Type 2 diabetes in Indigenous young people: management and prevention complexities

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Outline

- Diagnostic criteria
- Epidemiology and pathophysiology of youth onset diabetes
- Current treatments in children and adolescents
- Treatment options for ‘older’ young people
- Screening
- Prevention
- The complexities

Diagnosis

1. Fasting (min 8 hrs) plasma glucose ≥ 7mmol/L

OR

2. Classic symptoms (polyuria, polydipsia, weight loss) and casual BGL ≥ 11.1mmol/L

OR

3. 2 hour OGTT value ≥ 11.1mmol/L (75g or 1.75 g/kg (children) glucose)

OR

4. HbA1c > 6.5% (not POC)

ISPAD guidelines 2018

Glucose dysregulation

Impaired fasting glucose

- Fasting plasma glucose 5.6-6.9 mmol/L

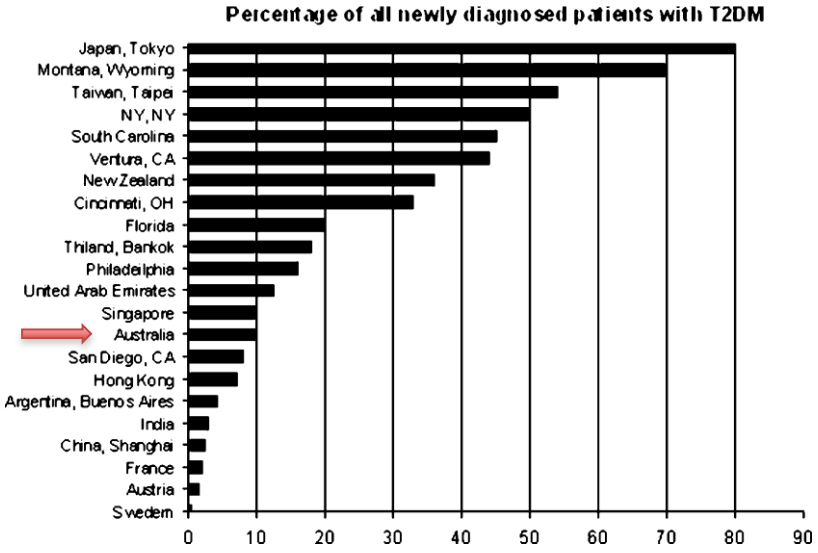
Impaired glucose tolerance

- 2 hour value ≥ 7.8 but < 11.1mmol/L

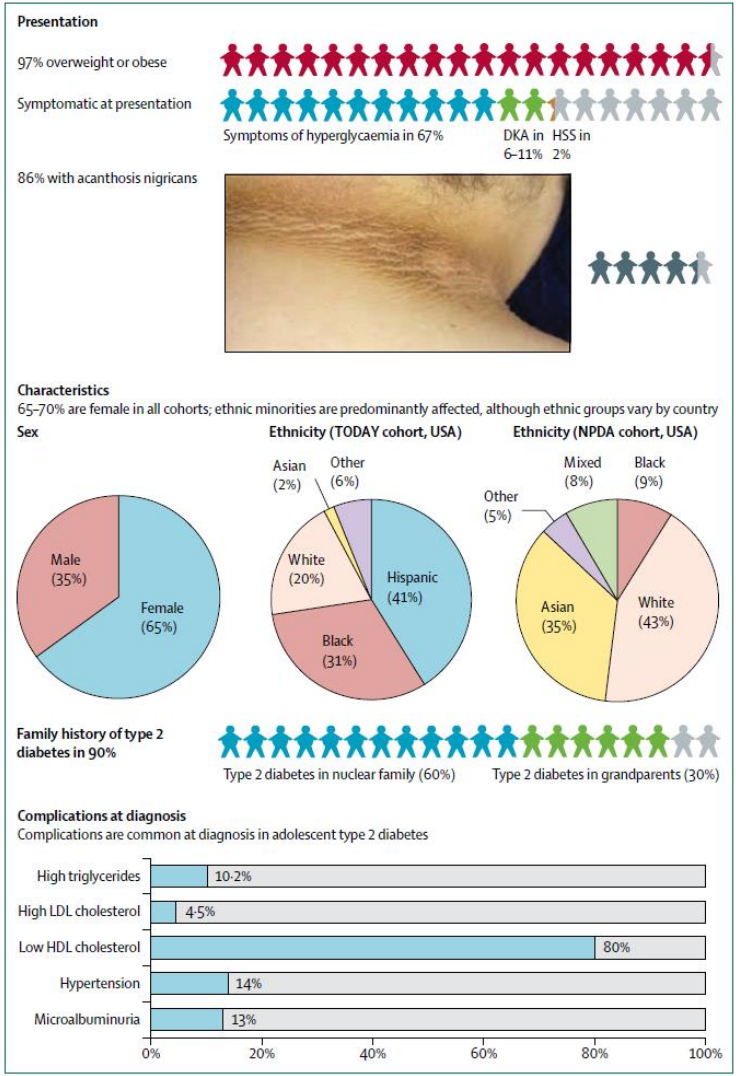
ISPAD guidelines 2018

Epidemiology

Youth onset diabetes worldwide



Pinhas-Hamiel and Zietler, 2005. J Ped; 146(5): 693-700.
Viner et al. 2017. Lancet; 389: 2252-60.



Type 2 diabetes in Indigenous young people

Case Report

A 5-year-old girl with type 2 diabetes

Dev Kevat, Dyanna Wilson, Ashim Sinha

In August, 2013, a 5-year-old Indigenous girl accompanied her mother to her diabetes outreach appointment in a remote community in Australia. Towards the end of her consultation, the mother mentioned concerns about non-healing sores on her daughter's thighs. Noting the child's obesity, two random blood glucose level tests were done, showing concentrations of 19·2 mmol/L and 18·7 mmol/L. A urine dipstick test was negative for ketones. The girl's mother reported that the sores had been present for roughly 5 weeks, and bedwetting for the past 12 months. There was no history of diarrhoea or vomiting. The child was born macrosomic (4·5 kg) at 38 weeks by caesarean section after a pregnancy complicated by poorly controlled gestational diabetes. Her diet was high in large portions of refined carbohydrates and simple sugars. There was a strong family history of type 2 diabetes.

The patient was above the 99th centile for weight (36 kg), body-mass index (24·5 kg/m²) and height (123 cm). Crusted sores on both upper thighs and right axilla were consistent with impetigo. The rest of the examination was unremarkable except for acanthosis nigricans in the axillae and around the neck (figure). The patient had high concentrations of HbA_{1c} (11·9%, normal range 4·3–6·0, or 107 mmol/mol, 23–42), plasma glucose (19·5 mmol/L, 3·0–7·8), C-peptide (1·4 nmol/L, 0·3–1·6), and insulin (201 pmol/L, 14–160). Urine albumin:creatinine ratio was normal (0·3 g/mol creatinine, normal <3·0). Tests for type 1 diabetes autoantibodies and genetic tests for *MODY1 (HNF4A)* and *MODY3 (HNF1A)* were negative. The patient was transferred to a tertiary centre and given intravenous antibiotics for infection, and metformin and insulin for type 2 diabetes. When seen for follow-up in November, 2013, she was no longer taking metformin because of intolerance, but remained on insulin. Blood glucose concentrations remained above target levels at 10–13 mmol/L.

Driven by increased urbanisation, high calorie diets, and increasingly sedentary lifestyles, the worldwide rise in the incidence of type 2 diabetes has predominantly occurred in adults. However, children are also being affected.[1] The continued burden of infectious diseases (eg, respiratory and diarrhoeal illnesses) coupled with an increasing prevalence of chronic diseases (particularly cardiovascular disease and type 2 diabetes) has resulted in Indigenous Australians having an additional 70% disease burden compared with the general Australian population.[2] Remote Indigenous communities are generally socioeconomically poor yet pay high prices for fresh food because of transport costs and limited competition. In addition to adverse socioeconomic determinants, genetic factors and in-utero exposure to hyperglycaemia[3] probably contributed to this child's risk of developing type 2 diabetes. The US SEARCH study[4] provides epidemiological data about the incidence of diabetes in young people. In our experience with this population, compliance and good diabetic control is often difficult to achieve and sustain—the TODAY trial[5] showed that even under ideal conditions 52% of children on metformin alone, and 39% of children on combination oral treatment lost glycaemic control (HbA_{1c} >8% for 6 months or required insulin), over an average follow-up period of 3·9 years. Further long-term outcome studies are needed to determine the most efficacious combinations of interventions for type 2 diabetes in children who have extra decades to accrue disabling complications.

