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Diabetes in Indigenous young people: management and prevention complexities

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February 2018

Outline

- Diagnostic criteria
- Epidemiology of youth onset diabetes
- Pathophysiology of T2DM in young people
- 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

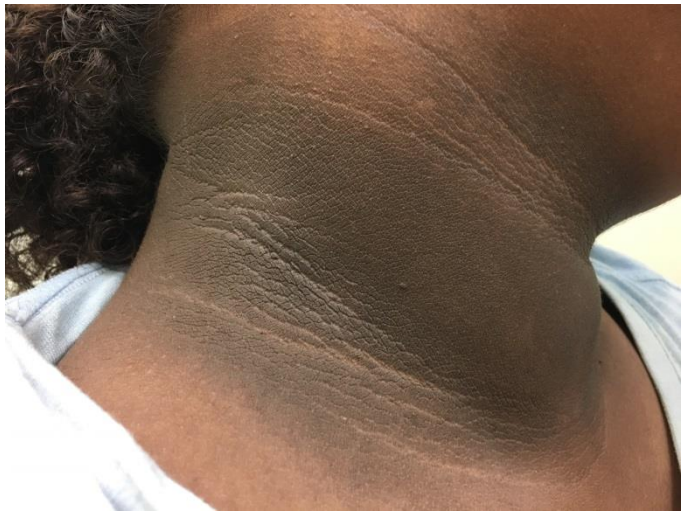
2. Classic symptoms (polyuria, polydipsia, weight loss) and random BGL ≥ 11.1mmol/L

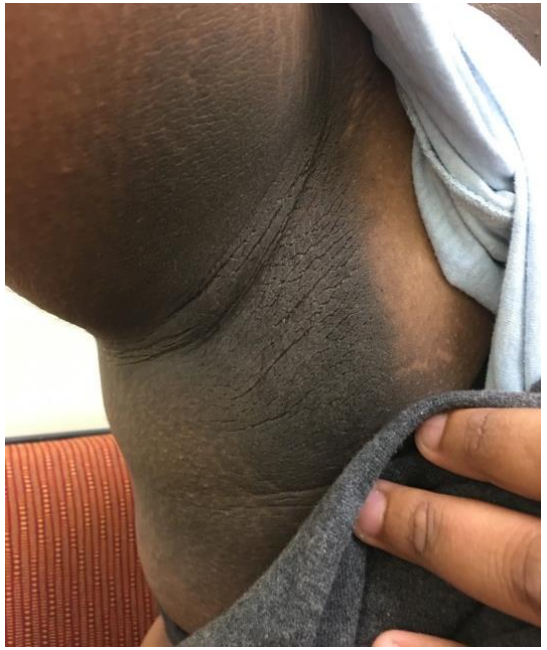
OR

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

OR

4. **HbA1c > 6.5% (not POC)**





ISPAD 2018 guidelines

* N.B. Not in CARPA 7th ed.

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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

