- **Given a symptomatic or asymptomatic patient at high risk for diabetes (e.g., patients with gestational diabetes, obese, certain ethnic groups, and those with a strong family history), screen at appropriate intervals with the right tests to confirm the diagnosis.**

First, it's probably important to be able to pick up on when your patient might be developing diabetes.

Signs and symptoms of diabetes may include:

- diabetic ketoacidosis (automatic diagnosis of diabetes as this is symptomatic hyperglycemia),
- the classic polyuria/polydipsia/polyphagia and weight loss, most often seen in type 1 diabetes
- acanthosis nigricans (particularly in children and adolescents with type 2 DM), and
- obesity
- among others.

Now, what if they don't have any symptoms like this to prompt you to investigate, when should I start screening people without symptoms?

The Diabetes Canada Clinical Practice Guidelines is an overriding guideline for when to screen essentially everyone, with some nuance for folks who might need to be screened earlier and/or more frequently.

- **Screening in the general population**
    - The general population should be screened for type 2 DM after age 40 at an interval of every 3 years using either fasting plasma glucose OR hemoglobin A1c (HbA1c);
        - you can use random plasma glucose but you'll need to confirm using a second DIFFERENT test.

    - All individuals should be evaluated annually for type 2 diabetes RISK on the basis of demographic and clinical criteria.
        - Can use the **CANRISK** as a risk scoring tool

- cANRISK or The Canadian diabetes risk questionnaire which includes age, sex, activity and diet, family history and other risk factors.

- If at high risk (>33% chance in developing diabetes over 10 years), start screening earlier using the same q3 years minimum frequency,
  - you may screen more frequently (e.g. every 6 or 12 months) for those at very high risk.

There is also a big list of risk factors that can increase your patient's risk of developing Diabetes, so let's run through them:

- previous gestational diabetes mellitus, up to 50% will develop diabetes later on
- prediabetes, which is defined as:
  - HbA1c of 6.0% -6.4%
  - OR Impaired fasting glucose (gluc 6.1-6.9 after 8 hours of fasting)
  - OR impaired glucose tolerance (2hOGTT 7.8-11.0)
  - *[though recent research calls into question, at least in older adults, whether these folks are actually more likely to develop into full-blown diabetes after all https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2775594]*
- family history of T2DM
- abdominal obesity or being overweight
- metabolic syndrome (3 of the following:
  - elevated waist circumference,
  - elevated TGs >=1.7 or treatment for elevated TGs,
  - decreased HDL <1.3 in women, <1.0 in men,
  - elevated BP with SBP >=130 or DBP >=85 or treatment for elevated BP,
  - elevated FPG >=5.6 or treatment of elevated glucose)
- hypertension
- ethnicities including South Pacific Islanders, Asian people, Indigenous North Americans, Black people
- smoking history
- associated diseases including:
  - PCOS
  - Acanthosis nigricans
  - History of pancreatitis

