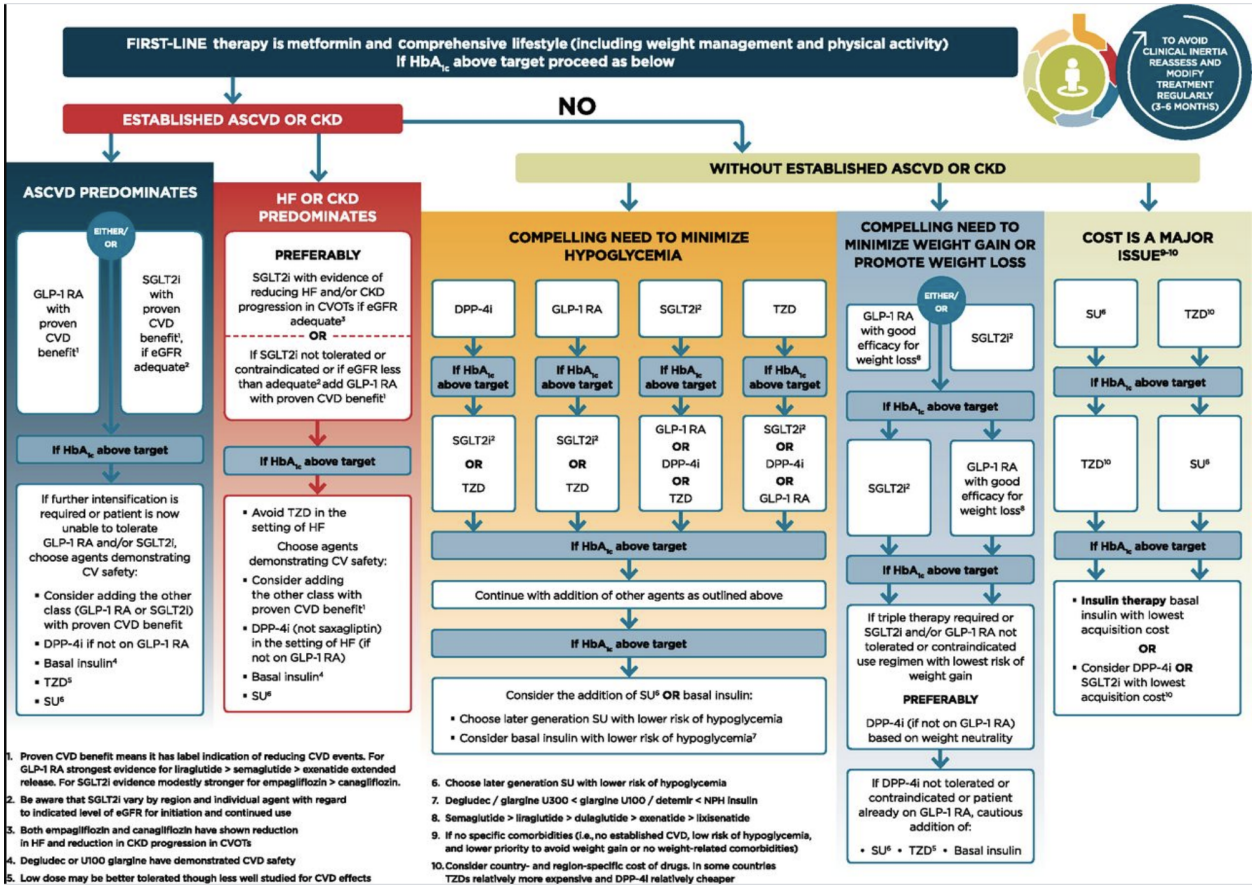
- Non-pharmacological measures: Education, lifestyle modification
  - Diet:
    - Has to be individualised specifically to the patient
    - Can consider meal replacements (optifast, glucerna)
    - Reduce portion size, avoid simple carbohydrates (sugary drinks, adding sugar to drinks), avoid processed food
  - Weight loss: At least 5%, but the more the better
  - Exercise:
    - Start slow, achievable goals
    - Other benefits such as cardiovascular effect, mood elevation, general fitness etc
- OGLDs (Oral Glucose Lowering Drugs; move away from terminology of 'OHGA' because not all oral diabetic medications cause hypoglycemia)
  - Metformin generally first-line
  - Factors determining choice of second-line agents
    - Disease considerations: Degree of hyperglycemia, presence of symptoms, duration of DM and beta cell reserve, comorbidities