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Epidemiology

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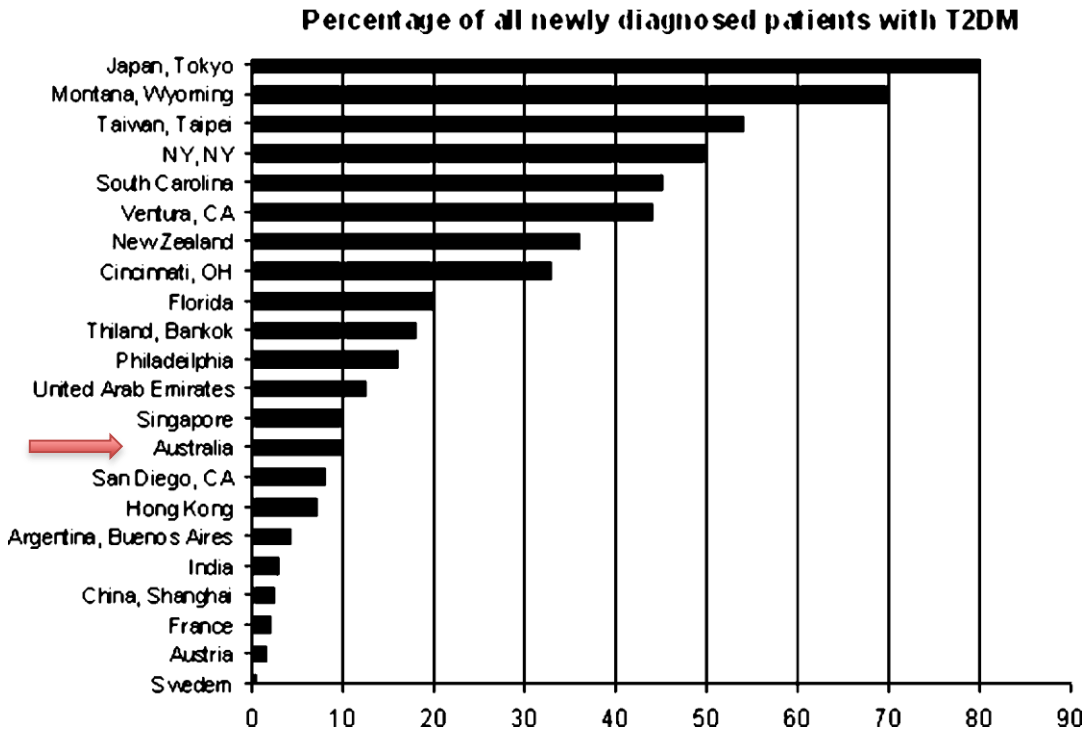
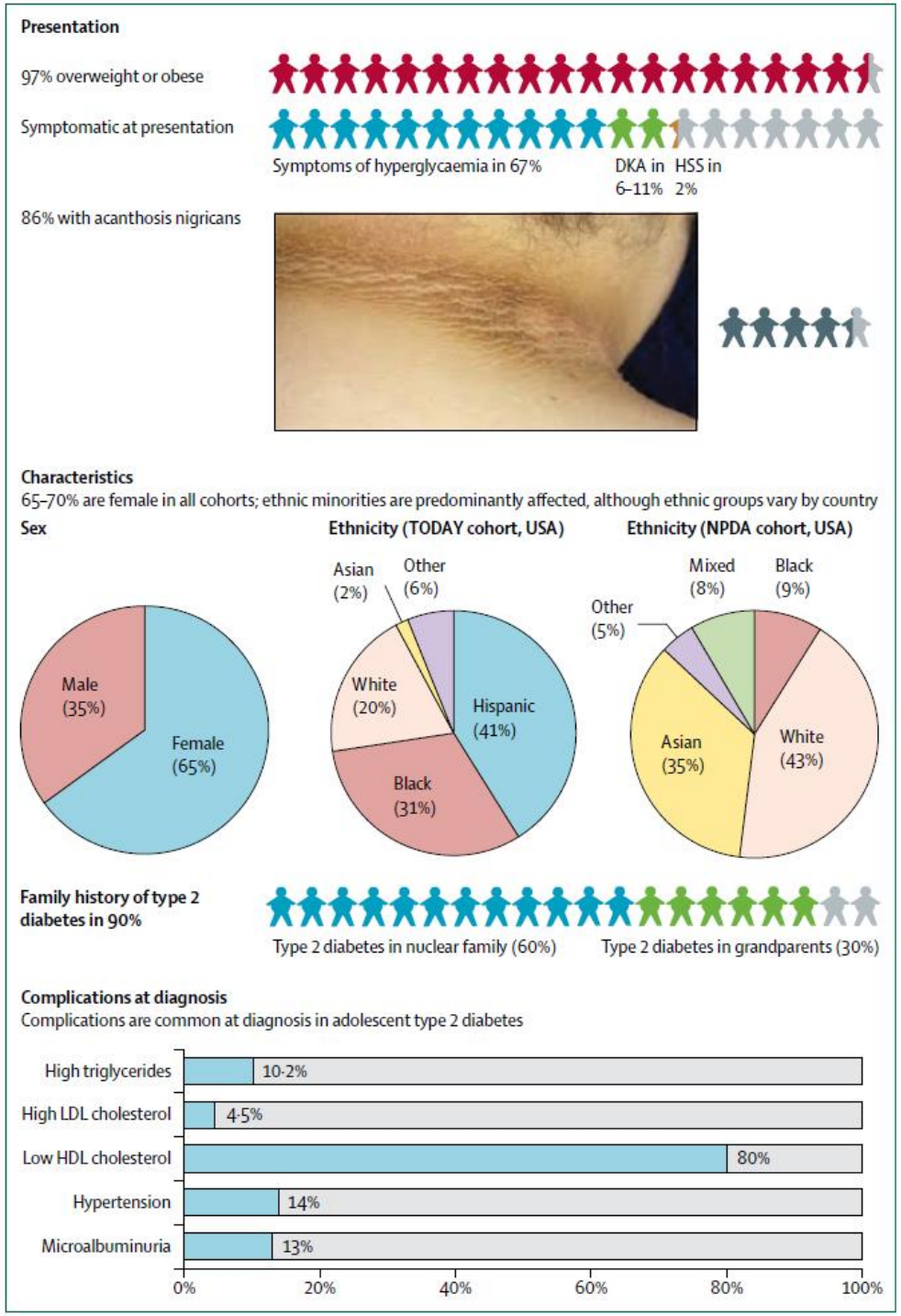
Youth onset diabetes worldwide





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, Dyanne Wilson, Ashim Sinha

Lancet 2014; 383: 1268

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Correspondence to: Dr Dev Kevat, Cairns Diabetes Centre, 165 Sheridan St, Cairns, QLD 4870, Australia dev.kevat@monash.edu

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 95th 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 (1·6 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 <1·0). 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.