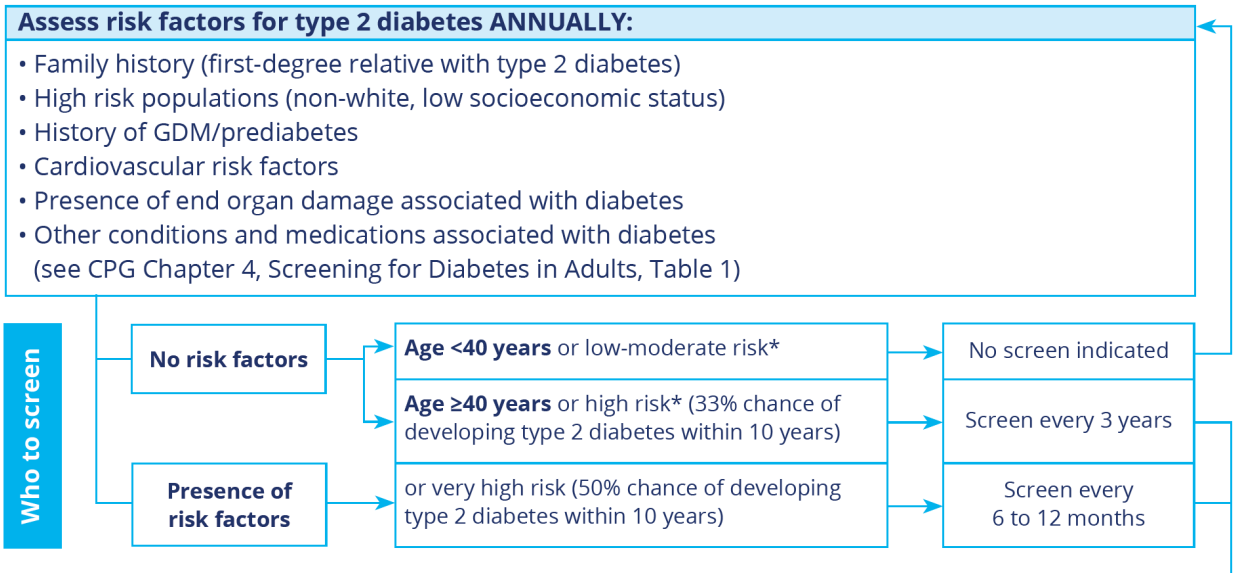
- Hyperuricemia/gout
- Non-alcoholic steatohepatitis
- Psychiatric disorders (e.g. bipolar disorder, depression, schizophrenia)
- HIV infection
- Obstructive sleep apnea
- Cystic fibrosis

There are also a number of **medications that are associated with the development of diabetes,** to read them all check the show notes, but a few are:

- Glucocorticoids
- Atypical antipsychotics
- Statins
  and a number of others that you can see in the show-notes. (stop reading off here)
- Highly-active anti-retroviral therapy
- Anti-rejection drugs
- Alpha-interferon
- Beta-adrenergic agonists
- Calcineurin inhibitors
- Diazoxide
- Dilantin
- Fluoroquinolones
- Nicotinic acid
- Pentamidine
- Thiazides
- Thyroid hormone
- Vacor (rodenticide)

the generEMlist
105 CCFP Topics Podcast

Screening and diagnosis of type 2 diabetes in adults



Your patient has turned 40, and so you discuss with them the rationale of why we screen for diabetes.

Once you get the results, what counts as diabetes?

Positive test results indicating diabetes are as follow:

- Fasting plasma glucose level > 7.0, or
- Random plasma glucose >= 11.1, or
- HbA1c >= 6.5%
- 2h Oral Glucose Tolerance Test with FPG >7.7, 2hr Gluc >= 11.1
- You should confirm any of the these results with a second test of the same type on another day
    - unless the first test is random glucose reading and then you need to confirm with A1c or FPG; you may also use FPG + A1c together or 2hOGTT as a confirmatory test. If the results of 2 tests are both above threshold, the diagnosis is made.
    - As previously mentioned, if a patient presents with symptomatic hyperglycemia then the diagnosis of diabetes is made.

Another group needing distinct screening for diabetes are **Pregnant patients.** They should be screened with **1**hr OGTT between 24 and 28 weeks GA, confirmation is with the **2**hr test

What about screening for type 1 diabetes?

- Screening should not be undertaken for type 1 DM as there is no evidence for interventions to prevent or delay type 1 DM.
- In patients diagnosed with diabetes before age 6 months, consider neonatal diabetes of monogenic form which is NON-INSULIN DEPENDENT and may respond to oral sulfonylurea -> therefore, all infants diagnosed with diabetes prior to 6 months of age should have genetic testing performed - likely peds will be involved at this point so this is just good to be aware of as family doctors!
- In adults with a diagnosis of diabetes mellitus before 30 to 40 years old, and their time to needing insulin is <1 to 2 years – this is more predictive of type 1 DM.
- In a patient with onset of diabetes before 25 years of age who is not obese with a fam hx with inheritance in more than 2 generations, consider genetic testing for monogenic diabetes (these are genetic mutations which cause pancreatic islet cell dysfunction).

