Published Online
December 3, 2024
https://doi.org/10.1016/
S2213-8587(24)00337-1

Dysglycaemia definitions and progression to clinical type 1 diabetes in children with multiple islet autoantibodies

The presymptomatic phase of type 1 diabetes is marked by the presence of two or more islet autoantibodies, classified into normoglycaemia (stage 1) and dysglycaemia (stage 2).[1–3] These stages guide the indication of therapies such as the anti-CD3 antibody, teplizumab, which is FDA approved for children aged 8 years or older with stage 2 type 1 diabetes. In the past decade, criteria for stage 2 have changed. TrialNet showed efficacy of teplizumab over placebo in delaying the clinical onset of type 1 diabetes and initially required two assessments that confirmed dysglycaemia, which was defined by impaired glucose tolerance (7·8–11·0 mmol/L at 120 min on an oral glucose tolerance test [OGTT]); impaired 30, 60, or 90 min OGTT values (≥11·1 mmol/L); or impaired fasting glucose (6·1–6·9 mmol/L) and was later modified to one assessment for people younger than 18 years.[1] The American Diabetes Association (ADA) has added an impaired HbA_{1c} concentration and extended the impaired fasting glucose range (5·6–6·9 mmol/L), but excludes impaired intermediate OGTT values altogether in the stage 2 definition.[4] The progression rate to clinical type 1 diabetes in individuals with ADA stage 2 remains unclear. To evaluate the suitability of TrialNet and ADA criteria, we analysed progression rates in children with presymptomatic type 1 diabetes identified from a large general population-wide screening programme.[5]

The Fr1da study offers islet autoantibody screening to children aged 1·75 to 10·99 years in Germany during well-child visits.[5] Families of children with presymptomatic type 1 diabetes are asked to participate in metabolic staging and monitoring with regular OGTT and HbA_{1c} assessments every 3–6 months for progression to clinical type 1 diabetes. Follow-up occurred until July 31, 2024, for the current analysis (appendix p 3). Stage 2 was defined by TrialNet or ADA criteria (table).[1,4] Clinical type 1 diabetes was defined using ADA criteria as HbA_{1c} (≥6·5%), FPG (≥7·0 mmol/L), or 2 h plasma glucose (≥11·1 mmol/L) during OGTT (in the absence of unequivocal hyperglycaemia, the diagnosis requires two abnormal test results obtained at the same time or at two different timepoints; or in an individual with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥11·1 mmol/L).[4] Kaplan–Meier survival analysis was conducted to estimate 2-year progression rate to clinical type 1 diabetes in children diagnosed with stage 2 type 1 diabetes.

Among 200 597 children screened for islet autoantibodies between Feb 1, 2015, and July 31, 2024, 576 (0·3%) were diagnosed with presymptomatic type 1 diabetes. Of these, 435 (75·5%) had metabolic staging. 309 (71·0%) of 435 had or developed stage 2 dysglycaemia at a median age of 5·6 years (IQR 4·0–8·3) and were included in