Contributors

DK wrote the report and initially managed the patient. DW and AS helped revise the report and assisted with references, and have provided ongoing care to the patient. Written consent to publish was obtained.

Declaration of interests

AS has been on advisory boards for Sanofi-Aventis and AstraZeneca (AZ); been on speakers bureaux for Eli Lilly, AstraZeneca (AZ), Novo Nordisk, Sanofi-Aventis, Merck Sharp & Dohme, Takeda, Servier, and Novartis; and received research grants from Novo Nordisk and Merck. DK and DW declare that they have no competing interests.

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1 Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes in children and adolescents. J Paediatr 2005; 146: 693–700.

2 Vos T, Barker B, Begg S, Stanley L, Lopez A. Burden of disease and injury in Aboriginal and Torres Strait Islander Peoples: the Indigenous health gap. Int J Epidemiol 2009; 38: 470–77.

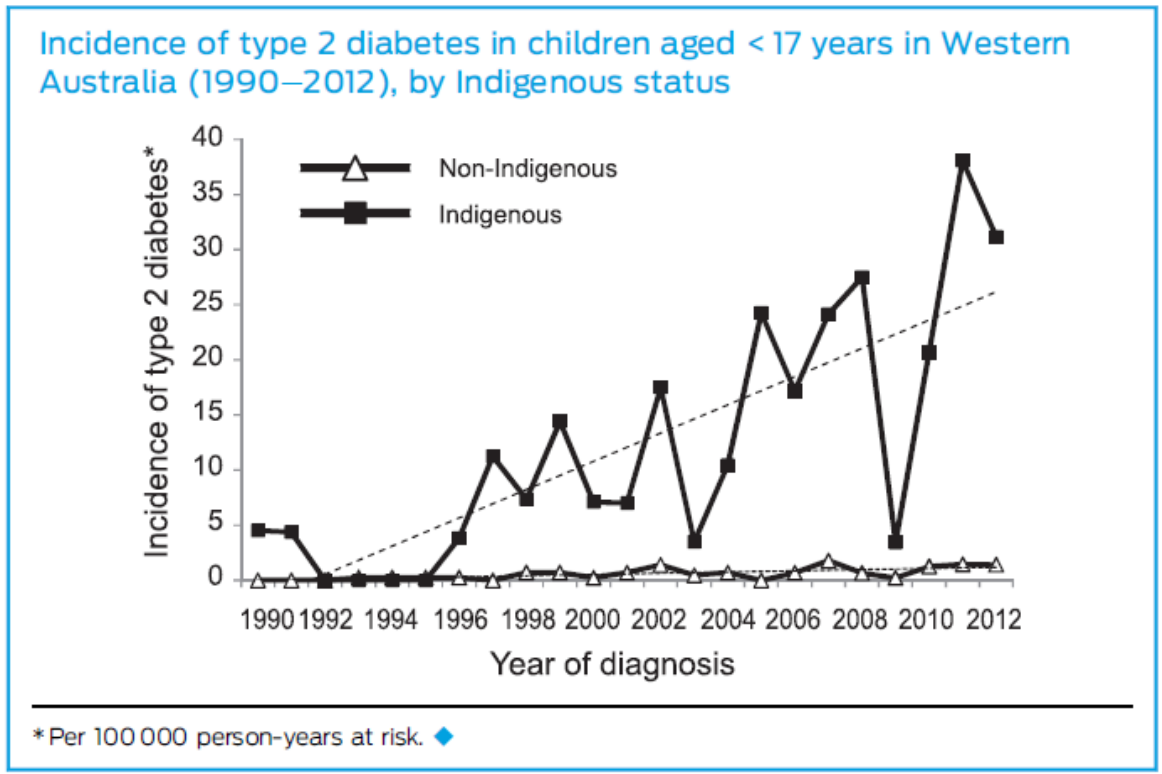
3 Dabelea D, Hanson R, Lindsay R, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes 2000; 49: 2208–11.

4 The Writing Group for the SEARCH for Diabetes in Youth Study Group. Incidence of diabetes in youth in the United States. JAMA 2007; 297: 2716–24.

5 TODAY Study Group. Clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med 2012; 366: 2247–56.

1268 www.thelancet.com Vol 383 April 5, 2014

Kevat et al. 2014. Lancet; 313.
Haynes et al. 2016. MJA; 204(8).



Emerging diabetes and metabolic conditions among Aboriginal and Torres Strait Islander young people

Intersectoral collaboration is needed to engage communities and design effective culturally and age appropriate interventions

The gap between the health of Aboriginal and Torres Strait Islander and non-Indigenous Australians is well documented, with many policies and programs currently working towards improving outcomes. Despite these efforts, life expectancy is 10–11 years less than that of non-Indigenous Australians,[1] and 65% of deaths occur before 65 years of age, compared with 19% in the non-Indigenous population.[1]

Cardiovascular and metabolic diseases are responsible for most of the gap in life expectancy and are associated with higher hospitalisation and mortality rates.[1] In 2013, hospitalisation rates for cardiovascular disease were 1.6–2.5 times higher in Indigenous people depending on age, and Indigenous adults are six times as likely to die from diabetes as non-Indigenous Australians.[1] Indigenous adolescents with type 2 diabetes are over ten times more likely

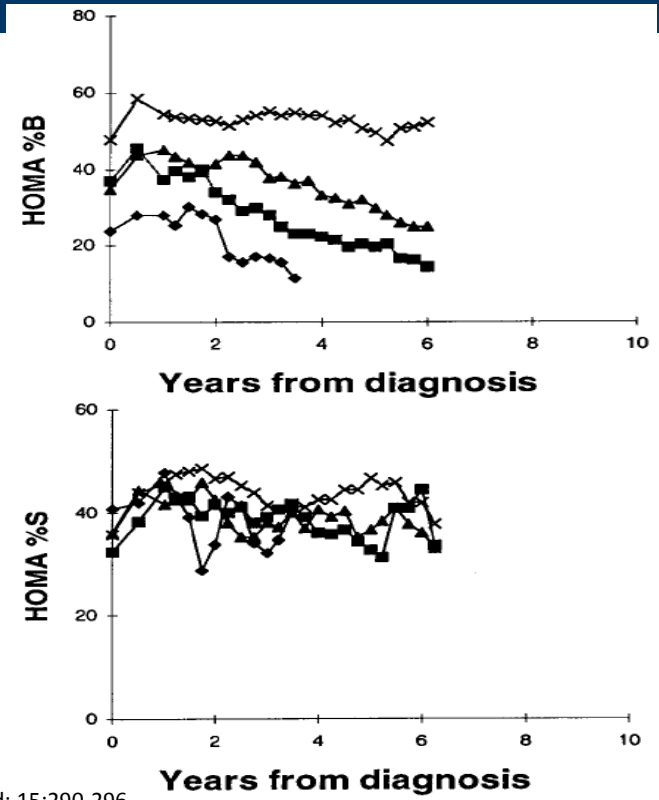
These statistics indicate the extent of the issue despite likely diagnostic underestimation, as many children with type 2 diabetes may be managed in primary

Titmuss A et al, 2019. MJA 210(3)