Figure: Acanthosis nigricans

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 trial 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-BMS; been on speakers bureaus for Eli Lilly, AstraZeneca-BMS, 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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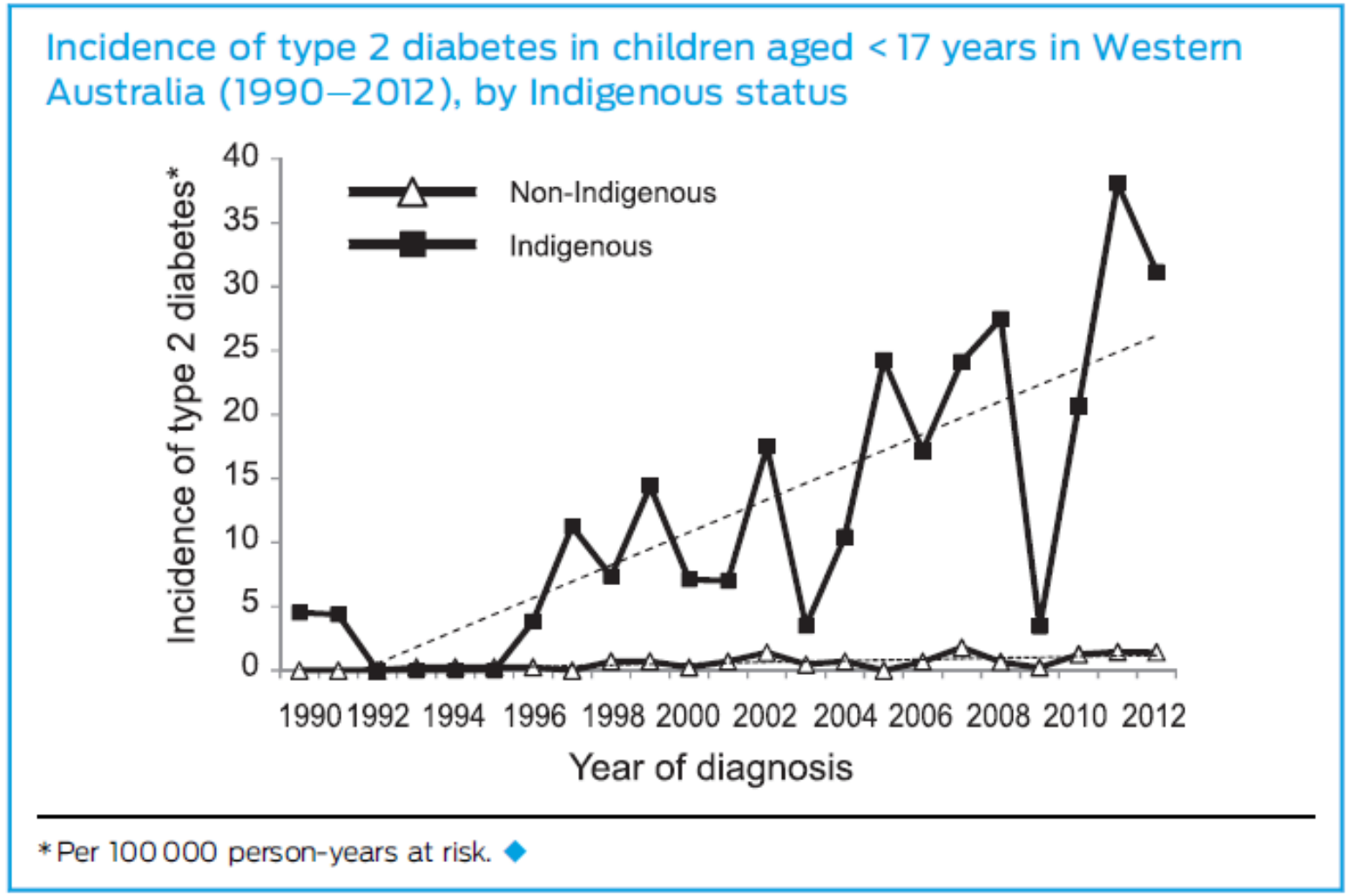
3 Dabelea D, Hanson R, Lindsay R, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant siblings. Diabetes 2000; 49: 2208–11.

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.

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



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Youth onset diabetes in the Top End

Retrospective study: 2007-2011

Top End population <25 years: 74 100

	Type 1 Diabetes	Type 2 Diabetes
Number	70	37
Female	38 (54%)	33 (89%)
Aboriginal &/or Torres Strait Islander	12 (17%)	31 (84%)
Age (yrs)	17 (6-24)	22 (10-25)
Age at diagnosis (yrs)	10 (2-22)	18 (10-25)
HbA1c (%, mmol/mol)	9.3% (6.7-14) 78 mmol/mol (50 -130)	10.5% (5.2-14.1) 91 mmol/mol (33 -130)

Data are n (%) or median (range)

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Stone M et al, J Paed Child Health, 2013; 49: 976-979