§ Pharmacological considerations: Glucose lowering effect, other benefits (e.g. cardio/renal protection), side effect profile, risk of hypoglycemia, effect on weight

§ Practical considerations: Cost, preference, availability

- Introduction of Insulin
  - Indications to consider early insulin initation
    - § Severe hyperglycemia (especially if presents with crisis)
    - § Severe symptoms of polyuria, polydipsia
    - § Hba1c > 10% (and BGM > 15-16mmol/L) - May be difficult achieve glycemic control with oral agents only
  - After glucose toxicity resolves, simplifying or changing to oral agents may be possible
- Overview of DM management – ADA algorithm 2020

https://care.diabetesjournals.org/content/diacare/42/Supplement_1/S90/F1.large.jpg



  - First line generally metformin
  - Second line
    - § Heavily takes into account comorbidities (cardiac/renal) – in favour of SGLT2i and GLP-1 RA in view of recent emerging evidence
    - § If no comorbidites, look at factors like hypoglycemia risk, weight, degree of hyperglycemia, cost etc

How should we go about initiating insulin for T2DM? 30:57

- Initiating basal insulin
  - Usually used as an **add on** to OGLD regimen
  - Start at 10u/day or 0.1-0.2u/kg BW
  - Increments: 2 units every 3-5 days based on titration with fasting BG target or until 0.5u/kg BW; **if patient has reach basal insulin dose of 0.5u/kg BW and is still not reaching targets, to consider prandial insulin**
  - Options: Intermediate acting (NPH), long acting (glargine, detemir)
    - Glargine has the advantage of once a day dosing
    - While detemir is long acting, it may not last the full 24 hours
    - NPH cheapest
- If glucose excursions remain high despite max doses of sulphonylureas, can consider prandial cover with insulin up front
- Can afford more rapid titrations inpatient compared to outpatient because of benefit of closer monitoring
- While pre-mixed is more convenient and affords fewer injections, but it is less flexible and less adjustable compared to a basal bolus, especially in patients with variable meal patterns
- Different types of insulin
  - Rapid acting: Lispro, aspart, glulisine; generally favoured because of increased flexibility (can be administered after meals vs regular insulin which has to be administered 30 min before meals)
  - Short acting: Regular insulin (actrapid)
  - Intermediate: NPH
  - Long: Glargine, detemir
- Adjusting insulin regimen based on SMBG (OUPATIENT)
  - Glycemic targets based on – risk of hypoglycemia, duration of diabetes, life expectancy, comorbidities
    - Generally aim Hba1c < 7%
    - Tighter targets (<6.5 or tighter, without hypoglycemia) in younger patients with long life expectancy with little comorbidities, especially if planning of pregnancy/pregnant
    - More relaxed targets (~<7.5-8%) for older patients with multiple comorbidites with established ASCVD shorter and shorter life expectancy; expected benefit likely lower and risks of hypoglycemia higher
  - Targets
    - Fasting: 4-8mmol/L; if prone to hypoglycemia then can aim looser at 6-8 mmol/L with BASAL INSULIN
    - Target pre-lunch, dinner and bedtime insulin with prandial insulin, aiming for <8-10
    - Avoid hypoglycemias