Pathophysiology

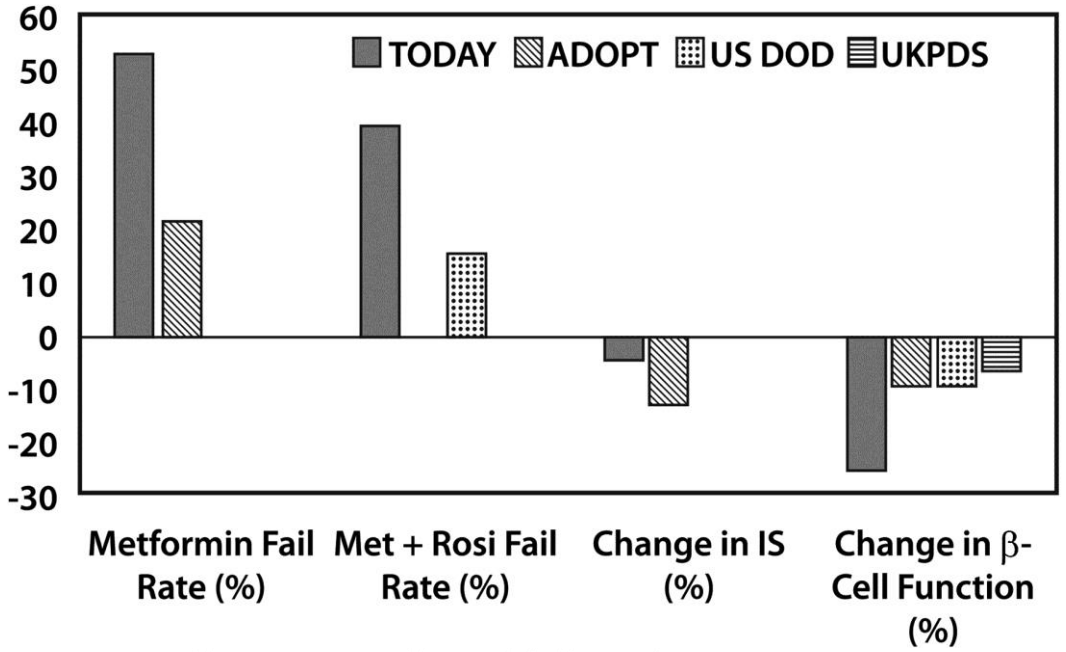
Pathophysiology of type 2 diabetes in young people

- **B-cell function is impaired in adolescents with obesity and Type 2 DM**
  - First change is loss of initial response to glucose load in terms of ↑ insulin secretion (ie post prandial hyperglycaemia)
  - Some obese adolescents will normalise OGTT as have transient insulin resistance of



Levy J et al. 1998. Diabet Med; 15:290-296

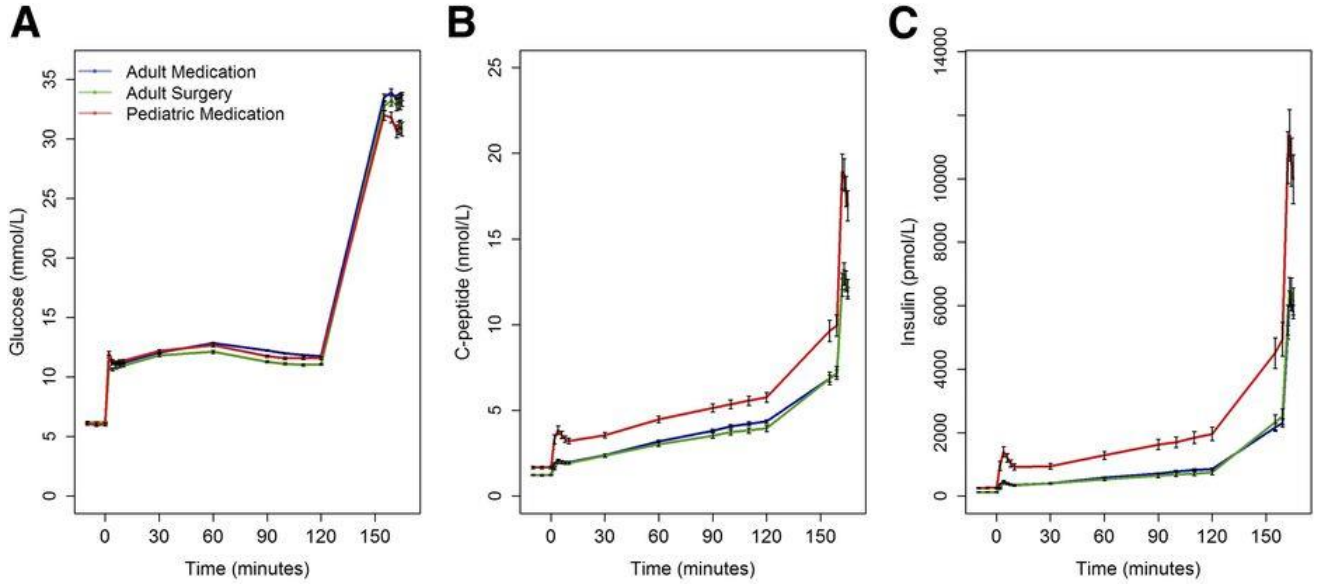
A different dx to that in adults:
poorer treatment response, worse ß cell function



- **80% of ß-cell function is reduced or lost at diagnosis** (cf 50% in adults)
- And further declines after diagnosis (2-4x faster loss than adults)

Nadeau et al. Diab Care 2016;39:1635-1642

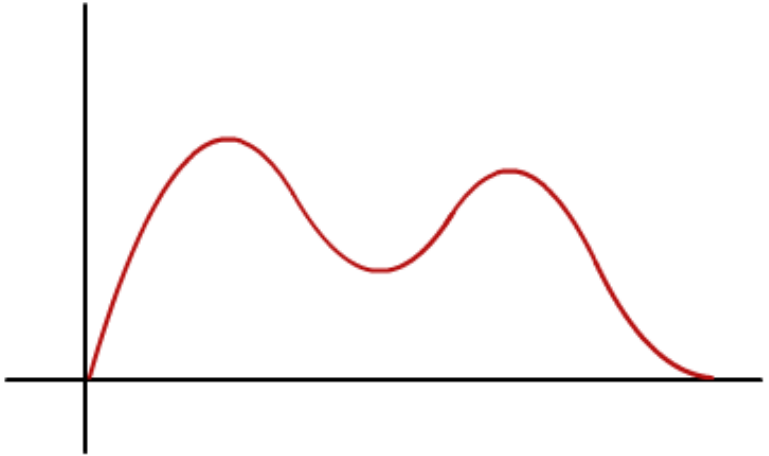
Young people are more insulin resistant at diagnosis and have hyperresponsive B cells to glucose load



RISE Consortium. Diab Care 2018;41:1696-1706

What determines glycaemic control in young people with T2D?

- Residual ß cell function at diagnosis appears to be most important factor (ie. Insulin secretion more important than insulin sensitivity)
- Weight gain and BMI
- Mental health
- Puberty related insulin resistance
- **Heterogenous population**
  - Bimodal distribution



Viner et al. 2017. Lancet; 389: 2252-60

Two groups of patients?

1. Stable normalisation of BGLs on initial treatment and HbA1c in target
2. Rapidly progressive disease and elevated HbA1c, treatment failure

Multiple subtypes of adult T2D?

- **Severe ‘autoimmune’ T2D (6.5%):**
  - Early onset, lower BMI, poor metabolic control, insulin deficiency, +ve GAD
- **Severe insulin deficient T2D (17.5%):**
  - Early onset, lower BMI, poor metabolic control, insulin deficiency, GAD –ve, higher risk retinopathy
- **Severe insulin resistance T2D (15%):**
  - Insulin resistance, high BMI, higher risk of renal complications
- **Mild obesity related T2D (21.6%):**
  - Obesity, mild/no insulin resistance, good metabolic control
- **Mild age related T2D (39%):**
  - Older onset, mild/no insulin resistance, good metabolic control

Ahlqvist et al, 2018. Lancet Diab Endo

Treatment

Importance of intensive early treatment

"We believe that adolescent type 2 diabetes needs to be reframed as a severe progressive phenotype"

(Viner et al, 2017. Lancet.)

- **Aim HbA1c <6.5%** (47.5mmol/mol)
  - **"treat to target"**
- 'Window of opportunity" to treat and improve long term outcomes
  - *Preserve B cell function for longer*
- Earlier and increased complications in youth onset diabetes
- Monitor for complications from diagnosis, then annually
- Higher rates of treatment failure – why?

