Screening for and managing early type 1 diabetes

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ABCD Webinar Oct 2024





Conflicts

- Clinical expert for NICE on teplizumab
- Advisory board: Abbott, Lilly, Insulet, Sanofi
- Speaker fees: Lilly
- Shares: Nil
- Grant funding: Nil

Insulitis



From Anne Cooke, University of Cambridge

Natural history of T1D



time



Rates of retinopathy according to baseline C-peptide



Rates per 100 Participant years

DCCT

C peptide and early T1D





Alice Carr 2022

The benefits of preserving C peptide on glucose control



Golimumab in new onset T1D



Quattrin 2020

ORIGINAL ARTICLE

An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes

- 76 first degree relatives at risk of T1D (Stage 2)
- Age 8-49 (most under 18 years)
- 2-week intervention with daily IV infusion of anti CD3
- 6 monthly OGTT for 5years

Herold NEJM 2019

Suppressing the immune system in those <u>at-risk</u> of T1D



Hazard ratio 0.41

Rates of diagnosis/year 15% vs 36%

Median time to diagnosis 48 months vs 24 months





FIRST EVER TREATMENT TO DELAY TYPE 1 DIABETES IS LICENSED IN THE US

2022-11-17

The US Food and Drugs Administration (FDA) has approved the world's first ever immunotherapy for type 1 diabetes, teplizumab, also called Tzield. This is the biggest treatment breakthrough for the condition since the discovery of insulin 100 years ago.

Show me more

Is there a cure for diabetes?



66 What is teplizumab? 79



First ever drug to delay type 1 diabetes **approved!**

idrf.orgi



Home > NICE Guidance > Conditions and diseases > Diabetes and other endocrinal, nutritional and metabolic conditions > Diabetes

Teplizumab for delaying the onset of type 1 diabetes in people 8 years and over at risk of developing the condition TS ID 10753

Awaiting development [GID-TA10981] Expected publication date: TBC

Submission due 2024

Can we tell who will get type 1 diabetes?

Autoantibodies predate and predict disease





2 or more autoantibodies imply near-definite progression to T1D



Zeigler 2013



ISPAD Clinical Practice Consensus Guidelines 2018 ADA Classification and Diagnosis of Diabetes 2021

Glucose challenge stratification of T1D risk in those that are positive for 2 or more Ab



OGTT (HbA1c)

Stage 1 Fasting: <5.6 2hr: <7.8 (HbA1c <39mmol/mol)

Stage 2 Fasting: 5.6-6.9 2hr: 7.8-11.1 (HbA1c 39-47mmol/mol)

Stage 3 Fasting: >7.0 2hr: >11.1 (HbA1c >48mmol/mol)





International SNOMED Code 'Presymptomatic type 1 diabetes'

- Suggested term: Presymptomatic type 1 diabetes
- Summary of request: Presymptomatic type 1 diabetes is a recognised precursor to type 1 diabetes, which does not require insulin treatment but there is no clinical code.
- The code was released by SNOMED International this month [October 2023]:
- 1290118005 | Presymptomatic diabetes mellitus type 1 (disorder).



Benefits of screening for T1D



FR1DA, Ziegler 2020. Duca 2018. Herold 2019.

Patient groups Clinical benefits Research interest



Cost Distress Practicalities

UK National Screening Committee

Issues in establishing an early surveillance programme for T1D in the UK















The **XELSA** Study

Population Intervention Comparator Outcomes Children aged 3-13 years Screening trial Usual care Feasibility and Acceptability









Research Active GP practices 40%

Community Research Nurses 25





Community Pharmacies for recruitment

Community Pharmacies for blood sampling

'Piggy backing' e.g. vaccine programme

Recruitment through schools











Community Connexions



ELSA Community clinics











Screening test – Dried Blood Spot







RSR-3 screen: GAD, IA2, ZnT8, + IAA GAD, IA2, ZnT8









Screen-detected type 1 diabetes is identified at an earlier stage of its natural history

Objective

A case series to describe the identification and management of general population screendetected type 1 diabetes (T1D) and share learnings for best practice.





LM Quinn, RP Dias, C Bidder, S Bhowmik, K Bumke, J Ganapathi, S Gorman, E Hind, S Karandikar, K Kumar, N Lipscomb, S McGovern, V Puthi, T Randell, G Watts, P Narendran. Presentation and characteristics of children with screen-detected type 1 diabetes; learnings from the ELSA general population paediatric screening study, 2024

In Press, Quinn, Dias et al 2024







HELMSLEY

JDRF

efpia SMedTech Europe

innovative health initiative Co-funded by

the European Union

European pre-T1D registry for children and adults with islet autoantibodies:

Included into the registry are children and adults with islet autoantibodies who have not yet progressed to clinical (stage 3) type 1 diabetes. Data from their last assessment are shown in this dashboard. For more information, please view <u>www.pre-t1d-registry.eu</u> or contact <u>pre-t1d-registry@helmholtz-munich.de</u>



pre-

The case of the military man

History	Results
 29yr old man, Royal Marines FH of T1D Oct 2022: transient osmotic symptoms 	 Weight 89Kg. BP 111/57 HbA1c: Aug 2023: 39 mmol/mol Mar 2024: 46 mmol/mol
 What is the diagnosis? 	 GAD 121 (<10) ZnT8 38 (<14) IA2 <10
 How would you manage him and what wrap-around support / education would you provide? 	 IAA 2.86 (<5) FSL: TIR 84%, above 15%, below 1% Occasional 10, 14mmol/L

Diabetologia https://doi.org/10.1007/s00125-024-06205-5

CONSENSUS REPORT



Consensus guidance for monitoring individuals with islet autoantibody-positive pre-stage 3 type 1 diabetes

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Consensus guidelines Relevance to UK clinical practice

- Frequency and intensity of follow up for adults and children with pre-T1D, glucose monitoring, safety, insulin initiation
- Urgent need to educate health care professional colleagues around pre-T1D
- Pre-T1D best managed in secondary care
- Potential need for psychosocial support

Follow up of mAb adults

- Education must be provided to reinforce the need for and value of longitudinal monitoring to prevent DKA. Written instructions with relevant emergency contact details should be provided in case of type 1 diabetes symptoms and/or hyperglycaemia.
- All multiple IAb+ adults can be provided with SMBG meters and strips to be used during illness or when symptoms may be present.
- In adults with stage 1 type 1 diabetes and normoglycaemia, glycaemic status should be monitored using HbA1c every 12 months. If duration of normoglycaemia extends to 5 years, metabolic monitoring every 2 years may be sufficient.
- In adults with confirmed stage 2 type 1 diabetes, metabolic status should be monitored using HbA1c every 6 months, in conjunction with one other of the following monitoring modalities: blinded CGM; higher frequency of SMBG; or 2 h plasma glucose following 75 g OGTT.



Immunotherapy could soon be available in the UK for T1D delay. How will we manage this?

Screening? 14-day infusion Which centres? Follow up? Equitable access?





Stakeholders' views

"If I could sit in front of a family and say it's definitely worth screening because this is what's on offer, and the chances that we can postpone, we can cure etc, are this, then I would be very comfortable." S23, Paediatric diabetes consultant



The case of the child diagnosed through a screening study

- 5 year old girl
- Parent T1D
- 3 AAB +ve on screening
- OGTT and HbA1c undertaken
- Clinical review: BG and weight stable for first 3 mths
- Attendances to PAU with concerns re: osmotic symptoms (weight loss and fatigue)
- Dexcom initiated

OGTT Results				
Time taken	Actual time taken	Glucose (mmol/L)	HbA1c (mmol/mol)	
-20 mins	09:35	4.5	41	
0 mins	10:12	4.1		
30 mins	10:45	10.1		
60 mins	11:20	9.9		
90 mins	11:45	9.6		
120 mins	12:20	9.9		

Stage 2 presymptomatic T1D

The case of the child diagnosed through a screening study



Glucose



What insulin to start and when?

- No randomised controlled trials to determine whether insulin therapy in the absence of clear symptoms early in stage 3 type 1 diabetes is beneficial.
- A child with early stage 3 type 1 diabetes might revert to stage 2.
- In the setting of an intercurrent illness, insulin might be needed only transiently.
- There are no studies assessing acceptability, feasibility, and adherence to insulin therapy in early stage 3 type 1 diabetes.
- It is unclear how to start insulin therapy in early stage 3 type 1 diabetes (basal or prandial insulin, combination of both, HCL)

Specific measures and thresholds to consider insulin initiation

- HbA1c: ≥48 mmol/mol (6.5%)
- Continuous glucose monitoring percentage time in range <70%
- Self-monitored blood glucose Fasting: persistently >7.0 mmol/L
 2-h post-meal: Persistently >11.1 mmol/L
- Insulin type and thresholds to consider initiation
 Prandial: recurring postprandial hyperglycaemia >11.1 mmol/L for >2 h
 Basal: rising glycaemia overnight

Besser 2024

Summary

Early identification of T1D has clinical advantages

Screening programmes need to be properly investigated

Guidelines and clinical coding for managing pre-symptomatic T1D are now available

Immunotherapy may be coming

UK is well placed



ELSA Study Team

University of Birmingham:

Parth Narendran	Professor of diabetes medicine
Tim Barrett	Professor of Paediatrics
Sheila Greenfield	Professor of Qualitative Research
Alex Richter	Professor of clinical immunology
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Morph and Nativve

All the parents and stakeholders who contributed to this study