Renal impairment and diabetes? 45:23

- OGLDs

Table 5. Properties of oral glucose-lowering agents

	Biguanides	Sulfonylureas	SGLT-2 inhibitors	DPP-4 inhibitors	Meglitinides	Thiazolidinediones	Alpha-glucosidase inhibitors
How do they work?	Decrease hepatic glucose production	Increase insulin secretion	Inhibit SGLT-2 in the proximal tubules, block glucose reabsorption, ↑ glucosuria (act independent of insulin)	Inhibit DPP-4 activity, prolong incretin action, ↑ insulin secretion & ↓ glucagon secretion (glucose-dependent)	Increase insulin secretion	Increase insulin sensitivity	Slow intestinal carbohydrate absorption
HbA1c lowering*	1 – 1.5%	1 – 1.5%	0.6 – 0.9%	0.5 – 0.8%	0.5 – 1.0%	0.5 – 1.5%	0.5 – 0.8%
Patient affordability†	$	$	$$	$$$	$$$	$$$	$$$
What to watch out for?							
Hypoglycaemia	Neutral	Moderate	Neutral	Neutral	Mild	Neutral	Neutral
Weight	Neutral or loss (mild)	Gain	Loss	Neutral	Gain (mild)	Gain	Neutral
Cardiovascular	↓ CVD events	–	↓ CVD events & mortality	↑ HF hospitalisations (saxagliptin, alogliptin)[14]	–	• HF, oedema • ↑ LDL-C (rosiglitazone) • ↓ CVD events	–
Renal	Avoid if eGFR < 30, reduce dose if eGFR < 45	Hypoglycaemia risk	Not recommended in severe impairment	Dose adjustment (except linagliptin)	Hypoglycaemia risk	Fluid retention	–
Other considerations	GI effects, vitamin B12 deficiency, lactic acidosis (rare), avoid in hypoxic states	–	DKA (rare), volume depletion or hypotension (especially with patients on diuretics, ACE-Is, ARBs), ↑ genitourinary infections, lower limb amputations (canagliflozin)	Skin reactions, joint pain, caution in patients with history of pancreatitis	• Improve postprandial control • Do not use with SUs	• 6 - 12 weeks required for maximal effect • Avoid in HF, liver failure (rare hepatotoxicity), ↑ fracture risk	• Improve postprandial control • GI effects - flatulence, diarrhoea

Appropriate Care Guide – Agency for Care Effectiveness

- Considerations
  - Reno-protection: SGLT2s shown to be reno-protective
  - Contraindication of Certain Drugs
    - § Metformin: Contraindicated if eGFR < 30 because of lactic acidosis risk
    - § SGLT2 Inhibitors: Contraindicated if eGFR <30 (because glucose lowering effect becomes less effective and risk of dehydration/AoCKD)
  - Side effects
    - § Sulphonylureas: While sulphonylureas can be used, increased risk of hypoglycemia; specifically avoid glibenglamide
    - § Thiazolidinediones: Avoid thiazolidinediones because of fluid retention risk
    - § Insulin: Increased risk for hypoglycemia with insulin also because of decreased insulin degradation in advanced CKD – hence start at lower doses
  - Dose adjustment to medications: DPP4 inhibitors (sitagliptin, vildagliptin; **no adjustment needed for linaglpitin**), SGLT2 inhibitors
  - Glycemic targets: Hba1c can be decreased or increased in CKD and ESRF, hence may want to take into account SMBG too

What should we take note of in terms of long-term follow-up? 54:13

- End-organ complication screening: Annual foot screen, retinal photography and renal function (creatinine and albuminuria)
- ADA guidance for glycemic targets

Table 12.1—Framework for considering treatment goals for glycemia, blood pressure, and dyslipidemia in older adults with diabetes (2)

Patient characteristics/ health status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.5% (58 mmol/mol)	90–130 mg/dL (5.0–7.2 mmol/L)	90–150 mg/dL (5.0–8.3 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<140/90 mmHg	Statin unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	<8.5%† (69 mmol/mol)	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<150/90 mmHg	Consider likelihood of benefit with statin (secondary prevention more so than primary)