TODAY study group, 2012. NEJM; 366(24): 2247–2256.

Current treatment recommendations in <18yo (ISPAD 2018)

- **Limited options** due to lack of evidence / licensed meds
- **Lifestyle changes**, whole of family approach

Note: first ever Australian/NZ guidelines, (which will also cover other agents), are currently being written **(APEG/ ADS)**

HbA1c <8.5% (69.4mmol/mol) and no symptoms

- **Metformin**
  - Start at 500-100mg daily for 1-2 weeks
  - Titrate by 500mg every week until reach maximal dose of 1g bd
  - Then change to XR formulation (2g daily) as less side effects

HbA1c ≥8.5% (69.4mmol/mol) or ketosis

- Need **lantus** 0.25-0.5U/kg/day
- Start **Metformin** at same time
- Transition to full dose metformin over 2-6 weeks while reducing insulin dose

If HbA1c ≥ 6.5% within 4 months of metformin monotherapy, consider insulin (up to 1.5U/kg/day)

Management pathway for Aboriginal young people under 18yo diagnosed with diabetes

Meets diagnostic criteria for diabetes

Any of:
1. Fasting BGL ≥ 7mmol/L
2. Symptomatic and random BGL ≥ 11.1mmol/L
3. 2 hour OGTT BGL ≥11.1mmol/L
4. HbA1c ≥6.5%

If BGL ≥15, check ketones

If ketones present and/or <10yo, discuss with paediatric team ASAP (may be type 1 diabetes and will need insulin and hospital admission ASAP)

No ketones and very strong suspicion for T2D

******Need intensive support and early management to change long term outcomes******

Diagnostic and complications screening bloods/urine
(do at time of diagnosis)

FBC, EUC, LFTs, Lipids, TFTs
eGFR
Antibodies (IAA, IA-2, GAD)
C-peptide
Urine ACR

Complications screening
Yearly FBC/EUC/LFTs/Lipids/TFTs /eGFR/ urine
Mental health
BP each visit
Measure weight, height, BMI, waist circumference,
waist: height ratio (aim <0.5)
PCOS
OSA
Neuropathy
Eye review
Smoking/ alcohol use

Involve multidisciplinary team
1. Phone consult re new diagnosis & mgt plan with paed and/or paed endo (adult endo an option if 16-17yo)
2. AHP
3. Local chronic disease nurse
3. Remote diabetes educator
4. Dietitian review
5. Whole of family approach essential
6. Create care plan

Intensive early management "treat to target"
1. Metformin XR (titrate up, max 2g daily)
2. Add insulin if HbA1c≥8.5% (start 0.25-0.5U/kg/day, titrate up to reach targets, max 1.5U/kg/day)
3. Weekly review initially
4. Aim HbA1c <6.5%

Management of complications

Accelerated complications cf adults

- Retinopathy
- Microalbuminuria
- Monitor weight, height, BMI, waist circumference
- Blood pressure
  - Aim <95th centile for gender, age and ht
  - Aim <50th centile if renal disease
- Annual FBC, EUC, LFTs, TFTs, fasting lipids
- Lipid aims:
  - LDL-C < 2.6mmol/L
  - HDL-C >0.91mmol/l
  - Triglycerides <1.7mmol/L
- Mental health
- Neuropathy, feet
- Screen for PCOS, OSA, smoking, alcohol use

What are the barriers in management?

- Socioeconomic disadvantage
- Access to health services
- Competing health needs
- Shame of diagnosis
- Normalisation of diabetes in family
- Food insecurity
- Limited health service resources
- Limited local resources for lifestyle change
- Health literacy
- Mental health

Type 2 diabetes in youth is a disease of poverty

We commend the Review by Russell Viner and colleagues (June 3, p 2252)[1] on the topic of type 2 diabetes in adolescents. We were pleased that the authors acknowledged the crucial importance of the psychological and social challenges that adolescents with type 2 diabetes face. However, few clinical guidelines or expert recommendations acknowledge that these challenges might be grounded in the social conditions in which these adolescents live.[2] Specifically, a substantial proportion of young people with type 2 diabetes live in poverty or socially disadvantaged households (table).[3–7] Factors that typically co-exist with poverty, such as food insecurity, disparities in access to care, and related mental health challenges, make the adoption of behavioural lifestyle changes, a cornerstone in clinical management of type 2 diabetes, challenging.

	Sample size	Prevalence of poverty
SEARCH for Diabetes in Youth[3]	1589	44%*
TODAY cohort[4]	704	41%*
Pediatric Diabetes Consortium[5]	503	43%*
Pediatric Diabetes Consortium, age <10 years[5]	38	56%*
UK cohort[6]	391	32±16†
Canadian cohort[7]	342	59%‡

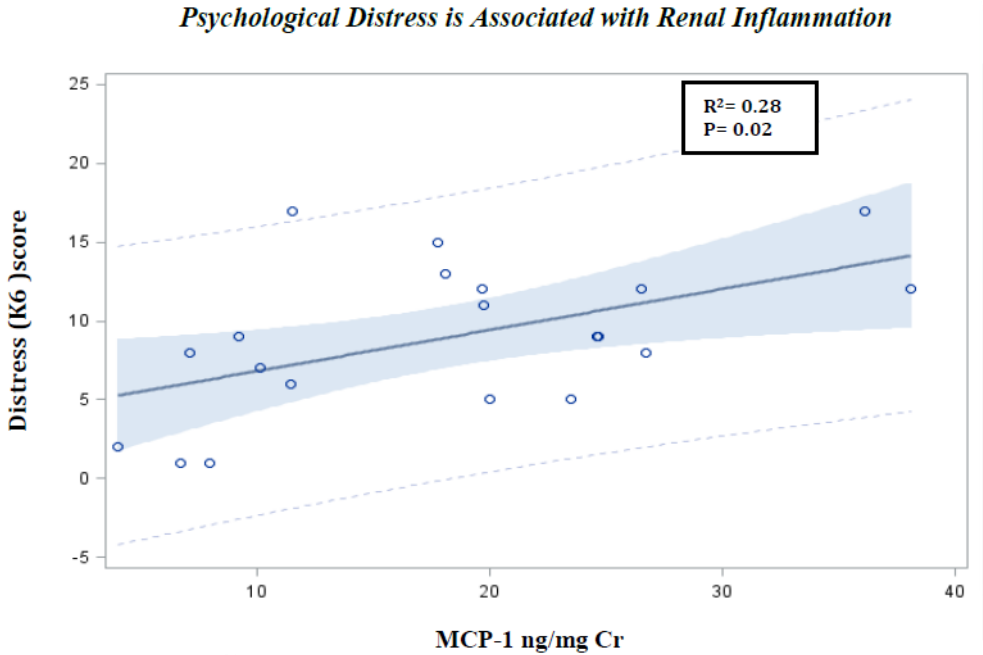
*Using percentage of household income of <US$25 000 as an indicator. †Using Index of Multiple Deprivation score as an indicator, expressed as mean±standard deviation. ‡Using lowest income quintile in region as an indicator.

