SUMMARY (Clinical) 5/9/25 ciT1zen science

Comparison of immunological and immunogenetic markers in recent-onset type 1 diabetes among children and adults
ciT1zen science summary

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Summary:
This study, conducted in Estonia, investigates the differences in immunological and immunogenetic profiles between children and adults with recently diagnosed Type 1 Diabetes (T1D). The researchers analyzed autoantibodies (DAA), HLA-II alleles, specific genetic polymorphisms (SNP), and anti-enterovirus antibodies in a cross-sectional cohort of 168 participants aged 2.9–68.2 years. A smaller longitudinal study also examined immune checkpoint gene expression in children at diagnosis and one year later. The findings confirm significant immunological variability between age groups, highlighting the more aggressive nature of the disease in younger individuals and suggesting a greater influence of environmental factors in adult-onset T1D.
Key Themes and Important Ideas:

1. **Age-Dependent Phenotypes of T1D:** The study reinforces the concept that T1D presents differently in children and adults at diagnosis.

- **Children (< 15 years):** More likely to be positive for multiple diabetes-associated autoantibodies (DAA), particularly ZnT8A and IA-2A. Younger children (< 5 years) show a higher prevalence of the high-risk *HLA-DR3/DR4* genotype. This suggests a more aggressive autoimmune attack on beta cells in younger individuals.
- **Adults (> 15 years):** More likely to be positive for a single DAA, most commonly GADA. The pre-diagnosis duration of symptoms is longer, and weight loss is more common. The high-risk *HLA-DR3/DR4* genotype is less prevalent. This indicates a subtler, less aggressive progression in adults.
- **Quote:** "These results confirm immunological variability in recent-onset T1D cases between children and adults and stress the importance of further research to define the comprehensive immunological profile of the disease age-related subgroups."
- **Quote:** "Similar to previous reports, we showed that multiple DAA autoantibodies are more characteristic of younger children with recently diagnosed T1D compared to older individuals and suggestive of a more aggressive progression of the disease."
- **Quote:** "Additionally, as expected, participants younger than 5 years belonged mainly to the *HLA-DR3/DR4* group which was less represented in older participants."

1. **Diabetes-Associated Autoantibodies (DAA):** The profile and prevalence of DAA vary with age and are important markers for understanding disease progression.

- GADA is the most prevalent autoantibody overall.
- ZnT8A and IA-2A are significantly more prevalent in participants younger than 15 years.
- Single DAA positivity is more common in older individuals.
- **Quote:** "GADA was the most prevalent autoantibody (80.1%) in the all participants, followed by ZnT8A (73.2%) and IA-2A (65.5%)."
- **Quote:** "As shown in Fig. 1a, participants aged < 15 years had significantly more ZnT8A and IA-2A (85.4% and 77.3%, respectively) compared with participants aged > 15 years (50.0% and 43.1%, respectively) (both $P < 0.001$)."
- **Quote:** "There were more participants positive for single DAA and less participants positive for ≥ 2 DAA in the participants aged > 15 years compared with participants aged < 15 years (both $P < 0.001$) (Fig. 1b)."

1. **The Significance of Enterovirus (EV) Antibodies:** EV antibodies are linked to increased DAA positivity, even in adults.

- Anti-EV IgG positivity increased the odds of being multiple DAA-positive.
- This association is observed in both childhood- and adulthood-onset T1D.
- **Quote:** "while anti-EV IgG positivity increased the odds of being multiple DAA-positive (adjusted OR 4.42; 95% CI 1.62–12.04)."
- **Quote:** "Although EV infections have been associated with the development of T1D in young children, we showed that EV antibodies increase the odds to have multiple DAA positivity also in adulthood-onset T1D, suggesting that repeated or prolonged EV infections are involved in T1D development in adults."

1. **Characteristics of DAA-Negative T1D:** The study highlights the profile of individuals with T1D who test negative for the common DAA.

- DAA-negative participants were older (median age 40.6 years) compared to DAA-positive individuals.
- They had a longer duration of symptoms before diagnosis.
- The absence of DAA suggests a subtler progression of T1D.
- It is important to test for IAA in DAA-negative individuals.
- A significant portion of DAA-negative individuals did not have the high-risk *HLA-DR3* or *DR4* alleles, potentially representing cases of idiopathic type 1b diabetes.
- **Quote:** "The DAA-negative T1D participants were older than the DAA-positive individuals."
- **Quote:** "The participants of the DAA-negative subgroup were all male adults... Presence of DAA is associated with a more rapid illness progression, while the absence of DAA can point to subtler progression."
- **Quote:** "We showed that it is crucial to examine IAA in these individuals, as one fourth of the GADA-, IA-2A- and ZnT8A-negative participants had IAA."