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Pathophysiology

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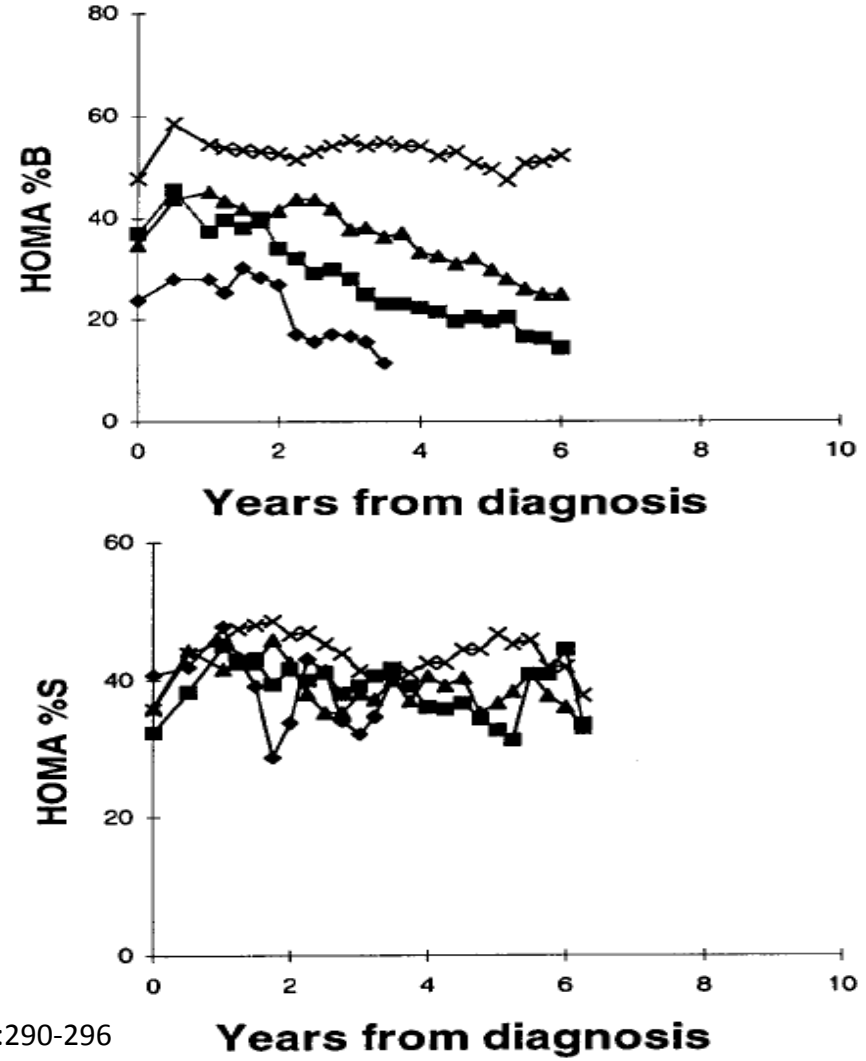
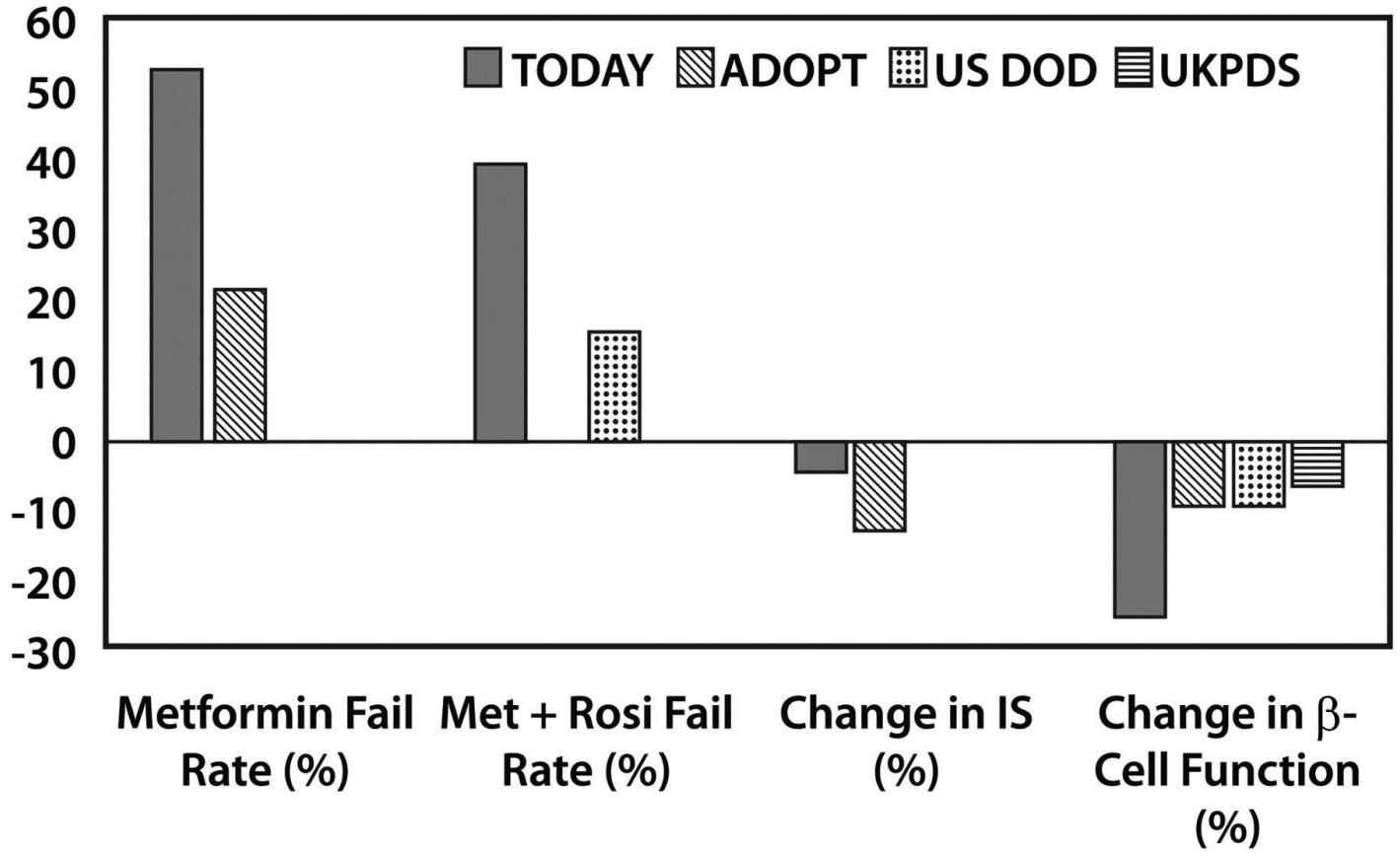
Pathophysiology of type 2 diabetes in young people

- **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
  - Insulin sensitivity does not change over time



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

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

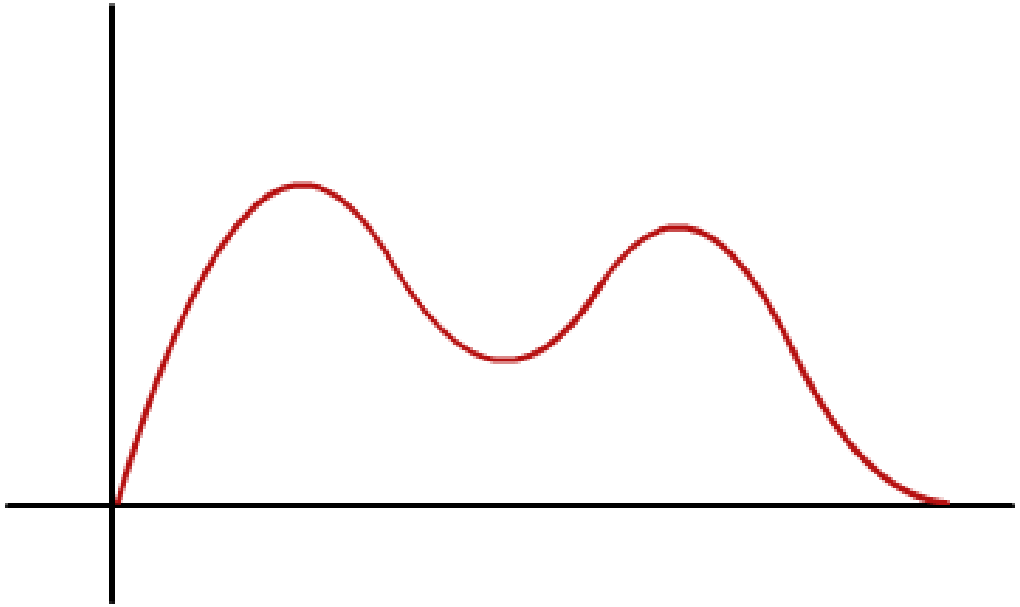


- **80% of ß-cell function is reduced or lost at diagnosis** (cf 50% in adults)
- And further declines after diagnosis (2-4x faster loss than adults)

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

What determines glycaemic control in young people with T2DM?