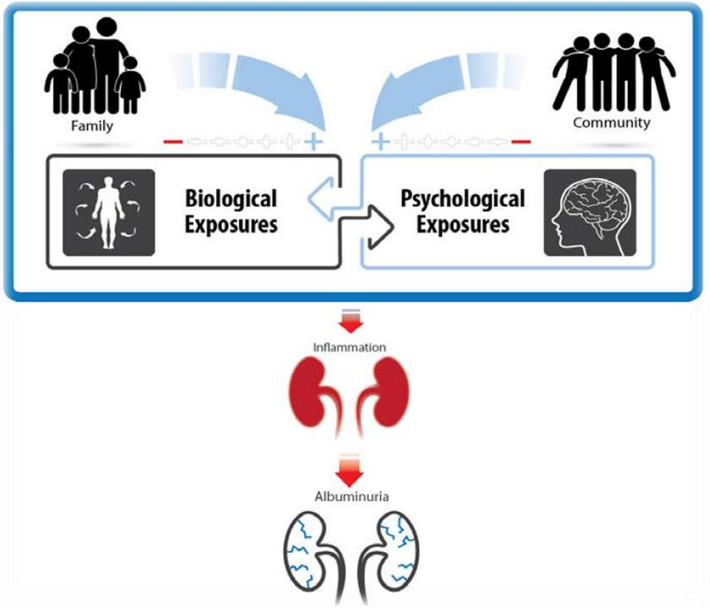
Table: **Prevalence of poverty among children and adolescents with type 2 diabetes in cohort studies**

McGovack et al, 2017. Lancet

Relationship between Distress and Renal Inflammation

Images courtesy of Brandy Wicklow (Manitoba, Canada)

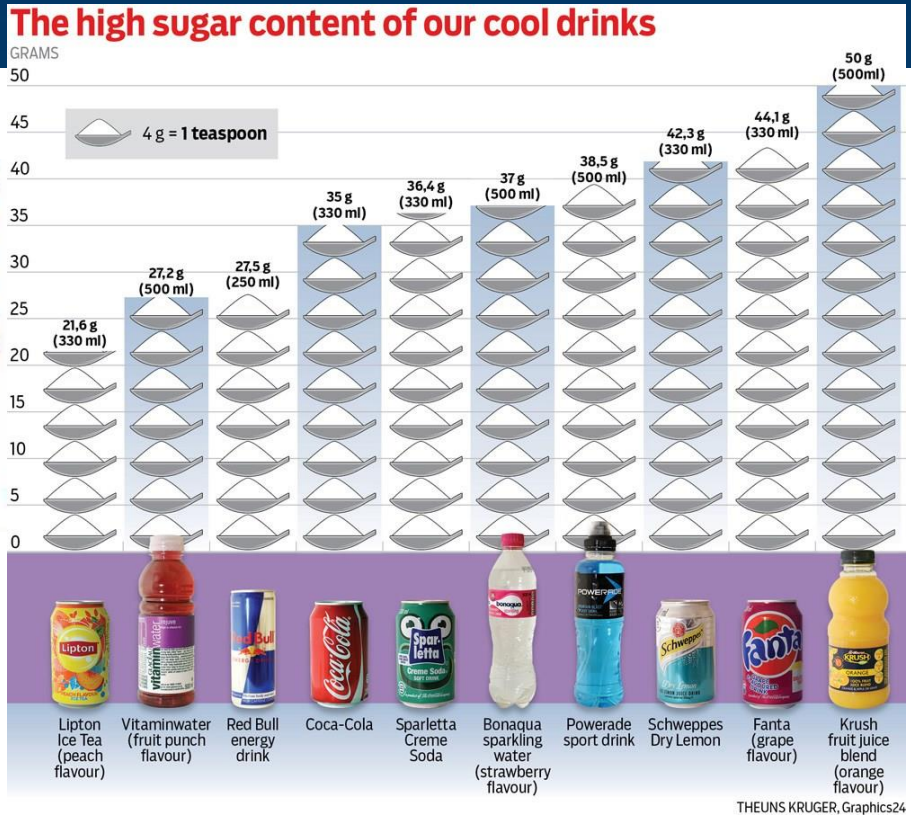




How do we engage young people and families?

- There is widespread fear (families and health professionals) about youth diabetes, particularly about ‘injections’
- Need to actively address those fears and allow plenty of time


If you drink 1 x 600ml regular soft drink every day for a year you will drink
23 KILOS OF SUGAR


The high sugar content of our cool drinks
GRAMS
50
45
40
35
30
25
20
15
10
5
0
4 g = 1 teaspoon
21,6 g (330 ml)
27,2 g (500 ml)
27,5 g (250 ml)
35 g (330 ml)
36,4 g (330 ml)
37 g (500 ml)
38,5 g (500 ml)
42,3 g (330 ml)
44,1 g (330 ml)
50 g (500ml)
Lipton Ice Tea (peach flavour)
Vitaminwater (fruit punch flavour)
Red Bull energy drink
Coca-Cola
Sparletta Creme Soda
Bonaqua sparkling water (strawberry flavour)
Powerade sport drink
Schweppes Dry Lemon
Fanta (grape flavour)
Krush fruit juice blend (orange flavour)
THEUNS KRUGER, Graphics24

Food security in remote communities

- Only 6% of housing has functioning food preparation space, storage facilities and cooking equipment
- Fresh food prices up to 70% higher than urban areas
- >30% report days without money in last 2 weeks
- >30% worry about going without food
- 38% of income spent on food (cf 13% Australia wide)

The future and the past….

Future trajectories post youth onset diabetes

- **High rate of complications**
  - 23x ↑ risk ESRF cf non-diabetic patients
  - Early foot ulceration (even 2 years post diagnosis)
  - 3.5x ↑ risk AMI cf later onset DM
- Complications at an early age
- **15 year reduction in life expectancy if diagnosed at <25yo**
- Pregnancies complicated by hyperglycaemia and increased risk to next generation

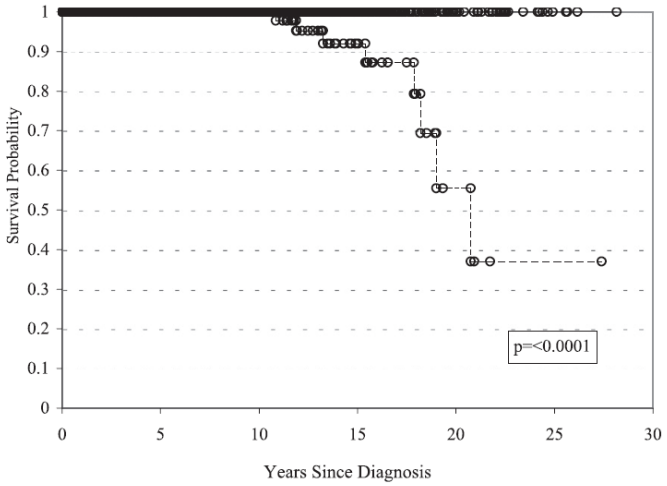


Figure 1—*Renal survival in youth-onset diabetic cohorts. Patients at risk are the number of patients in each group with follow-up to that time period. T1DM, ——; T2DM, - - - -.*

Renal Survival:

- 100% for T1 & T2 at 10yrs since diagnosis
- 15yrs: 92% T2 vs 100% T1
- 20yrs: 55% T2 vs 100% T1

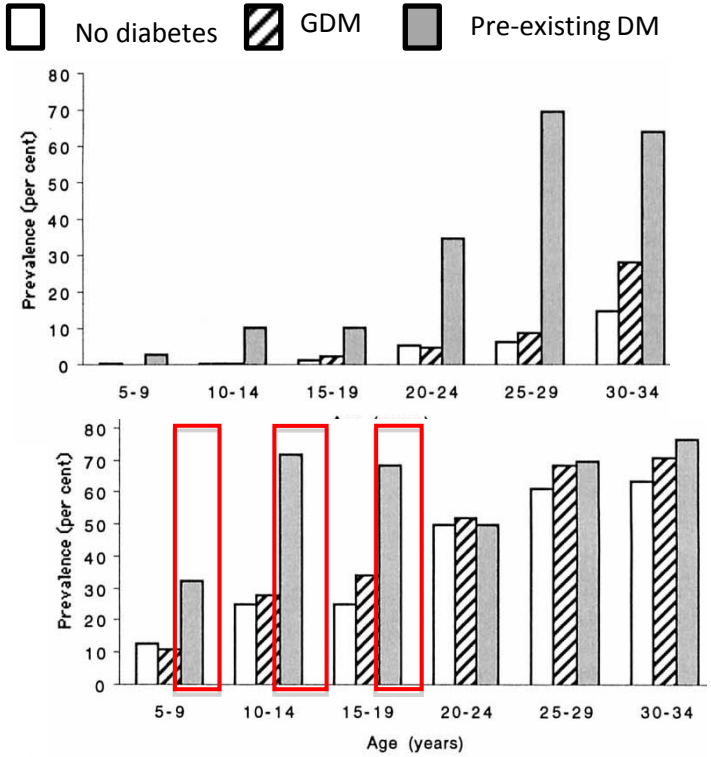
Rhodes et al, 2012. Diab Med.
Wilmot et al, 2014. Ther Adv Chron Dis
Dart et al, 2012. Diab Care