- **Given a patient diagnosed with diabetes, either new-onset or established, treat and modify treatment according to disease status (e.g., use oral hypoglycemic agents, insulin, diet, and/or lifestyle changes).**

Of course, as with any medical intervention, your first step should be lifestyle changes. Diet and exercise. Generally, if their A1C is less than 1.5% above target at diagnosis, so this would be 8.4% or less, and you expect lifestyle to be effective, then you can suggest a 3 month trial of lifestyle and reassess. If they're still not at target in 3 months, then initiate metformin.

If their A1C is already 8.5% or higher, start metformin immediately **with a second agent** and reassess in 3-6 months.

the generEMlist
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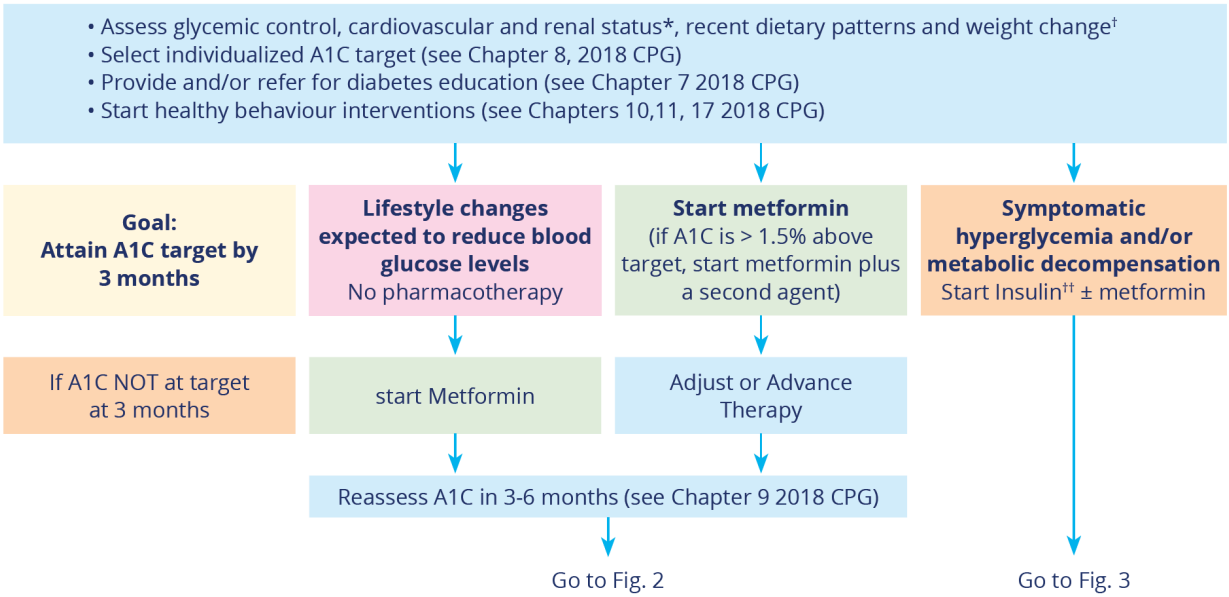
At diagnosis of type 2 diabetes (Fig. 1)

2020



Your patient has an A1C of 7.5% at diagnosis, and they want to try to remedy it without medications, what is available to you?

<u>Non-pharmacological interventions:</u>

- In prediabetes, healthy behaviour changes that result in a 5% body weight loss can help reduce the risk of developing diabetes
- Recommend diets high in fibre, low in saturated fat, low in fat, and low in calories to help achieve weight loss goals
- Recommend medical nutrition therapy with a registered dietitian
- The Mediterranean diet is recommended for DM prevention.
    - Benefit has also been seen with:
        - DASH diet,
        - Alternate Healthy Eating Index (AHEI), and
        - diets high in
            - whole grains,
            - fruits,
            - vegetables,
            - legumes,
            - olive oil,
            - white meat/ seafood,
            - little or moderate alcohol, and

        - reduced intake of red and processed meats and sugar-sweetened beverages. Diets emphasizing whole grain and dairy product consumption are associated with lower risk of diabetes.
    - Benefits are noted with 300-400g of dairy intake a day, up to 120 to 140 g/day of yogurt and ~50 g/day of cheese.
- Physical activity 150 mins per week of moderate to vigorous activity are recommended.
    - People with twice the activity time (300 minutes or more per week) had even lower risk of developing diabetes mellitus.
- Bariatric surgery – uncertain cost-benefit analysis for prevention of DM, so more data is needed before recommending bariatric surgery routinely to prevent diabetes.

