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Dissecting the etiology of type 1 diabetes and associated celiac and thyroid diseases.

Daniel Agardh, Alexander Lind, Flemming Pociot, Sara Juul Mansachs, Jesper Johansen, Finn Kristensen and colleagues





medicon valley aliance Creating Opportunities



The DiaUnion TRIAD

- **T1D** The pancreatic islet beta-cells are destroyed. Insulin replacement therapy is the life-saving treatment.
- CD The intestinal mucosa is destroyed promoted by gluten-Gluten-free diet for life is the treatment. About 10% of T1D also have CD.

AITD The thyroid is infiltrated by immune cells. The production of thyroid hormone will cease. Thyroid hormone replacement therapy is the treatment. More than 25% of patients with T1D. About 5-10% of patients with CD also have AITD.



TRIAD About 5% OF THE POPULATION





Nature Reviews | Disease Primers

BIOMARKERS OF ETIOLOGY AND PATHOGENESIS

- T1D Insulin (IAA), GAD (GADA), islet antigen-2 (IA-2A) and ZnT8 transporter (ZNT8A) are standardized.
 Predict clinical onset of diabetes prevention trials.
- **CD** Tissue transglutaminase (tTGA) are standardized. Predict CD – some use tTGA as diagnostic criteria.
- AITD Thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) are standardized. Predict AITD.



TRIAD About 5% OF THE POPULATION



IT'S ALL ABOUT TIMING

IT WAS KNOWN THAT THESE AUTOANTIBODIES COULD BE DETECTED YEARS BEFORE CLINICAL DIAGNOSIS.

WHEN THEN TO START INVESTIGATING ETIOLOGY?

AT BIRTH!



Secondary endpoints:

tTGA

TPOA, ThGA, TSH

Celiac Disease Thyroid Disease

Appearance of islet autoimmunity (IA) - the two endotypes of T1D

Incidence of IAA and GADA as the first appearing islet autoantibody (/1000 children per year)



IAA first DR4-DQ8

GADA first DR3-DQ2

The 6 year incidence of diabetes-associated autoantibodies in genetically at-risk children: the TEDDY study

Jeffrey P. Krischer • Kristian F. Lynch • Desmond A. Schatz • Jorma Ilonen • Åke Lernmark • William A. Hagopian • Marian J. Rewers • Jin-Xiong She • Olli G. Simell • Jorma Toppari • Anette-G. Ziegler • Beena Akolkar • Ezio Bonifacio • the TEDDY Study Group

Diabetologia. 2015; 58(5):980-7. doi: 10.1007/s00125-015-3514-y

Timing of autoantibodies and diagnosed T1D or CD

What happened to the child prior to the appearance of the first autoantibody?

TEDDY Islet aab seroconversion and diagnosed T1D



TEDDY Celiac tTG aab seroconversion and diagnosed CD



Viral metagenomics

Viral metagenomics of 8654 stool samples from 383 pairs



621 viral taxa were identified

- 72% bacteriophages
- 20% human/mammalian viruses
- 8% viruses of food stream (mostly plant viruses)



Early stool virome at the age 3 to 6 months and the appearance of IAA vs. GADA after 6 months of age



medicine

LETTERS https://doi.org/10.1038/s41591-019-0667-0

Early enterovirus B infections (18% infected) are associated with appearance of IAA

Kendra Vehik 🖲¹⁺, Kristian F. Lynch¹, Matthew C. Wong², Xiangjun Tian², Matthew C. Ross², Richard A. Gibbs³, Nadim J. Ajami², Joseph F. Petrosino², Marian Rewers⁴, Jorma Toppari^{5,6}, Anette G. Zlegler^{23,8}, Jin-Xiong She¹⁰, Ake Lernmark ^{O,11}, Beena Akolkar², William A. Hagopian¹³, Desmond A. Schatz¹⁴, Jeffrey P. Krischer¹, Heikki Hyöty^{15,16}, Richard E. Lloyd² and the TEDDY Study Group⁷⁰

Prospective virome analyses in young children at

increased genetic risk for type 1 diabetes

Gastroenteritis and the appearance of GADA



TRIAD –etiology so far.....

T1D Two endotypes:

IAA-first at 1-4 years of age after prolonged shedding of enterovirus B – DR4-DQ8 children.
GADA-first at 2 years and older after prolonged shedding of adenovirus F or norovirus – DR3-DQ2 children

- **CD** *Tissue transglutaminase (tTGA)* at 2-4 years of age after gluten exposure combined with enterovirus infection. Which virus?
- AITD Which autoantibody appears first TPOAb or TGAb? Which virus? Other exposures?



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TRIAD – future directions



- 1. HOW DOES A VIRUS INFECTED CELL TRIGGER AN AUTOIMMUNE REACTION AND NOT NEUTRALIZING VIRUS ANTIBODIES? **KEY TO CURE!**
- 2. VACCINATE AGAINST THE **TRIAD** DISEASES. Provention Bio has begun trial
- 3. PRIMARY PREVENTION: ORAL INSULIN PROBIOTICS GLUTEN FREE DIET

4. SECONDARY PREVENTION: SCREENING DEMO DiaUnion

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THANK YOU!

- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institute of Child Health and Human Development (NICHD)
- National Institute of Environmental Health Sciences (NIEHS)
- Centers for Disease Control and Prevention (CDC)
- JDRF











Öresund-Kattegat-Skagerrak