Intergenerational diabetes

- 90% of young people with diabetes have a parent or grandparent affected
- Altered growth patterns, obesity
- Hyperglycaemia in pregnancy:
  - ↑ risk of T2DM later in life, additive to genetic susceptibility (differing risk between siblings)
  - Continuum of risk
- ↑ BP

T2D

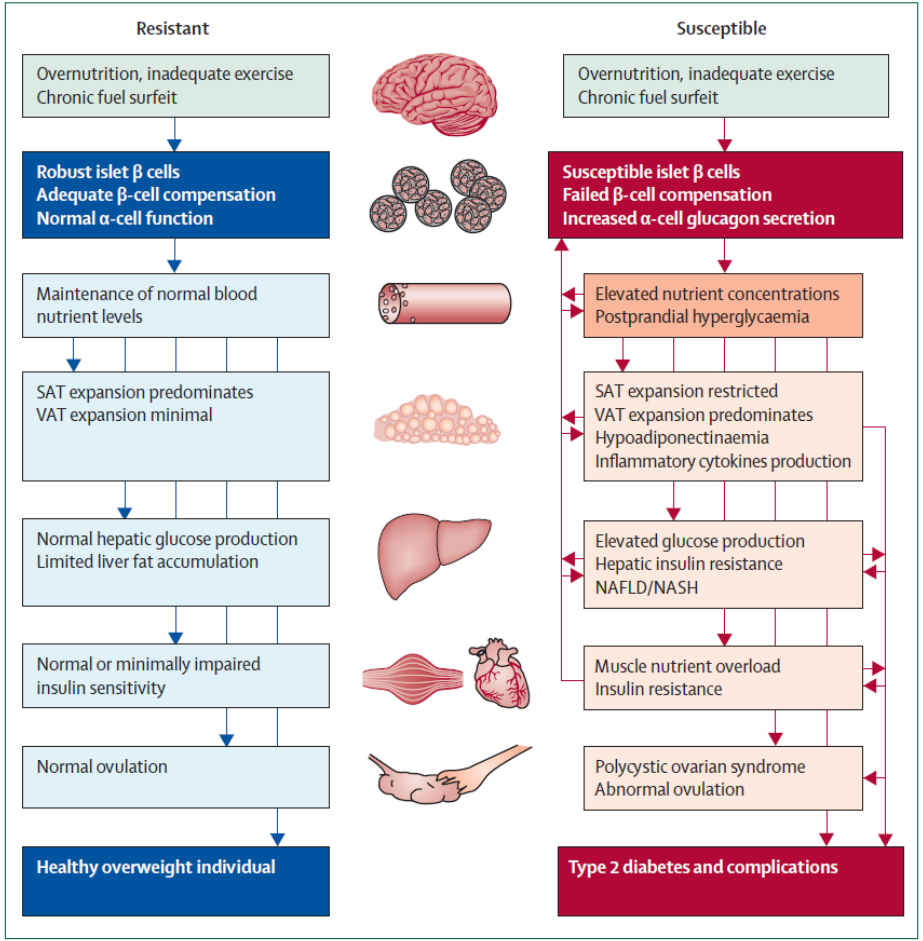
Obesity



Dabelea D et al. J Mat-Fet Med 2000; 9(1):83-8.
Dabelea D et al. Diabetes 2000; 49(12): 2208-11.
Dabelea D et al. Diabetes Care 2007; 30(2)

The scene is set early in life…..

- Interactions between environment, epigenetic changes, organ programming, neurohormonal signalling
- **Low risk individuals:**
  - Contain chronic fuel overload
  - Healthy β cells and increased s/c adipose tissue
- **At-risk young people:**
  - Unable to contain fuel overload
  - Vulnerable islets (susceptible to failure if overworked)
  - Adipose tissue develops an abnormal phenotype when stressed (visceral)
  - Leads to ↑ inflammatory cytokines
    - → stress and injury in multiple tissues, and Type 2 diabetes



Nolan et al, 2011. Lancet.

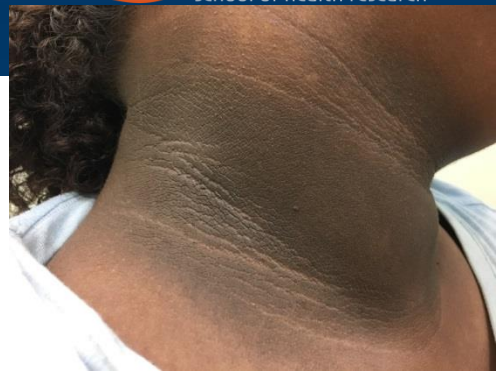
Screening and prevention

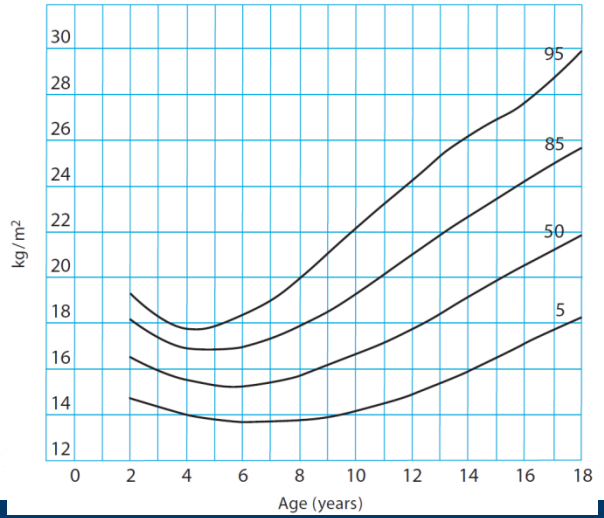
Screening

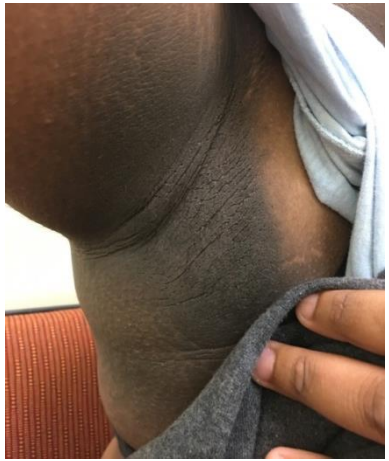
2012 Azzopardi et al (MJA)

From 10yo (or earlier if pubertal) in Indigenous children with any of:

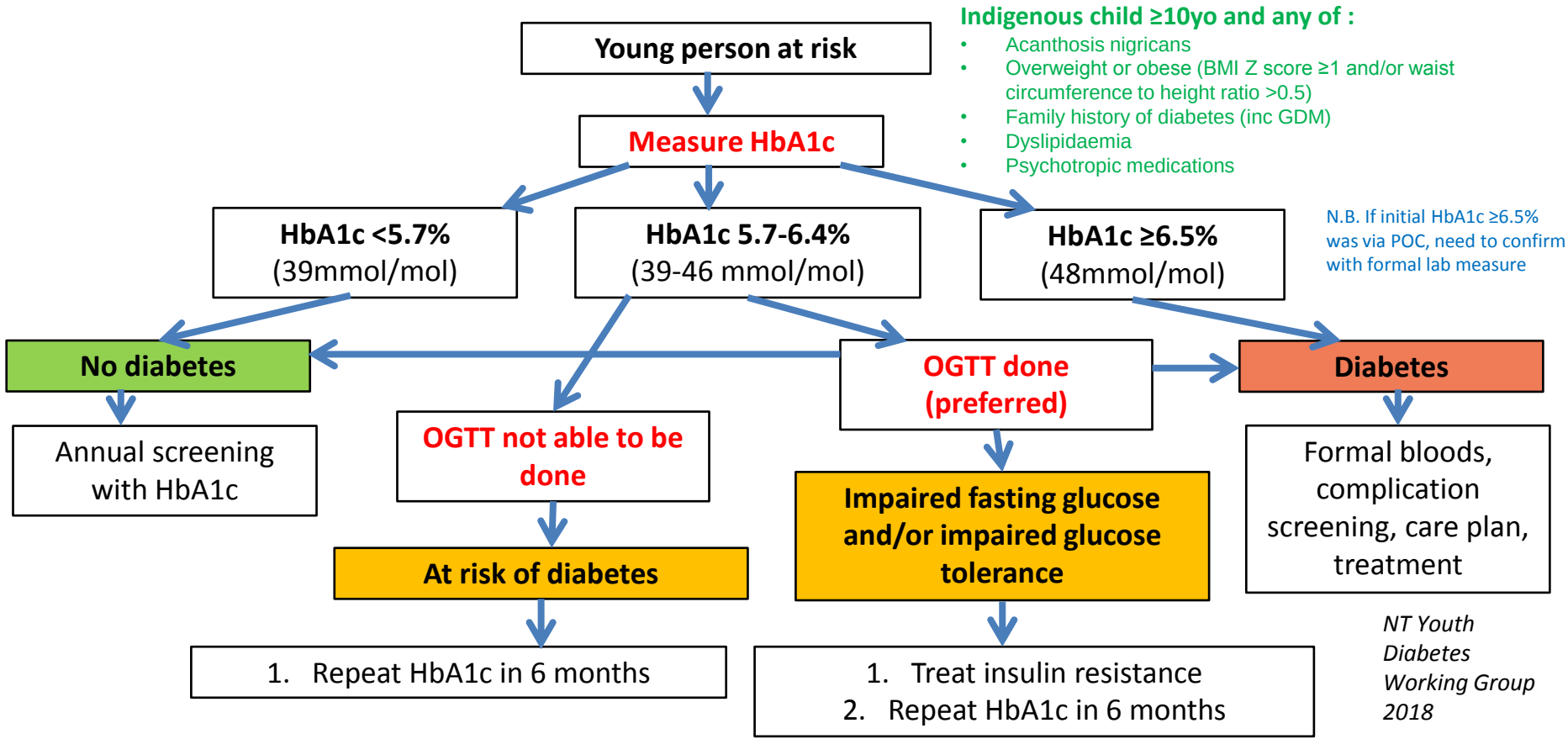
- Acanthosis nigricans
- Overweight or obese (BMI Z score ≥1)
- Family history of diabetes
- Dyslipidaemia
- Psychotropic medications
- Maternal history of diabetes in pregnancy







Screening pathway for type 2 diabetes in Aboriginal young people in NT



The complexities……

Prevention of youth onset diabetes

- Complex, no clear evidence
- Need to focus upstream of individuals
  - Multi-sector
  - Need innovative approaches
  - Whole of family, whole of community
  - Peer involvement
- Prevention of childhood obesity
- Target high risk families
- Interventions early in life (prevent intergenerational transmission)
- Address mental health
- Address social inequities

What don’t we know about youth onset T2D?

- How do we preserve β cell function long term?
- What treatments (or combinations) will be safe long term in young people and most effective?
- Why do some young people have such a severe phenotype?
- How and when to intervene to prevent intergenerational diabetes and metabolic disease?
- How are mental health issues and T2D best addressed?
- How do we prevent complications?

What don't we know in Australia?

- The true number of children and young people with T2D in northern Australia
  - *2018 Hot North Pilot project underway (Dr Aveni Haynes)*
- How do young people and families understand diabetes?
- What are the priorities of young people and families?
- How best to engage young people and avoid stigma?
- What is the best model of care?
- What innovative 'outside of the box' approaches will work?
- What is an effective intervention for childhood obesity in remote communities?

2018 Hot North Early Career Fellowship (Dr Renae Kirkham) and NHMRC 2019 grant (Prof Louise Maple-Brown)

2018 Central Australian Academic Health Science Centre grant (Leisa McCarthy, Renae Kirkham)

A call to action…..

"One cannot tackle the epidemic of diabetes without addressing the underlying social issues that contribute to the disease and create barriers to its management….."

Harris et al, 2016. Diab Res Clin Prac.

Systems change is required …..

"To make healthy choices, you've got to have healthy choices to make that are accessible and affordable.

It isn't easy, and that's why this isn't a conversation about individual choices; it's about systems."

Natasha Huey, project manager for the Bigger Picture (USA)

QUESTIONS?

GLP-1 agonists in young people (eg exenatide)

- Off license in <18yo
- Weekly s/c injection (bydureon, trulicity) only on PBS in conjunction with metformin
- Need contraception

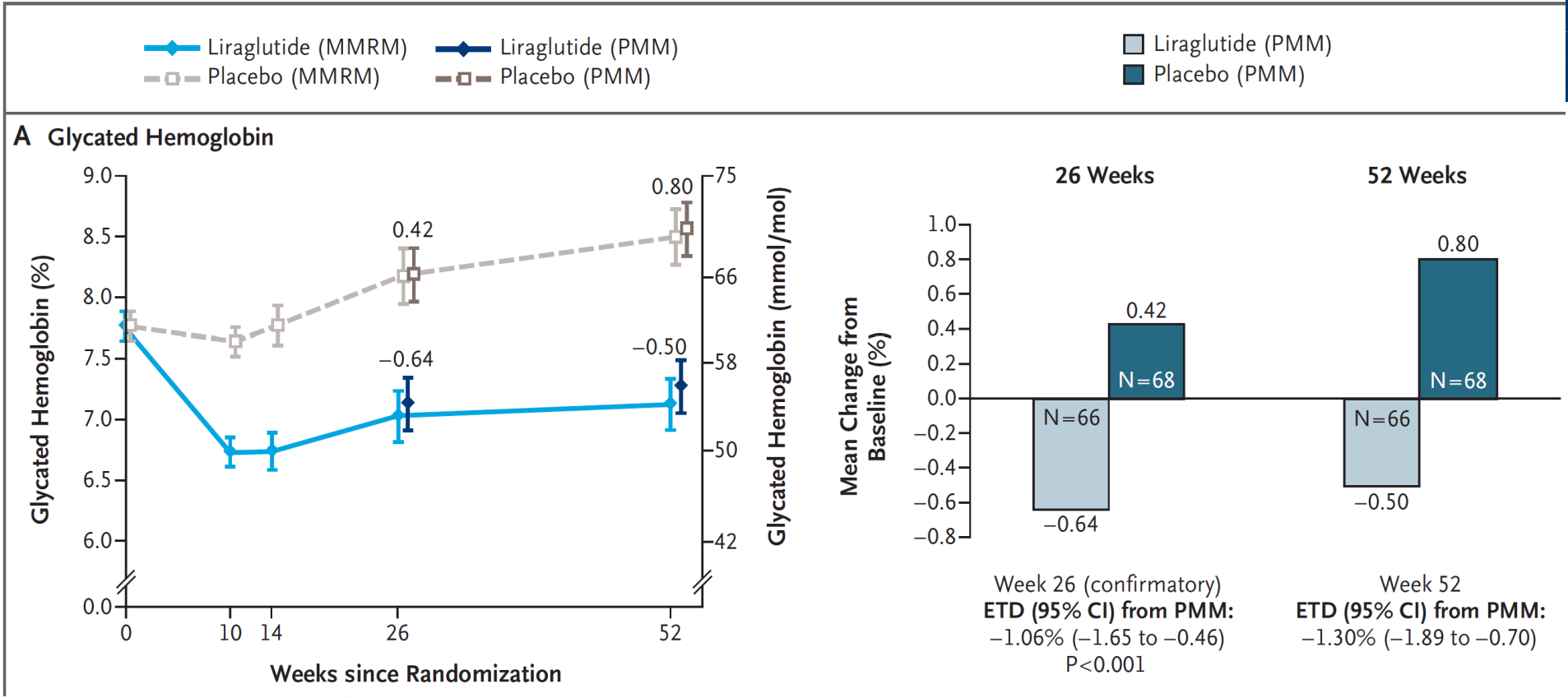
- Improved HbA1c (> 1%)
- Weight loss
- Improved ß cell function
- Low risk hypoglycaemia
- Weight loss
- Tachyphylaxis?
- Side effects mostly GIT related (20-60%)