- 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



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

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

Treatment

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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

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)

Current treatment recommendations in 18-25yo (CARPA 2017)

Lifestyle changes

↓

Metformin (reduce dose in renal impairment)

↓

Add second agent

- Exenatide (GLP1 agonist) *
- SGLT2 inhibitor *
- Insulin
- Gliptin (DPP4 inhibitor) *
- Gliclazide MR (Sulfonylurea) *
- Pioglitazone (thiazolidinedione)

↓

Add third agent

** Avoid in pregnancy*

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)
- Annual FBC, EUC, LFTs, TFTs, fasting lipids, Vitamin D
- 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

The future and the past….

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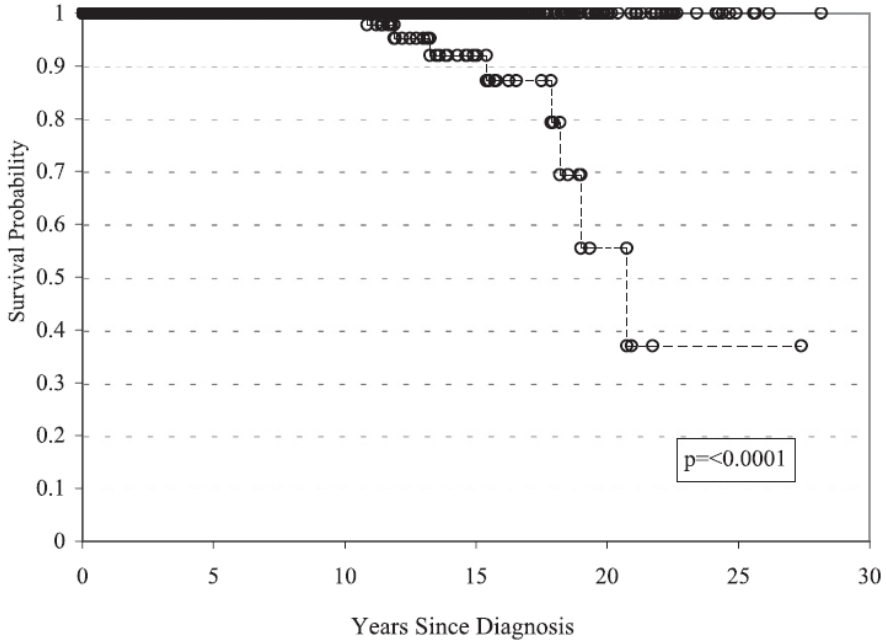
Future trajectories post youth onset diabetes

- **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



Patients at risk

T1DM	1,011	608	365	152	37	4
T2DM	342	153	56	25	6	1

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

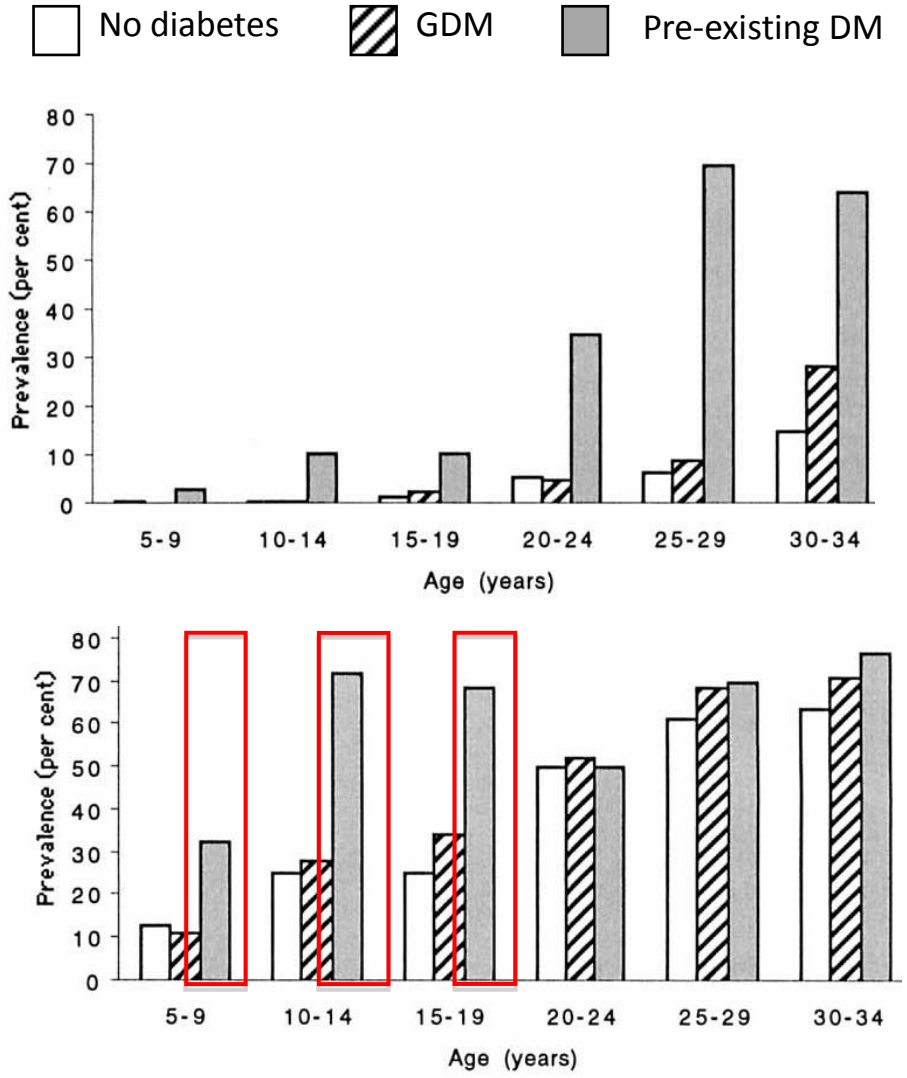
Rhodes et al, 2012. Diab Med.
Wilmot et al, 2014. Ther Adv Chron Dis
Dart et al, 2012. Diab Care