Now, your patient tried to make the needed lifestyle changes to get their A1C down, but it wasn't enough unfortunately, so you are starting to consider what pharmacologic options are available to help.

1. **First line agents**. or agent, because this is basically just the ubiquitous Biguanide, Metformin.
    - It works by increasing the body's tissue sensitivity to insulin and reducing glucose production in the liver
    - Has cardiac benefits, a relatively robust safety profile, and has low hypoglycemic risk. There is generally no weight gain seen. It is also low in cost.
    - Common side effects are nausea and diarrhea; these can be mitigated by slow introduction of metformin by titrating the dose up over a few weeks to the target dose.
    - It is contraindicated below a CrCl of 30 mL/min and in hepatic failure; caution with CrCl 30 to 60 mL/min
    - Long-term use may lead to vitamin B12 deficiency so it can be helpful to check for this if a patient presents with neurological symptoms
    - In patients diagnosed with prediabetes, treating with metformin can reduce the risk of progression to type 2 diabetes (~30% reduction); benefits may persist for over 10 years AFTER therapy is DISCONTINUED.

- In patients diagnosed with prediabetes, consideration for metformin therapy at 850 mg PO twice daily is best in younger patients (< 60 yo) and in patients with BMI < 35 – more relative preventative effect in these groups.
    - Also may be more effective in women with hx of GDM vs parous women without GDM

2. **Second line agents** include the secretagogues, the SGLT2 inhibitors, the incretins and the insulins.

- First, the insulin secretagogues, which include the sulfonylureas, and meglitinides, both of which appear to be going the way of the dodo.

  They have higher risk of hypoglycemia and weight gain and must be discontinued when insulin is started due to the risk of hypoglycemia.

  In general, they help the pancreas release more insulin by activating the sulfonylurea receptor on the Beta-cell to stimulate endogenous insulin secretion

Sulfonylureas *(common ones are glyburide and gliclazide)*

- *They are relatively cheap*
- *Gliclazide carries a minimal to moderate hypoglycemia risk, while glyburide has a moderate hypoglycemia risk*
- *Can expect an HbA1c lowering of 0.7 to 1.3%*
- *You can also expect a weight gain of 1.5 to 2.5 kg*
- *Gliclazide is preferred to glyburide for lower hypoglycemia risk, CV events, and mortality*
- *Both have a relatively rapid BG-lowering response*

Another second line agent is the new superstars,
Sodium glucose transporter 2 inhibitors (-gliflozins)

- These prevent the SGLT-2 transport protein from reabsorbing glucose in the kidney
- They are associated with weight loss of 2 to 3 kg
- They carry low risk of hypoglycemia as monotherapy
- Critically, they have also shown reduction in MACE (specifically, empagliflozin and canagliflozin) and CV death (empagliflozin) in participants with clinical CVD

- $$$ Costly
- A1c lowering 0.4 to 0.7%
- *Some side effects to consider and inform patients about are:*
    - *Genital yeast infections*
    - *UTIs*
    - *Polyuria*
    - *Hypotension, as they are a diuretic*
- *Other clinical considerations:*
    - *Reduced progression of nephropathy and reduction in heart failure in participants with clinical CVD with empagliflozin and canagliflozin*
    - *Side effects:*
        - *Genital mycotic infections*
        - *UTIs*
        - *Hypotension*
        - *Small increase in LDL-C*
        - *Rare cases of (possibly) euglycemic DKA*
        - *Increased risk of fractures with canagliflozin*
        - *Increased risk of lower extremity amputation with canagliflozin (avoid if prior amputation)*
        - *Reports of AKI with canagliflozin and dapagliflozin*
        - *Fournier's gangrene has been reported*
            - *The SGLT2inhibitors are contraindicated if CrCl/eGFR < 45 mL/min (cana, empa) or < 60 mL/min (dapa)*
            - *Caution with renal dysfunction, loop diuretics, the elderly*
            - *Treatment should be withheld prior to major surgery or with serious illness or infections*