  Nausea, hypoglycaemia, vomiting, headache, diarrhoea

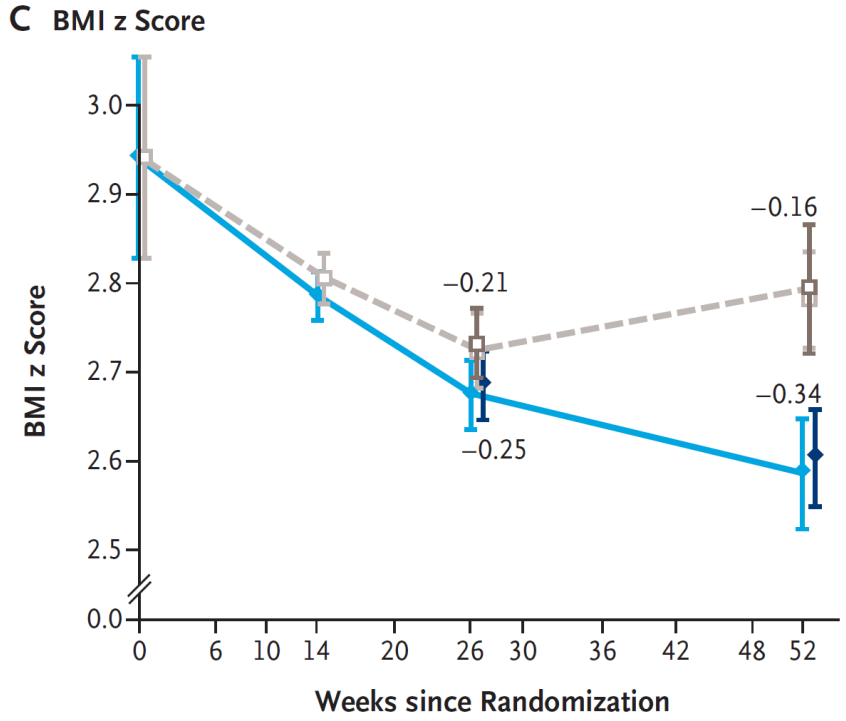
GLP-1 agonists – 2019 NEJM study

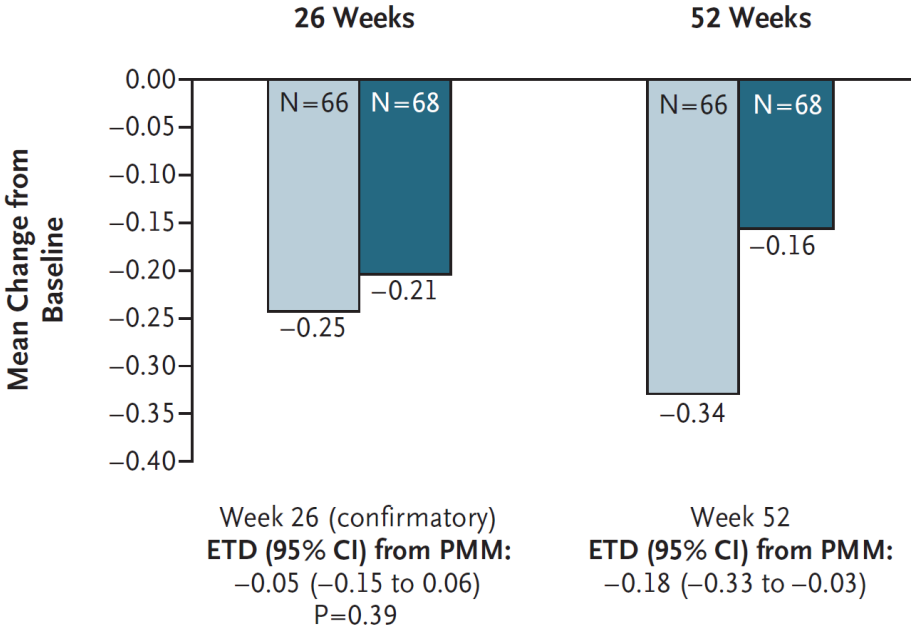
- 134 10-16yo patients (mean 14yo) , 52 week f/u – 84 countries
- All patients also on metformin +/- basal insulin
- Randomised to liraglutide (up to 1.8mg daily) or placebo
- <u>At one year:</u>
  - HbA1c ↓ by 1.3% with liraglutide cf placebo
  - GI side effects more common with liraglutide
  - 63.7% on liraglutide vs 36.5% achieved HbA1c <7%
  - 1.8mmol/L ↓ in fasting glucose with liraglutide
  - No difference in BMI

Tamborlane, WV. et al, 2019. NEJM.



Tamborlane, WV. et al, 2019. NEJM.





Tamborlane, WV. et al, 2019. NEJM.

SGLT-2 inhibitors (eg empagliflozin)

- Off licence in <18yo
- Beneficial in terms of weight loss (up to 3kg), BP (up to 5mmHg systolic), renal function (preserved), cardiovascular risk
- Inhibit renal tubular reabsorption of glucose
  - → ↑ urinary glucose loss, ↓ serum glucose, and weight loss
- Low risk hypoglycaemia
- **Similar efficacy to metformin**
- **↓ HbA1c by >0.5% when added to tx**

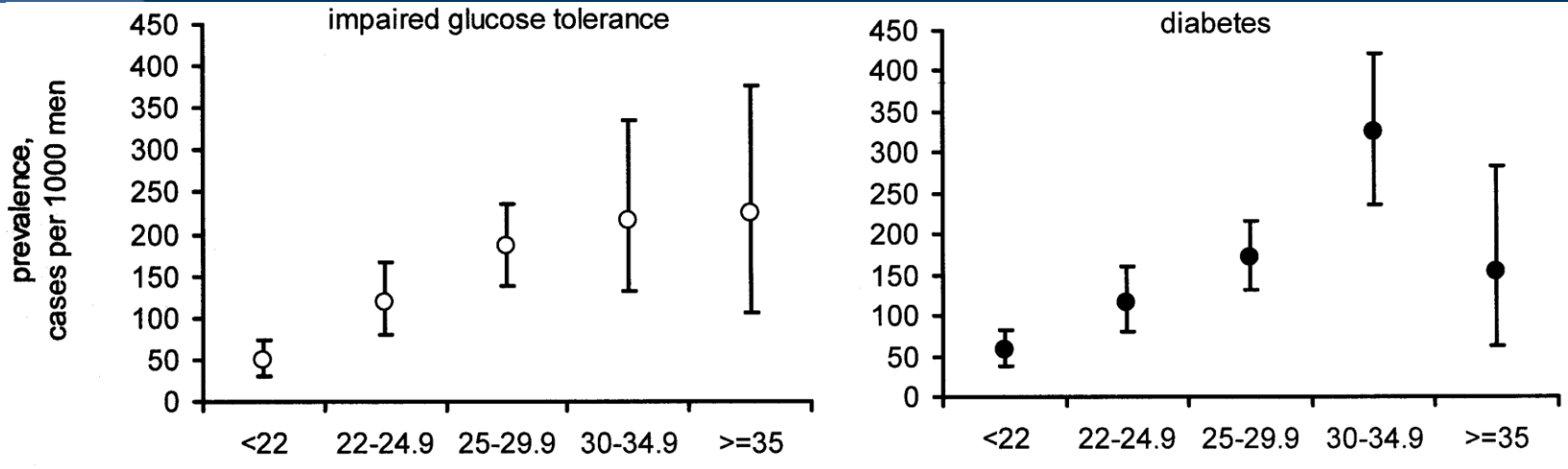
- Once daily

SGLT-2 Inhibitor concerns

- Appear to be well tolerated
- Use only if eGFR >45ml/min
- Need contraception
- Mechanism relies upon intact eGFR

- S/E:
  - **Euglycaemic DKA**
  - Genitourinary infections, thrush
  - UTIs
  - Syncope
  - ? Fracture risk
  - ? Bladder cancer risk

T2D risk and BMI in Indigenous Australians



Risk increases with BMI >22

- **Waist circumference better marker of risk than BMI**
  - Don't use centiles, follow trend over time
- **From 6yo, can use waist: height ratio >0.5 as indicator of risk**

Daniel et al, 2002. Diabetes Research and Clinical Practice; 57: 23–33