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

T2DM

Obesity



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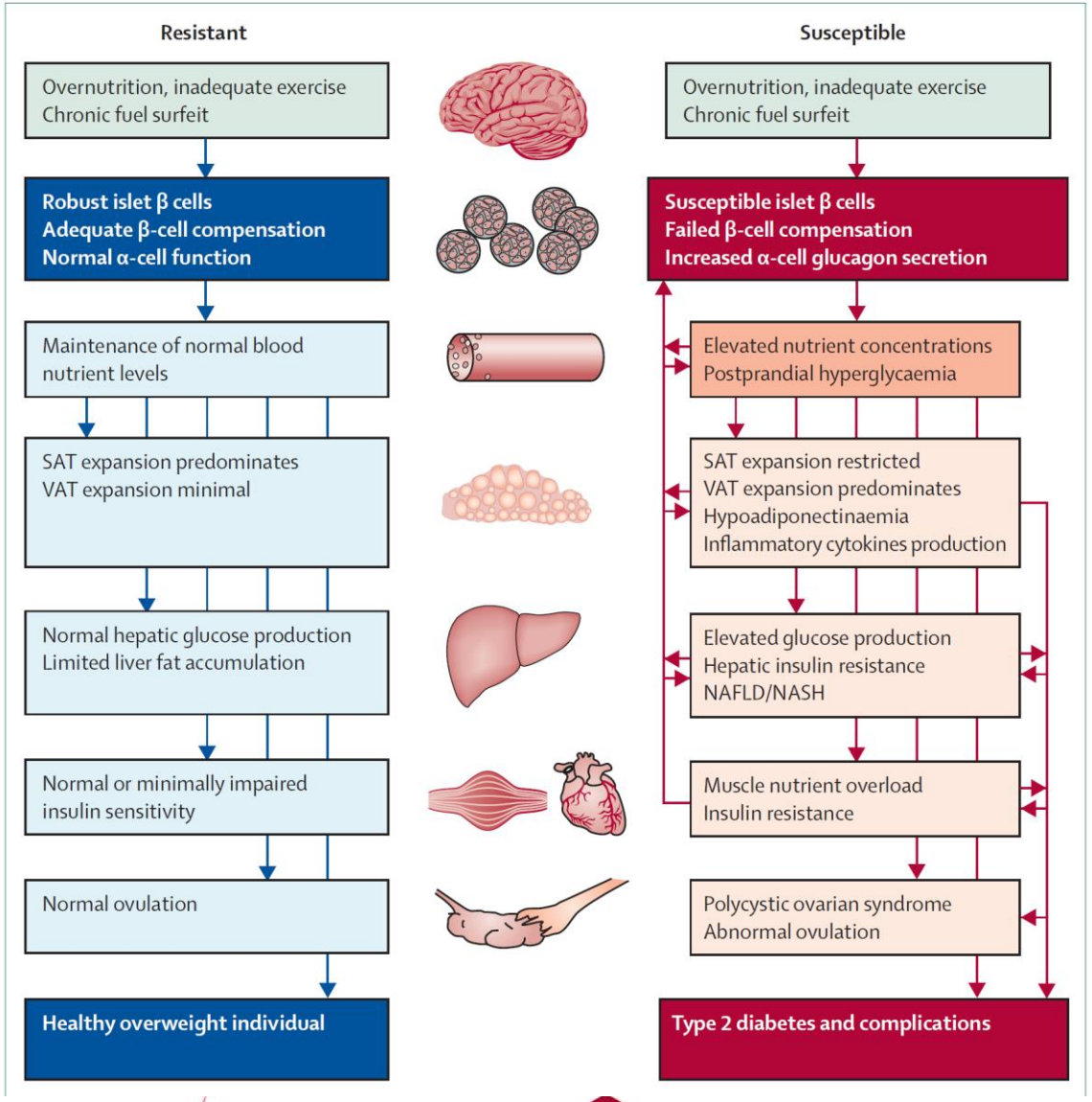
Dabelea D et al. Diabetes Care 2007; 30(2)

