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 $> 7$mmol/L
   OR

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

3. 2 hour OGTT value $> 11.1$mmol/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 < 11.1 mmol/L

ISPAD guidelines 2018
Epidemiology
Youth onset diabetes worldwide

Type 2 diabetes in Indigenous young people

Incidence of type 2 diabetes in children aged <17 years in Western Australia (1990–2012), by Indigenous status

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

*Per 100,000 person-years at risk.
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, and 65% of deaths occur before 65 years of age, compared with 19% in the non-Indigenous population.

Cardiovascular and metabolic diseases are responsible for most of the gap in life expectancy and are associated with higher hospitalisation and mortality rates. 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. 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
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 puberty

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

- 80% of β-cell function is reduced or lost at diagnosis (cf 50% in adults)
- And further declines after diagnosis (2-4x faster loss than adults)
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 β cell function at diagnosis appears to be most important factor (i.e., insulin secretion more important than insulin sensitivity)
- Weight gain and BMI
- Mental health
- Puberty related insulin resistance
- Heterogenous population
  - Bimodal distribution

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?

Current treatment recommendations in <18yo (ISPAD 2018)

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

<table>
<thead>
<tr>
<th>HbA1c &lt;8.5% (69.4mmol/mol) and no symptoms</th>
<th>HbA1c ≥8.5% (69.4mmol/mol) or ketosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metformin</strong></td>
<td><strong>Need lantus</strong> 0.25-0.5U/kg/day</td>
</tr>
<tr>
<td>• Start at 500-100mg daily for 1-2 weeks</td>
<td>• Start <strong>Metformin</strong> at same time</td>
</tr>
<tr>
<td>• Titrate by 500mg every week until reach</td>
<td>• Transition to full dose metformin over</td>
</tr>
<tr>
<td>maximal dose of 1g bd</td>
<td>2-6 weeks while reducing insulin</td>
</tr>
<tr>
<td>• Then change to XR formulation (2g daily)</td>
<td>dose</td>
</tr>
<tr>
<td>as less side effects</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

If BGL ≥15, check ketones

No ketones and very strong suspicion for T2D

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**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%

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**Diagnostic and complications screening bloods/urine** (do at time of diagnosis)
- FBC, EUC, LFTs, Lipids, TFTs /eGFR/ urine
- Antibodies (IAA, IA-2, GAD)
- C-peptide
- Urine ACR

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**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

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

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**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%

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

Accelerated complications of adults

- Retinopathy
- Microalbuminuria
- Monitor weight, height, BMI, waist circumference
- Blood pressure
  - Aim <95<sup>th</sup> centile for gender, age and ht
  - Aim <50<sup>th</sup> 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) 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. Specifically, a substantial proportion of young people with type 2 diabetes live in poverty or socially disadvantaged households (table). Factors that typically coexist 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.

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Prevalence of poverty</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEARCH for Diabetes in Youth</td>
<td>1589</td>
</tr>
<tr>
<td>TODAY cohort</td>
<td>704</td>
</tr>
<tr>
<td>Pediatric Diabetes Consortium</td>
<td>503</td>
</tr>
<tr>
<td>Pediatric Diabetes Consortium, age &lt;10 years</td>
<td>38</td>
</tr>
<tr>
<td>UK cohort</td>
<td>391</td>
</tr>
<tr>
<td>Canadian cohort</td>
<td>342</td>
</tr>
</tbody>
</table>

*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**

4 g = 1 teaspoon

<table>
<thead>
<tr>
<th>Drink</th>
<th>Sugar Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipton Ice Tea (peach flavour)</td>
<td>21.5 g (330 ml)</td>
</tr>
<tr>
<td>Vitaminwater (fruit punch flavour)</td>
<td>22.2 g (500 ml)</td>
</tr>
<tr>
<td>Red Bull energy drink</td>
<td>27.5 g (250 ml)</td>
</tr>
<tr>
<td>Coca-Cola</td>
<td>35 g (330 ml)</td>
</tr>
<tr>
<td>Sparletta Creme Soda</td>
<td>36.4 g (330 ml)</td>
</tr>
<tr>
<td>Bonaqua sparkling water (strawberry flavour)</td>
<td>37 g (500 ml)</td>
</tr>
<tr>
<td>Powerade sport drink</td>
<td>38.5 g (500 ml)</td>
</tr>
<tr>
<td>Schweppes Dry Lemon</td>
<td>42.3 g (330 ml)</td>
</tr>
<tr>
<td>Fanta (grape flavour)</td>
<td>44.1 g (330 ml)</td>
</tr>
<tr>
<td>Krush fruit juice blend (orange flavour)</td>
<td>50 g (500ml)</td>
</tr>
</tbody>
</table>

THEUNIS KRUGER Graphics54
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

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

Renal Survival:

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

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

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

Indigenous child ≥10yo and any of:
- Acanthosis nigricans
- Overweight or obese (BMI Z score ≥1 and/or waist circumference to height ratio >0.5)
- Family history of diabetes (inc GDM)
- Dyslipidaemia
- Psychotropic medications

Young person at risk

- Measure HbA1c

HbA1c <5.7% (39mmol/mol)
- No diabetes
  - Annual screening with HbA1c
  - At risk of diabetes
    - 1. Repeat HbA1c in 6 months

HbA1c 5.7-6.4% (39-46 mmol/mol)
- OGTt not able to be done
- Impaired fasting glucose and/or impaired glucose tolerance
  - 1. Repeat HbA1c in 6 months
  - 2. Repeat HbA1c in 6 months

HbA1c ≥6.5% (48mmol/mol)
- OGTt done (preferred)
- At risk of diabetes
  - 1. Treat insulin resistance
  - 2. Repeat HbA1c in 6 months

Diabetes
- Formal bloods, complication screening, care plan, treatment

N.B. If initial HbA1c ≥6.5% was via POC, need to confirm with formal lab measure

NT Youth Diabetes Working Group 2018
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…..”

“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
- **At one year:**
  - 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.
A Glycated Hemoglobin

Week 26 (confirmatory) ETD (95% CI) from PMM:
-1.06% (-1.65 to -0.46)
P<0.001

Week 52 ETD (95% CI) from PMM:
-1.30% (-1.89 to -0.70)

Tamborlane, WV. et al, 2019. NEJM.
C  BMI z Score

Week 26 (confirmatory)
ETD (95% CI) from PMM:
-0.05 (-0.15 to 0.06)
P=0.39

Week 52
ETD (95% CI) from PMM:
-0.18 (-0.33 to -0.03)

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