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	Median follow-up (IQR), months	2-year progression rate to clinical type 1 diabetes (95% CI)	Median survival (95% CI), months
TrialNet stage 2 definition			
At least one occasion* (n=173)	17·5 (6·2–35·6)	45·8% (36·9–53·5)	29·3 (21·9–37·4)
Confirmed by consecutive test† (n=30)	9·6 (5·3–28·7)	62·9% (40·0–77·0)	9·8 (5·7–45·9)
ADA stage 2 definition‡ (n=285)	22·1 (9·4–45·3)	32·2% (26·0–37·9)	46·2 (36·6–72·2)
ADA and TrialNet criteria			
Both criteria fulfilled§ (n=131)	11·9 (5·4–29·5)	54·1% (43·4–62·8)	20·5 (15·3–35·6)
Only ADA criteria fulfilled¶ (n=154)	24·2 (11·7–48·1)	26·6% (18·5–33·8)‖	59·0 (42·1–82·6)
Only TrialNet criteria fulfilled** (n=53)	30·6 (17·9–45·8)	21·3% (8·6–32·2)‖	57·7 (35·4–NR)
Any dysglycaemia abnormality†† (n=309)	22·2 (9·4–45·3)	31·4% (25·4–36·8)	51·0 (38·5–75·7)
≥2 dysglycaemia abnormalities‡‡ (n=106)	10·4 (3·5–23·1)	66·6% (54·7–75·4)	14·2 (10·8–20·5)
HbA_{1c}			
5·7–6·4% (≥1 OGTT abnormality; n=97)	7·8 (3·4–16·5)	80·1% (68·7–87·3)	10·8 (6·5–14·0)
5·7–6·4% (OGTT not reviewed; n=193)	15·4 (5·3–32·0)	44·5% (36·2–51·7)	30·6 (21·4–40·8)
Single abnormalities			
FPG (normal HbA_{1c} and remaining OGTT)			
5·6–6·9 mmol/L (n=40)	43·6 (12·6–60·7)	9·4% (0·1–18·9)	75·7 (72·2–NR)
5·6–6·0 mmol/L (100–109 mg/dL; n=31)	47·7 (19·2–64·2)	7·7% (0·1–17·4)	75·7 (72·2–NR)
6·1–6·9 mmol/L (n=9)	30·8 (6·5–45·7)	16·7% (0·1–41·7)	NA
2 h plasma glucose (7·8–11·0 mmol/L, normal HbA_{1c} and remaining OGTT; n=52)	21·2 (11·9–35·4)	36·0% (19·9–48·9)	35·6 (26·2–NR)
HbA_{1c} 5·7–6·4% (normal OGTT; n=112)	22·1 (11·7–39·3)	31·6% (21·4–40·5)	40·8 (34·0–56·3)
≥10% increase in HbA_{1c} (normal OGTT; n=39)	30·1 (8·9–66·4)	23·3% (7·6–36·4)	NA

Since we considered all OGTT and HbA_{1c} measurements of each child, one child can fulfil different criteria. OGTT=oral glucose tolerance test. ADA=American Diabetes Association. FPG=fasting plasma glucose. NA=not applicable. NR=not reached. *FPG 6·1–6·9 mmol/L; 2 h plasma glucose 7·8–11·0 mmol/L; or 30, 60, or 90 min plasma glucose (≥11·1 mmol/L) on at least one measurement. †FPG 6·1–6·9 mmol/L; 2 h plasma glucose 7·8–11·0 mmol/L; or 30, 60, or 90 min plasma glucose (≥11·1 mmol/L) on two consecutive measurements. ‡FPG 5·6–6·9 mmol/L, 2 h plasma glucose 7·8–11·0 mmol/L, HbA_{1c} 5·7–6·4%, or at least a 10% increase in two consecutive HbA_{1c} values. §FPG 6·1–6·9 mmol/L or 2 h plasma glucose 7·8–11·0 mmol/L and 30, 60, or 90 min plasma glucose and HbA_{1c} not reviewed. ¶FPG 5·6–6·0 mmol/L, HbA_{1c} 5·7–6·4%, or at least a 10% increase in two consecutive HbA_{1c} values and normal remaining OGTT. ‖p<0·0001 by log-rank test comparing only ADA criteria fulfilled and only TrialNet criteria fulfilled versus both criteria fulfilled. **30, 60, or 90 min plasma glucose of 11·1 mmol/L or higher, normal HbA_{1c}, and normal remaining OGTT. ††At least one abnormality from the following: FPG 5·6–6·9 mmol/L; 2 h plasma glucose 7·8–11·0 mmol/L; 30, 60, or 90 min plasma glucose of 11·1 mmol/L or higher; HbA_{1c} 5·7–6·4%; at least a 10% increase in HbA_{1c}. ‡‡Two or more abnormalities of FPG 5·6–6·9 mmol/L; 2 h plasma glucose 7·8–11·0 mmol/L; or 30, 60, or 90 min plasma glucose of 11·1 mmol/L or higher; HbA_{1c} 5·7–6·4%; or at least a 10% increase in HbA_{1c}.