Take Home Points? 58:20

- Glycemic targets should be individualized to patients
- Understanding the basics of insulin initiation and titration
- Understand the various disease and pharmacological considerations of choosing between OGLDs

Specific OGLD Agents

- Metformin
  - Usually first line
  - Starting Dose: 250-500mg BD
  - Ceiling Dose: 850mg TDS
  - Renal Impairment: Contraindicated when eGFR < 30
  - Side Effects: GI side effects, metformin associated lactic acidosis
  - Benefits: Low risk for hypoglycemia, favourable cardiovascular profile, weight neutral
  - Consider extended release dosing for compliance or concerns of GI side effects
- Sulphonylureas
  - Dosing
    - Glipizide: Can start 2.5mg OM up to 10mg BD
    - Gliclazide (usually modified release): Can start 30mg OM, up to 120mg OM
    - Glibenclamide (glyburide) or gliperimide are long acting agents with high risk of hypoglycemia, ideally should be avoided
  - Side effects: Hypoglycemia, weight gain
  - Benefits: Effective BGM control, can use in renal impairment
- DPP4 Inhibitors
  - Mechanism: Acts on DPP4 which prevents breakdown of incretins Increase in incretin levels
  - Dosing
    - Sitagliptin:
      - Full dose: 100mg OM
      - eGFR 30-45: 50mg OM
      - eGFR < 30 / ESRF on dialysis: 25mg OM

        - Vildaglipitin
            - CrCL ≥50ml/min: 50mg BD
            - CrCL <50ml/min: 50mg daily
        - **Linagliptin**: 5mg OM; no renal dose adjustment needed
    - Side Effects: Joint pains, skin reactions, headache, nasopharyngitis, caution in pancreatitis
    - Benefits: Low risk for hypoglycemia, weight neutral, can use in renal impairment
- SLGT 2 Inhibitors
    - Mechanism: SGLT2 (sodium-glucose cotransporter-2) inhibitors block SGLT2 found on the epithelial cells of the proximal convoluted tubule of the kidneys to prevent reabsorption of glucose from glomerular filtration
    - Benefits: Favourable cardiovascular and renal profile, low risk for hypoglycemia, some weight loss and BP reduction
    - Side Effects: Euglycemic DKA (**HOLD OFF WHEN UNWELL**), genitourinary infections, ? risk for LL amputations, dehydration/hypovolemia
    - Dosing
        - Dapagliflozin – Forxiga
            - eGFR ≥ 45: 10mg OM
            - eGFR 30-45: Initiation not recommended, consider discontinuation or continuation at low dose (5mg OM) as off label use
        - Empagliflozin – Jardiance
            - eGFR ≥ 45: 10mg or 25mg OM
            - eGFR ≥ 45: 10mg OM
            - eGFR 30-45: Initiation not recommended, consider discontinuation or continuation at low dose (10mg OM) as off label use

Resources

- Singapore CPG: https://www.moh.gov.sg/docs/librariesprovider4/guidelines/cpg_diabetes-mellitus-booklet--jul-2014.pdf
- Appropriate Care Guidelines from Agency for Care Effectiveness
    - Insulin Initiation for T2DM: https://www.ace-hta.gov.sg/our-guidance/initiating-basal-insulin-in-type-2-diabetes-mellitus.html
    - Managing Pre Diabetes: https://www.ace-hta.gov.sg/our-guidance/managing-pre-diabetes-a-growing-health-concern.html
    - OGLDs for T2DM: https://www.ace-hta.gov.sg/our-guidance/oral-glucose-lowering-agents-in-type-2-diabetes-mellitus-an-update.html
- ADA Pharmacology Management of T2DM Guidelines: https://care.diabetesjournals.org/content/43/Supplement_1/S98