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

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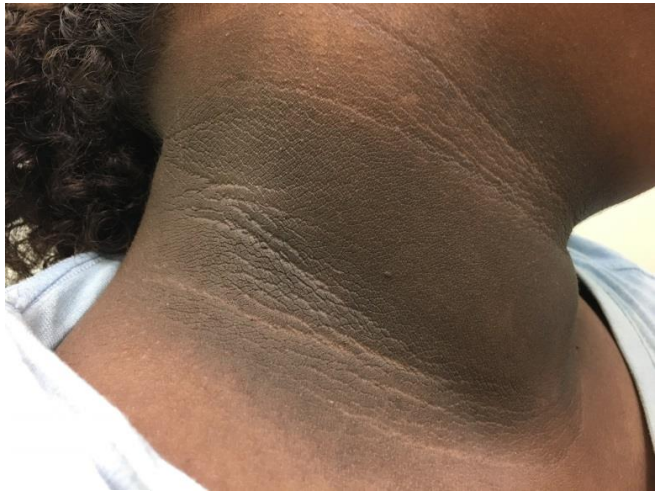
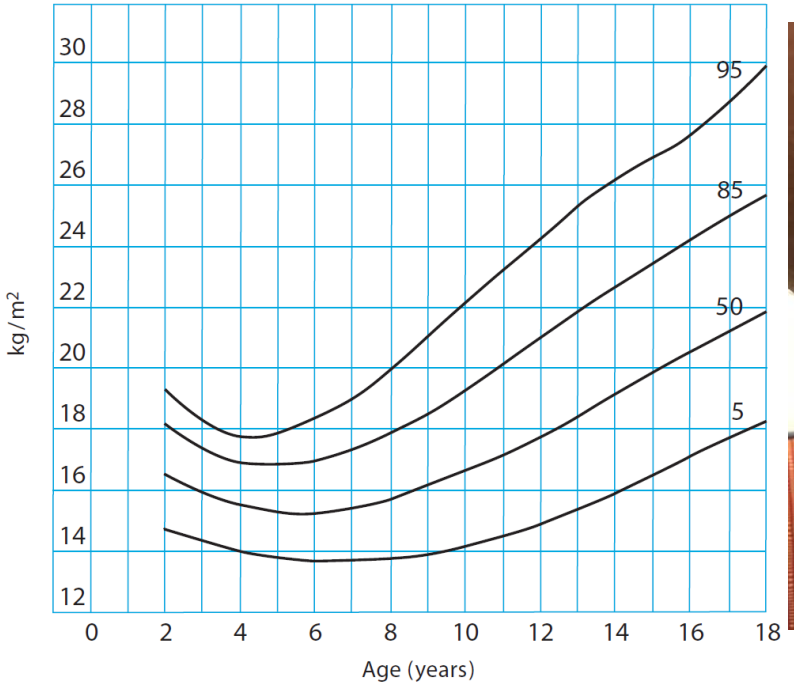
Screening

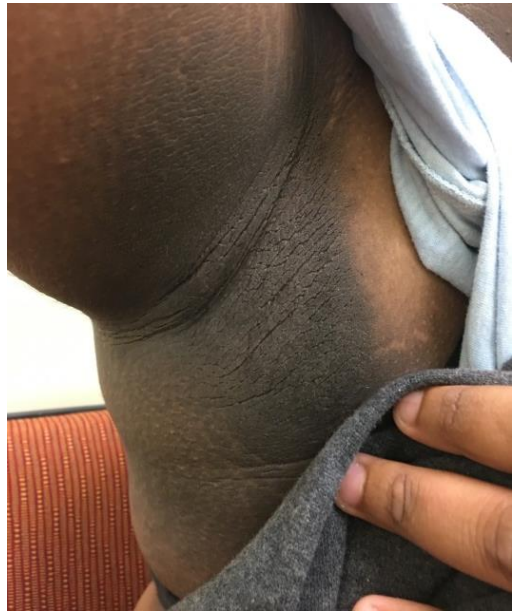
2012 Azzopardi et al (MJA)

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







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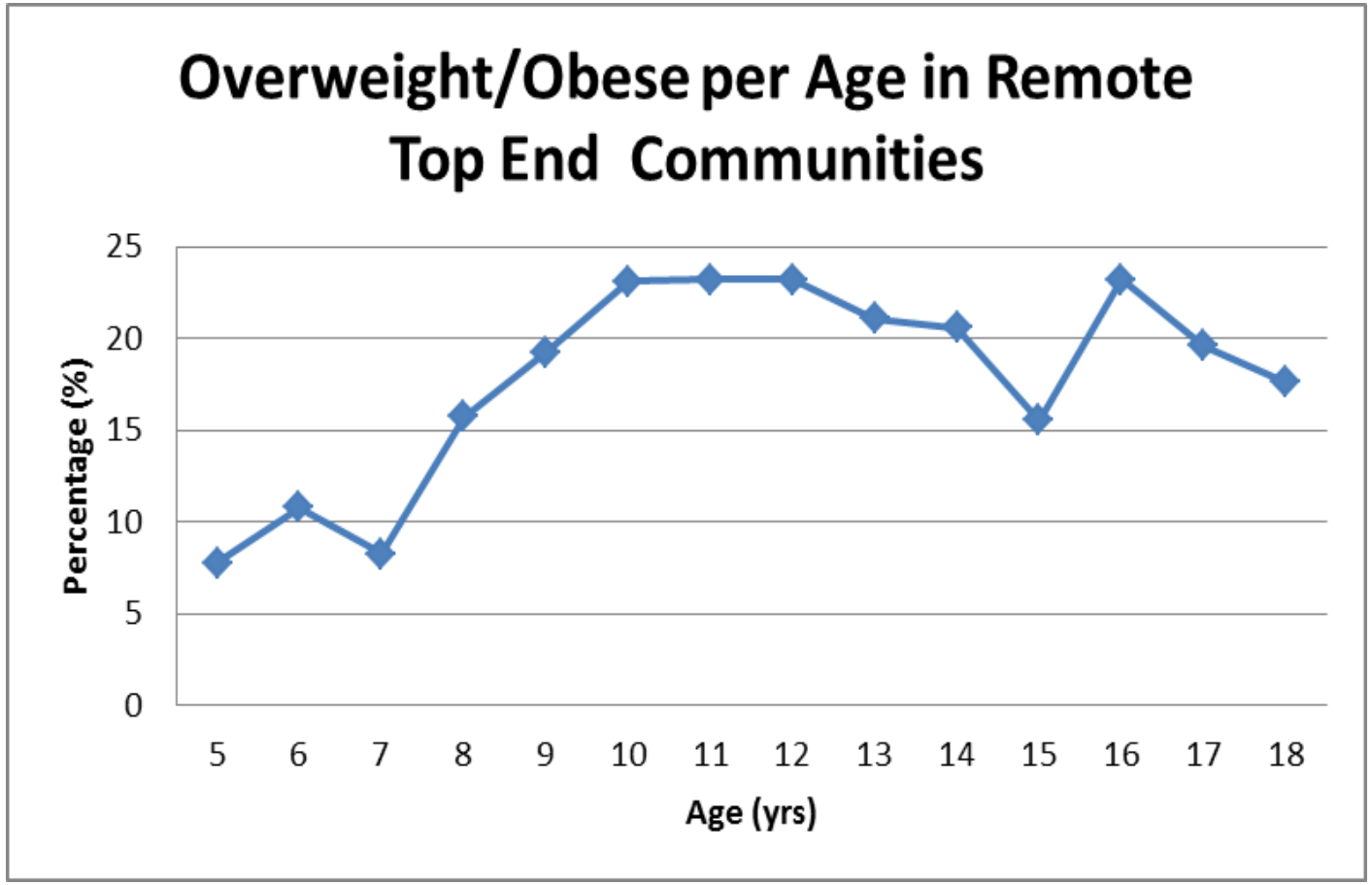
Childhood obesity in Top End