- **Quote:** "Of the DAA-negative participants, 50% did not have *HLA-DR3* or *DR4* risk alleles. These participants could be considered as individuals with idiopathic type 1b diabetes described previously in persons of European ethnicity."

1. **Genetic Factors (HLA and SNP):** The distribution of HLA genotypes differs between children and adults, while the studied SNP genotypes are similar.

- The high-risk *HLA-DR3/DR4* genotype is more prevalent in children, especially those diagnosed at a very young age.
- *HLA DR4/x* was associated with decreased odds of being single DAA-positive compared to multiple DAA-positive.
- The distribution of *PTPN22* rs2476601, *CTLA4* rs3087243, *IFIH1* rs1990760, and *SLC30A8* rs13266634 genotypes was similar between children and adults.
- **Quote:** "The distribution of HLA genotypes was different between children and adults ($P = 0.031$)."
- **Quote:** "The most prevalent HLA genotype in children was *DR3/DR4*, which was the least common in adults."

1. **Immune Checkpoint Gene Expression:** Gene expression patterns show more variability at the time of diagnosis.

- No significant difference was detected in gene expression levels of studied immune checkpoint molecules between diagnosis and one year later in children.
- However, samples taken at diagnosis showed more outlier values, suggesting this time point is more informative for evaluating disease subtypes.
- Some weak correlations were found between specific gene expression levels (e.g., *TIGIT*, *CD28*, *FoxP3*, *CD155*) and DAA levels at diagnosis, but these were not significant after adjustment.
- **Quote:** "At the 1st time point, the gene expression levels of more than half (13 out of 25) of the participants revealed at least one outlying value. One year after diagnosis, the outlying values were lower and distributed more evenly."
- **Quote:** "Instead, we detected more outlier values in the samples taken at diagnosis compared to those taken one year later, suggesting that the time point closer to diagnosis is more informative for evaluating the different pathway-related endotypes and thereby influencing subsequent clinical treatment."

1. **Environmental Factors in Adult-Onset T1D:** The findings suggest that environmental factors may play a more prominent role in T1D development in adults.

- The lower prevalence of T1D risk haplotypes in adults, combined with the association between EV antibodies and multiple DAA positivity, supports this notion.
- **Quote:** "Overall, our findings suggest that with increasing age, environmental factors become more important in the development of T1D."

- **Quote:** "Specifically, we observed that T1D risk haplotypes were less common in adults, suggesting a potential shift in the underlying mechanisms contributing to the disease across different age groups."

Important Facts and Findings:

- 168 participants with recently diagnosed T1D (aged 2.9–68.2 years) were included in the cross-sectional study.
- 25 children were part of a longitudinal study examining gene expression at diagnosis and 1 year later.
- GADA was the most prevalent DAA (80.1%), followed by ZnT8A (73.2%) and IA-2A (65.5%).
- Nearly half of participants (45.8%) were positive for all three DAA, mostly children.
- 16.7% of participants were positive for a single DAA, mostly adults.
- Participants aged < 15 years had significantly more ZnT8A and IA-2A (85.4% and 77.3%) than those > 15 years (50.0% and 43.1%).
- Participants aged > 15 years had significantly more single DAA positivity and less multiple DAA positivity than those < 15 years.
- The median age of single DAA-positive participants was 21.2 years, while multiple DAA-positive participants had a median age of 11.6 years.
- Older age increased the odds of being single DAA-positive (OR 1.05; 95% CI 1.02–1.09).
- Anti-EV IgG positivity was a risk factor for multiple DAA positivity in adults (adOR 4.42; 95% CI 1.62–12.04).
- The prevalence of DAA negativity was 3.6% (6 out of 168).
- DAA-negative participants had a median age of 40.6 years and a longer duration of symptoms before diagnosis (82 days vs 28 days for DAA-positive).
- Thyroid autoimmunity was the most common concomitant autoimmune disease (8.3%).
- The *HLA-DR3/DR4* genotype was the most prevalent in children but least common in adults.
- DAA-negative participants were more likely to be male adults.

Limitations:

- Relatively small sample size, particularly for the longitudinal gene expression study and the DAA-negative subgroup.
- IAA was not measured in all participants.
- Incomplete baseline and clinical data for some participants (e.g., BMI).

Future Directions:

- Further research is needed to define the comprehensive immunological profile of age-related subgroups in T1D.

- Extensive exposome studies are necessary to understand the role of environmental factors.
- Metagenomic and quantitative trait locus (QTL) analysis of immune cell genes could help characterize age-dependent subtypes.
- This research aims to contribute to the development of effective, tailored treatment modalities for the diverse clinical presentations of T1D.