Meglitinide *(Repaglinide)*

- *Costs a bit more*
- *Similar Hba1c lowering of 0.7 to 1.1%*
- *But generally less weight gain of 0.7 to 1.8 kg*
- *It carries a Min to mod risk of hypoglycemia*
- *Postprandial glycemia is especially reduced*
- *It can be a bit annoying with TID dosing*
- *Contraindicated when co-administered with clopidogrel or gemfibrozil*
    - Next up are the Incretin agents, which are the DPP4 inhibitors and the GLP-1's.
      These increase glucose-dependent insulin release while inhibiting

the release of glucagon, and delaying gastric emptying.
They have low risk of hypoglycemia when used as monotherapy.

DPP4 inhibitors (-gliptins) "saxagliptin, sitagliptin"

- These work by increasing glucose-dependent insulin release, slowing gastric emptying, and inhibiting glucagon release
- +++ Costly
- A1c lowers – 0.5 to 0.7%
- Weight neutral
- Low risk hypoglycemia as monotherapy
- *Neutral for primary CVD outcomes*
- *Side effects/ therapeutic considerations:*
    - *Rare cases of pancreatitis*
    - *Rare cases of severe joint pain*
    - *Caution with saxagliptin in patients with heart failure*

GLP-1 Agonists"liraglutide, semaglutide"

- Injectable (subcutaneous)
- Work when blood gluc increases after a meal; they increase insulin levels, which helps lower BG and lower glucagon levels
- They also slow digestion and reduce appetite and are associated with weight loss (1.6 to 3.0 kg)
- Low risk of hypoglycemia as monotherapy
- They also reduce risk of MACE and CV death in participants with clinical CVD (for liraglutide)
- ++++ Costly
- Contraindicated with family or personal history of medullary thyroid cancer or Multiple Endocrine Neoplasia syndrome type 2
- *There are both short-acting and long-acting options (daily vs weekly use), which can be nice for an injectable.*
    - *Short-acting: Exenatide, Lixisenatide*
    - *Longer-acting: Dulaglutide, Exenatide extended-release, Liraglutide*
- *Side effects:*
    - *Nausea, vomiting, diarrhea*
    - *Rare cases of acute gallstone disease*
- *Other therapeutic considerations*
    - *Subcut injection*

- *Less A1c lowering with short-acting agents than longer-acting agents*
- *Reduced progression of nephropathy with liraglutide*

- Next up, the Insulins (subcutaneous injection)
  - Multiple insulin options; better to use rapid than short for bolus, and long than intermediate for basal
  - Better to add SGLT2-I or GLP-1 before adding bolus insulin.

- **Third line agents**
  - Thiazoledinediones (-glitazones)
    - Some evidence for thiazolidinediones exists for prevention of progression of diabetes but the adverse outcomes seen in trials with these meds make recommendations for their usage difficult
      - bladder cancer risk with pioglitazone, and ?CHF/MACE risk with rosiglitazone.
  - Alpha glucosidase inhibitor (acarbose)
    - Acarbose shown to reduce risk of progression to T2DM but effect did not persist after medication discontinued.
    - *Inihibits pancreatic alpha-amylase and intestinal alpha-glucosidase*
    - *$$*
    - *0.7 to 0.8% A1c lowering*
    - *Negligible risk of hypoglycemia as monotherapy*
    - *Neutral weight*
    - *GI side effects common*
    - *Requires TID dosing*
  - Orlistat
    - *$$$ Cost*
    - *0.2 to 0.4% A1c reduction*
    - *Negligible hypoPG risk as monotherapy*
      - *Loss of 3 to 4 kg*
      - *Promotes weight loss*
      - *Can cause diarrhea and other GI side effects*
        i. *Requires TID dosing*

- Vit D supplementation not shown to aid in prevention or reduction of T2DM

resources to know about from Dr Winston:

diabetesatschool.ca has great learning modules and videos

baqsimi.ca shows you how to use intranasal glucagon - one of my favorite advances in diabetes technology in recent years

Tandem has an app that you can download to mimic a pump on your phone so you can see what it is like to adjust pump settings