- 2017 audit by remote nutritionists of TEHS PHC sites (data courtesy of Khia de Silva)
- Only 42% of children <15yo had both height and weight measured (so unknown BMI in 58%)
- Obesity rates increase from 7yo, large regional variation
- Only 21.5% of obese children were identified as such in PCIS, only 10% given care plan



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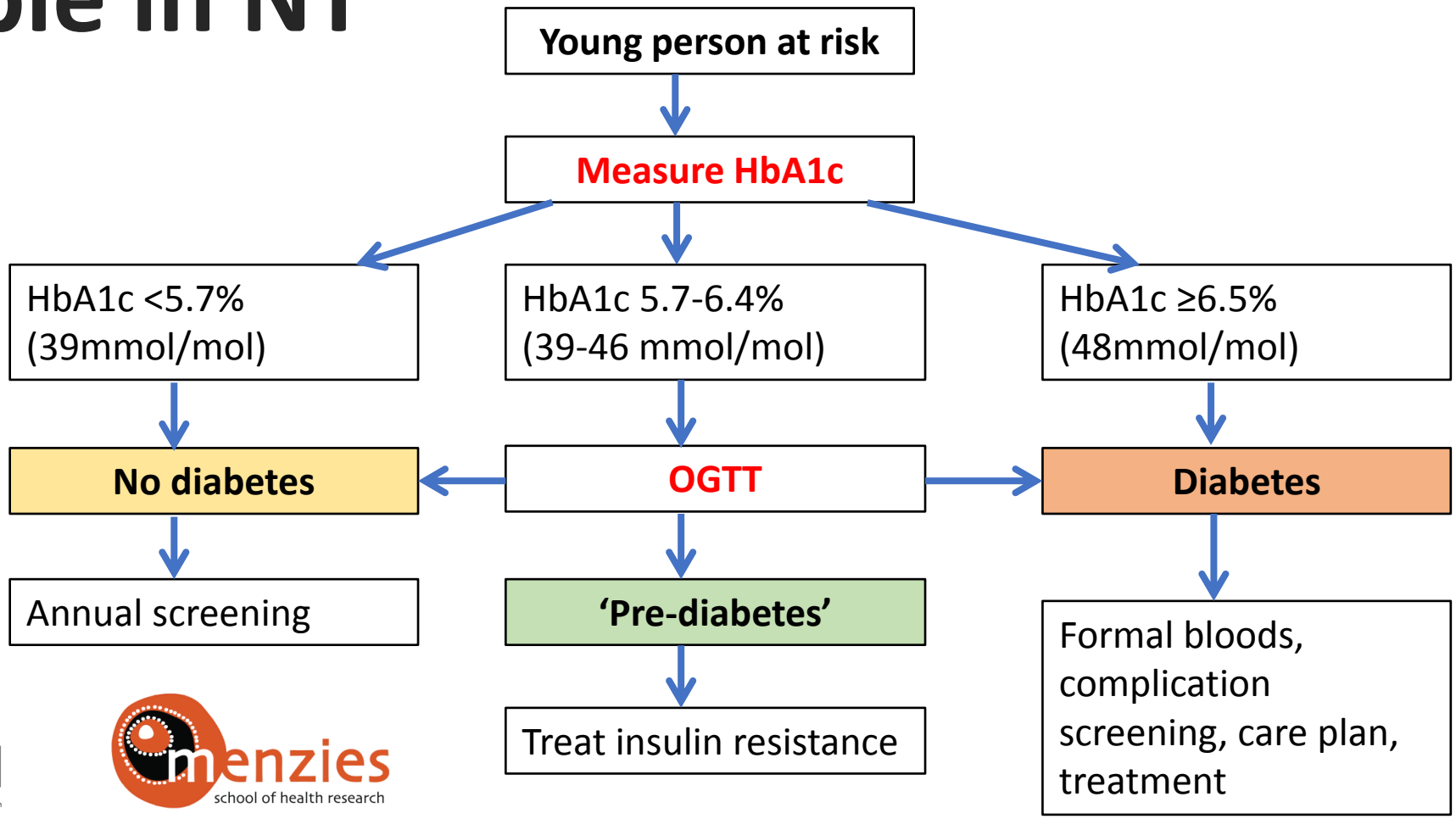
Is there any evidence for screening if no indication of insulin resistance?

- **Limited**
- **Canadian First Nations** (Dean et al 1998)
  - Recommend screening from 7yo
  - 15% of children with T2DM were <10yo (all obese, all with insulin resistance and asymptomatic)
- **USA** (Baranowski et al 2006)
  - Fasting and OGTT detected <1% T2DM prevalence in high risk ethnicity adolescents
  - 5.6% had IFG, 2% had IGT, 36% with insulin resistance (all high BMI)
- **Japan** (Urakami et al 2007)
  - School aged screening for urinary glycosuria

Suggested screening pathway for young people in NT



NT Youth Diabetes Working Group 2018

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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
- Prevention of childhood obesity
- Target high risk families
- Interventions early in life (prevent intergenerational transmission)
- Address mental health

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The complexities……

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What don’t we know about youth onset T2DM?

- 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 T2DM best addressed?
- How do we prevent complications?

What don’t we know in the NT?

- The true number of children and young people with T2DM in NT (and 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)

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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.

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QUESTIONS?

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