Table: **Kaplan–Meier risk estimates of clinical type 1 diabetes in children with multiple islet autoantibodies and dysglycaemia (stage 2)**

the current study (appendix p 4). 136 (44·0%) of participants were female and 173 (56·0%) were male according to questionnaires collected at the well-child visit. 132 (33·0%) of 309 with stage 2 developed clinical type 1 diabetes during a median follow-up of 22·2 months (0·9–45·3; appendix pp 4–5).

The 2-year risk of developing clinical type 1 diabetes was 32·2% (95% CI 26·0–37·9) for those meeting the ADA stage 2 definition, 45·8% (36·9–53·5) for those diagnosed by TrialNet stage 2 criteria on at least one occasion (table; appendix p 6), and 62·9% (40·0–77·0) for those meeting the TrialNet criteria on two consecutive occasions. The risk was 54·1% (43·4–62·8) for children meeting both ADA and TrialNet criteria, compared with 26·6% (18·5–33·8) for those who only fulfilled ADA criteria (hazard ratio [HR] 2·07 [95% CI 1·47–2·92]; p<0·0001) and 21·3% (8·6–32·2) for those who only fulfilled TrialNet criteria (HR 2·14 [1·33–3·46]; p<0·0001; appendix p 6). Single dysglycaemia abnormalities in the absence of other abnormalities were associated with lower 2-year progression rates than having at least two abnormalities (HR 0·39 [0·29–0·53]; p<0·0001), ranging from 9·4% (0·1–18·9) in children with the ADA definition of impaired fasting glucose to 36·0% (19·9–48·9) in those with impaired glucose tolerance (appendix p 7). Risk was elevated in children with at least two dysglycaemia abnormalities (66·6% [54·7–75·4]) and was highest in those with impaired HbA_{1c} concurrent with at least one OGTT abnormality (80·1% [68·7–87·3]). Notably, 193 (62·5%) of 309 children had an impaired HbA_{1c}, with a 2-year progression rate to clinical type 1 diabetes of 44·5% (36·2–51·7; table; appendix p 7).

This study has limitations, such as inclusion of a predominantly White population, which might not represent other racial or ethnic groups, and the focus on children. The analysis was not based on a priori power estimates and some of the risks for single dysglycaemia categories have large 95% CIs. Although progression to clinical diabetes was similar in children with and without a first-degree family history of type 1 diabetes,[5,6] some of the findings might not be generalisable to those with a family history whose data were considered when defining the TrialNet and ADA criteria. Furthermore, other potential confounding factors associated with dysglycaemia abnormalities, such as weight or viral infection and age of seroconversion, were not considered.

These findings underscore the differences in the 2-year risk of progressing to clinical type 1 diabetes based on stage 2 definitions. The efficacy of teplizumab in stage 2 was greater among individuals whose C-peptide concentration fell within the lower 50th percentile (1·75 nmol/L) of those enrolled (HR 0·19 in low C-peptide group and 0·86 in high C-peptide group).[1] A lower C-peptide concentration is typically observed late in the presymptomatic stage,[7,8] indicating that treatment is more effective in the more active presymptomatic stage of the disease. Similarly, the 12–18 months before a clinical type 1 diabetes diagnosis has been suggested to represent a period of active disease and is suitable for intervention.[9] These observations suggest that interventions, such as teplizumab, might be administered late—eg, when the 2-year risk is 50% or greater as in the TrialNet trial assessing teplizumab efficacy.[1] Our findings indicate that the current ADA criteria for stage 2 did not reach this risk by a considerable margin; therefore, modifications to these criteria (such as incorporating two of the TrialNet or ADA dysglycaemia criteria simultaneously, as proposed by an expert committee consensus report,[3] or excluding individuals with only impaired fasting glucose) might be justified, particularly for children. Follow-up of children with presymptomatic type 1 diabetes for impaired HbA_{1c} without performing OGTTs might also be considered, as this test was able to capture most children with one or more dysglycaemia parameters and is less expensive and more practical than repeated OGTTs. In conclusion, our findings offer valuable guidance on the timing of interventional therapies in children with presymptomatic type 1 diabetes and inform the design of future clinical trials.

A-GZ participated in advisory boards for Sanofi; is a member of data monitoring committees for Sanofi and ITB-MED; and is a member of the Drug Agnostic Strategic Screening advisory board for Sanofi. SH, MK, and EB declare no competing interests. The Fr1da study was funded by Breakthrough T1D (formerly Juvenile Diabetes Research Foundation International); 1-SRA-2014–310-M-R, 3-SRA-2015–72-M-R, and 3-SRA-2019–718-Q-R), Life Science-Stiftung (HMGU 2014·01 and 2016·01), The Leona M and Harry B Helmsley Charitable Trust (G-1911–3274, 2308–06252, 2103–05017), and the German Center for Diabetes Research. SH, EB, and A-GZ are investigators in EDENT1FI, which is supported by the Innovative Health Initiative Joint Undertaking (grant 101132379). The funders of the study had no role in study design, data collection, data analysis, and data interpretation or writing of the report.

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Evaluation of a type 2 diabetes remission programme

We are writing in response to the recent Article by Jonathan Valabhji and colleagues regarding the NHS Type 2 Diabetes Path to Remission Programme.[1] While we commend the authors for their substantial effort in conducting this real-world implementation study, we believe that certain aspects of the interpretation of the results and discussion warrant further consideration. Specifically, in our opinion, there are some conclusions that seem somewhat overstated or lack sufficient nuance, particularly in the discussion of the remission rates and weight loss outcomes.

The study concludes that the remission rates, while lower than those observed in randomised controlled trials, demonstrate the practical feasibility of achieving remission in real-world settings. However, it is important to acknowledge that these lower rates might not solely be attributable to the difference between real-world and controlled settings. For instance, the authors mention that 27% of participants had remission, but it is also essential to explore why the remaining 73% did not have the same outcome. The study hints at variations in adherence, but does not delve deeply into the psychological and socioeconomic barriers that participants might have faced. Previous evidence has consistently shown that weight loss maintenance and adherence to lifestyle changes can be greatly impacted by socioeconomic factors, such as education level and financial stability.[2,3] Including a more thorough discussion on these potential barriers and suggesting specific strategies for overcoming them would provide a more balanced interpretation of the data.

Furthermore, although the study shows that those who lost more weight were more likely to have remission, it does not adequately discuss the plateau in weight loss observed after the food reintroduction phase. Weight regain or plateau is a common phenomenon in weight management interventions, often attributed to metabolic adaptations, psychological factors, and environmental triggers.[4] By not addressing the potential for long-term weight regain and how it might affect remission sustainability, the study leaves an important gap in understanding the full picture of type 2 diabetes remission. A more detailed exploration of how weight maintenance strategies could be improved in this programme, supported by existing research on long-term weight management, would have been beneficial. For instance, evidence highlights the importance of ongoing behavioural support for sustained weight loss,[5] which could be emphasised more strongly in the original study.[1]

Finally, the study suggests that the programme's implementation at scale was effective despite the reduced rates of remission and weight loss compared with those seen in randomised controlled trials. Although this is a valid observation, it is crucial to temper this conclusion with a more explicit acknowledgment of the study's limitations, such as the self-reported weight data in the remote programme groups. Self-reported data can often be inaccurate due to social desirability bias or recall errors, as noted in previous studies on dietary and weight reporting.[6] The authors could have explored this limitation more thoroughly and perhaps recommended more rigorous methods of data collection for future evaluations, such as using wearable technology or frequent in-person weight checks.

In conclusion, the study provides valuable insights into the real-world application of a remission programme for type 2 diabetes. However, we believe a more cautious interpretation of the findings, along with a deeper exploration of the factors influencing participant outcomes, would have enriched the study. By addressing these aspects, future programmes could be better equipped to provide long-term support and improve overall remission rates of type 2 diabetes.

We declare no competing interests.

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